Title: A Phase 2, Randomized, Open-Label Study Comparing Oral Ixazomib/Dexamethasone and Oral Pomalidomide/Dexamethasone in Relapsed and/or Refractory Multiple Myeloma

NCT Number: NCT03170882

Protocol Approve Date: 31 August 2020

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

PROTOCOL

A Phase 2, Randomized, Open-Label Study Comparing Oral Ixazomib/Dexamethasone and Oral Pomalidomide/Dexamethasone in Relapsed and/or Refractory Multiple Myeloma

Sponsor:	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited 40 Landsdowne Street Cambridge, MA 02139, USA Telephone: +1 (617) 679-7000 Note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium," "Sponsor," or "Takeda."
Study Number:	C16029
IND Number:	IND 104,482
EudraCT Number:	2016-004742-28
Compound:	Ixazomib (NINLARO)
Date:	31 August 2020
Version/Amendment Number:	06 (global)

Amendment History:

Date	Amendment Number	Amendment Type (for Regional Europe Purposes Only)	Region
29 March 2017	Initial protocol		Global
09 August 2017	01	Nonsubstantial	Global
30 January 2019	02	Nonsubstantial	Global
23 April 2019	03	Substantial	United Kingdom
11 June 2019	04	Substantial	Germany
16 September 2019	05	Substantial	Global
31 August 2020	06	Substantial	Global

1.0 ADMINISTRATIVE

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints and medication errors.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	North America Contact	European Union Contact	Japan Contact
Serious adverse event and pregnancy reporting	See Section 10.2	See Section 10.2	See Section 10.2
Medical Monitor (medical advice on protocol and compound)	See Study Manual	See Study Manual	See Study Manual
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	See Study Manual	See Study Manual	See Study Manual

1.2 Approval

REPRESENTATIVES OF MILLENNIUM

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Millennium medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures can be found on the last page of this document.

PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.0 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Responsibilities of the Investigator (Appendix B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

1.3 Protocol Amendment 06 Summary of Changes

Rationale for Amendment 06

This document describes the changes in reference to the protocol incorporating Amendment 06. The primary reason for this amendment is to modify the study assessments, now that the data cutoff date for the study analysis (the only planned formal analysis) has been reached (31 May 2020). 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. Because 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 End of Treatment (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 adverse events (AEs) and serious adverse events (SAEs). All other study assessments are no longer required. All central laboratory assessments are discontinued. Quality of life and health care utilization (HU) assessments and collection of concomitant medications and procedures are discontinued. Patients will not be followed for the progression-free survival (PFS) or overall survival (OS) follow-up periods, because PFS and OS data are no longer being collected. See the updated Schedule of Events in Appendix A for more detailed information (the previous, full Schedule of Events is now moved to Appendix L for reference only).

Descriptions of how to manage study procedures during unavoidable circumstances, such as the coronavirus disease 2019 (COVID-19) pandemic, have additionally been added.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

For specific descriptions of text changes and location of the changes, see Appendix M.

Changes in Amendment 06

1. To note that the data cutoff date for the study analysis, which is the only planned formal analysis for this study, has now occurred.
2. To note that, now that the data cutoff date for the study analysis has occurred, all central efficacy and investigator assessments of response for protocol purposes are now discontinued.
3. To note that, now that the data cutoff date for the study analysis has occurred, the objective and endpoint of the study has changed to solely continue to collect long-term safety data.

4. To note that as of the current amendment, now that the data cutoff date for the study analysis has occurred, only patients who continue to demonstrate clinical benefit but have no access to study drugs other than staying in the study may stay in the study.
5. To clarify that, as of the current amendment, the reason for a patient's treatment discontinuation must be recorded in the electronic case report form (eCRF) but no approval by the sponsor is required to discontinue treatment.
6. To clarify that local laboratory evaluations are to be used henceforth.
7. To simplify the Schedule of Events to reflect the other changes noted.
8. To clarify that pharmacokinetic (PK) sample collection is now complete.
9. To clarify that the previous, full Schedule of Events and the now-completed PK sampling schedule have been moved to a new appendix (Appendix L) for reference only.
10. Identify, as needed, text in the protocol that is no longer applicable as of the current amendment, now that the data cutoff date for the study analysis has occurred.
11. To add flexibility in study conduct in unavoidable circumstances (eg, the COVID-19 pandemic).
12. To indicate that, given the changes in the current amendment, patients remaining on study will need to be reconsented.
13. Update language about management of clinical events in patients receiving ixazomib.
14. To clarify details about ixazomib packaging, handling, and storage guidelines.
15. To clarify that PFS and OS data will be analyzed using unstratified tests, among others.
16. To add information about submitting SAE reports.
17. To correct a typographical error and clarify that there is only 1 study analysis planned (and as such, no interim analyses).

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2.0 STUDY SUMMARY

Name of Sponsor(s): Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited	**Compound:** Ixazomib (NINLARO)
Title of Protocol: A Phase 2, Randomized, Open-Label Study Comparing Oral Ixazomib/Dexamethasone and Oral Pomalidomide/Dexamethasone in Relapsed and/or Refractory Multiple Myeloma	
Study Number: C16029	**Phase**: 2
Study Design: Study C16029 is a randomized, open-label, phase 2 study. The 3 stratification factors are 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). Patients will be randomized in a 3:2 ratio to receive ixazomib+dexamethasone (ixa+dex; Arm A) or pomalidomide+dexamethasone (pom+dex; Arm B), until first confirmed progressive disease (PD) or unacceptable toxicities.	
Primary Objective: As of Amendment 06, the objective is to continue to collect long-term safety data from patients who are continuing on ixazomib and dexamethasone or pomalidomide and dexamethasone because of continuing clinical benefit. Data collection for all other study objectives and endpoints is complete and no further formal analyses will be conducted. However, the original primary objective is retained below for reference only. To compare the effect of ixa+dex versus pom+dex on progression-free survival (PFS) in patients with relapsed and/or refractory multiple myeloma (RRMM) who have received at least 2 prior lines of therapy, including lenalidomide and a proteasome inhibitor, and are refractory to lenalidomide but not refractory to proteasome inhibitors.	
Secondary Objectives: As of Amendment 06, the objective is to continue to collect long-term safety data from patients who are continuing on ixazomib and dexamethasone or pomalidomide and dexamethasone because of continuing clinical benefit. Data collection for all other study objectives and endpoints is complete and no further formal analyses will be conducted. However, the original secondary objectives are retained below for reference only. • To compare overall survival (OS) in patients treated with ixa+dex versus pom+dex. • To compare duration of response, overall response rate (ORR), time to response, and time to progression with ixa+dex versus pom+dex. • To obtain health-related quality of life (QOL) data related to physical functioning of patients treated with ixa+dex versus pom+dex. • To assess health-related QOL by additional function and symptom domains of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) instrument and by the EORTC Quality of Life Questionnaire–multiple myeloma module (EORTC QLQ-MY20) and 5-level classification system of the EuroQol 5-Dimensional Health Questionnaire (EQ-5D-5L) instruments. • To evaluate health care utilization (HU) by patients receiving ixa+dex versus those receiving pom+dex. • To collect plasma concentration-time data for ixazomib to contribute to population pharmacokinetic characterization of ixazomib and to conduct exposure-response analyses for patients receiving ixa+dex. Safety: • To compare safety/tolerability of ixa+dex to that of pom+dex.	
Study Population: Patients with RRMM, aged ≥18 years, for whom pomalidomide is clinically indicated, who have had at least 2 prior lines of systemic therapy, including at least 2 consecutive cycles of bortezomib or carfilzomib (without having had PD during treatment with or within 60 days after the last dose of bortezomib or carfilzomib), and are refractory to lenalidomide.	

Number of Subjects:	**Number of Sites:**
Estimated total: approximately 120 patients randomized—approximately 72 in Arm A (ixa+dex) and approximately 48 in Arm B (pom+dex).	Estimated total: approximately 100 globally
Dose Levels: *Arm A* Ixazomib will be administered at a 4 mg starting dose, with escalation to 5.5 mg at Cycle 2 for patients who tolerate the 4 mg dose in Cycle 1 (specifically, patients who do not experience any new Grade 1 peripheral neuropathy with pain or other ixazomib-related Grade ≥2 nonhematologic or Grade ≥3 neutropenia or thrombocytopenia in Cycle 1). 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. Ixazomib will be administered orally on Days 1, 8, and 15 of each 28-day cycle, combined with dexamethasone 20 mg (or 10 mg if patient is aged ≥75 years) orally on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day cycle until PD. 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 ≥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. *Arm B* Pomalidomide will be administered at 4 mg orally on Days 1 to 21 of each 28-day cycle, combined with dexamethasone 40 mg (or 20 mg if patient is aged ≥75 years) orally on Days 1, 8, 15, and 22 of each 28-day cycle until PD.	**Route of Administration:** Arm A and Arm B are both all-oral therapies.
Duration of Treatment: Patients will receive study therapy until PD, unacceptable toxicity, withdrawal of consent, or sponsor termination of study.	**Period of Evaluation:** Up to 28 months

Main Criteria for Inclusion:

- Adult patients (aged ≥18 years) who have been diagnosed with multiple myeloma (MM) according to standard criteria.
- 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 stem-cell transplantation, followed by maintenance is considered 1 line of therapy. 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 a prospective study participant.)
- 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.
- All patients must have received at least 2 consecutive cycles of a bortezomib- or carfilzomib-containing regimen, and either:
  - Achieved at least a partial response (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 adverse

events (AEs) before completion of the planned treatment course) without PD upon the start of the next regimen.

- All patients must have an Eastern Cooperative Oncology Group score of 0 to 2.
- All patients must have measurable disease defined by serum M-protein ≥1 g/dL (≥10 g/L) or urine M-protein ≥200 mg/24 hours and must have documented MM isotype by immunofixation (central laboratory).

Main Criterion for Exclusion:

- Patients must not have received prior ixazomib or pomalidomide and must not have participated in a previous ixazomib clinical study.

Main Criteria for Evaluation and Analyses:

The primary endpoint for this study is PFS, defined as the time from randomization to the first occurrence of confirmed PD, as evaluated by investigators on the basis of central laboratory results according to International Myeloma Working Group (IMWG) criteria, or death from any cause, whichever occurs first.

The secondary endpoints are OS; ORR (defined as complete response, very good partial response (VGPR), or PR [per IMWG criteria]); duration of response; time to response; time to progression (TTP); 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; health care utilization as measured by the number and duration of medical encounters; and safety/tolerability.

After the data cutoff date for the study analysis (including for PFS) has occurred, all central efficacy and investigator assessments of response for protocol purposes will be discontinued.

As of Amendment 06, the data cutoff date for the study analysis (31 May 2020) has been reached. 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 End of Treatment 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 serious AEs. All other study assessments are no longer required. All central laboratory assessments are discontinued. Quality of life and health care utilization assessments and collection of concomitant medications and procedures are discontinued. Patients will not be followed for the PFS or OS follow-up periods, as PFS and OS data are no longer being collected.

Statistical Considerations:

There will be 1 study analysis for PFS and secondary endpoints.

Sample Size Justification:

Approximately 120 patients will be enrolled in total.

The primary endpoint is PFS. Approximately 81 PFS events would be needed to provide 80% power at a 2-sided 0.20 level of significance with an HR of 0.62.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor or designee will perform all study-related activities with the exception of those identified in the Clinical Study Supplier List or equivalent.

3.2 Principal Investigator/Coordinating Investigator

Millennium will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AE	adverse event
ANC	absolute neutrophil count
ASCT	autologous stem cell transplantation
CFR	Code of Federal Regulations
CR	complete response
CRO	contract research organization
CT	computed tomography
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
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
EOT	End of Treatment
EQ-5D-5L	5-level classification system of the EuroQol 5-Dimensional Health Questionnaire
EQ VAS	EuroQol visual analogue scale
EU	European Union
FDA	Food and Drug Administration
G-CSF	granulocyte colony stimulating factor
GCP	Good Clinical Practice
HR	hazard ratio
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IRB	institutional review board
IRT	interactive response technology
ISS	International Staging System
ITT	intent-to-treat
IV	intravenous
ixa+dex	ixazomib+dexamethasone (investigational study therapy, given in Arm A)
KM	Kaplan-Meier
LenDex	lenalidomide and dexamethasone

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

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

4.0 INTRODUCTION

4.1 Background

4.1.1 Ixazomib Clinical Development Program

Ixazomib, an oral inhibitor of the 20S proteasome, is under development for the treatment of multiple myeloma (MM), plasma cell dyscrasias, amyloidosis, lymphoma, nonhematologic malignancies, and lupus nephritis. Inhibition of the 20S proteasome has been validated as a therapeutic target for the treatment of malignancies using VELCADE (bortezomib) for Injection, Millennium Pharmaceuticals, Inc's first-in-class proteasome inhibitor [2].

Ixazomib (MLN2238) refers to the biologically active boronic acid form of the drug substance. The drug substance is administered as a stable citrate ester, designated as ixazomib citrate (MLN9708). Under physiological conditions, ixazomib citrate rapidly hydrolyzes to the biologically active boronic acid, ixazomib. Ixazomib is a peptide boronic acid that is structurally different from bortezomib. Detailed information regarding the nonclinical pharmacology and toxicology of ixazomib can be found in the ixazomib Investigator's Brochure (IB).

4.1.1.1 Approval of Ixazomib+Lenalidomide and Dexamethasone for Relapsed and/or Refractory Multiple Myeloma

Ixazomib in combination with lenalidomide and dexamethasone (LenDex) was approved (under the brand name NINLARO) by the United States (US) Food and Drug Administration (FDA) in November 2015 for the treatment of patients with MM who have received at least 1 prior therapy [3,4], with approvals subsequently in Canada, Israel, Australia, the European Union (EU), and Singapore and in Switzerland for patients who have received at least 1 prior therapy and have high-risk characteristics or have received at least 2 prior therapies. Additionally, NINLARO is approved as a Medical Service Product in Venezuela.

The pivotal phase 3 Study C16010 was the basis for the approval, involving 722 patients with relapsed and/or refractory multiple myeloma (RRMM) [4]. The primary endpoint of PFS was met in the intent-to-treat (ITT) population at the primary analysis, with a significant PFS benefit for patients receiving ixazomib+LenDex versus placebo+LenDex (hazard ratio [HR]=0.742, p=0.012; median PFS 20.6 vs 14.7 months). The PFS benefit in the ixazomib regimen was supported by improvements versus the placebo regimen in other efficacy data. At a median follow-up of approximately 23 months, the median OS had not been reached in either regimen. The rates of SAEs were similar in the 2 regimens (47% with ixazomib, 49% with placebo), as were the rates of death during the study period (4% and 6%, respectively); Grade ≥3 AEs occurred in 74% and 69% of the patients, respectively. Overall, the addition of ixazomib to LenDex did not add substantial toxicity.

The PFS benefit and safety profile seen in global Study C16010 have been substantiated in the China Continuation study, a second double-blind, placebo-controlled study of similar design and the same inclusion criteria, with 115 patients with RRMM, all enrolled in China [5]. In addition, an OS benefit in favor of the ixazomib+LenDex group was observed at the final analysis [6].

More details are given in Section 4.2.3.1.

4.1.1.2 Other Clinical Development

Ixazomib has been tested as an intravenous (IV) and an oral formulation (during the early development of ixazomib); however, only the oral formulation is currently being developed for commercialization. Regardless of the route of administration, in the twice-weekly dosing schedule, ixazomib is given on Days 1, 4, 8, and 11 of a 21-day cycle, and in the weekly dosing schedule, ixazomib is given on Days 1, 8, and 15 of a 28-day cycle.

Phase 1, phase 1/2, and phase 2 studies are ongoing in MM, relapsed and/or refractory systemic light-chain amyloidosis (RRAL), solid tumors, and lymphoma. In addition, phase 1 studies have been completed in patients with renal impairment who have RRMM or advanced solid tumors (Study C16015); patients with hepatic impairment who have advanced solid tumors or hematologic malignancies (Study C16018); and in an absorption, distribution, metabolism, and excretion study in patients with advanced solid tumors or lymphoma (Study C16016). Phase 3 studies in RRMM, newly diagnosed multiple myeloma (NDMM), and RRAL are under way.

As of 27 March 2016, for SAE and fatality incidences, a total of 3346 patients have been exposed to ixazomib. Specifically, data are available from 929 patients known to have received at least 1 dose of either the IV or oral ixazomib formulations across the clinical development program; in addition, 2417 patients have been enrolled in the following phase 3 clinical trials:

- Double-blind, placebo-controlled Study C16010 and Study C16010 China Continuation study of ixazomib versus placebo in combination with LenDex in patients with RRMM (described in Section 4.1.1.1).
- Double-blind, placebo-controlled Study C16014 and Study C16014 extension in South Korea of ixazomib versus placebo in combination with LenDex in patients with NDMM.
- Double-blind, placebo-controlled Study C16019 of ixazomib versus placebo as maintenance in patients with NDMM who have undergone autologous stem cell transplantation (ASCT) before entering the study.
- Double-blind, placebo-controlled Study C16021 of ixazomib versus placebo as maintenance in patients with NDMM who have not undergone ASCT.
- Open-label Study C16011 of ixazomib and dexamethasone (ixa+dex) versus physician's choice of a dexamethasone-containing regimen in patients with RRAL.

4.1.1.3 Investigator-Initiated Study Relevant to This Protocol

Results of the investigator-initiated study of ixa+dex in patients with RRMM (MC1181, NCT01415882; principal investigator, PPD) are of particular importance for Study C16029, the focus of this protocol [7,8]. In that study, patients with relapsed MM were treated with ixazomib 4.0 or 5.5 mg weekly for 3 of 4 weeks and with dexamethasone 40 mg weekly. The overall response rate (ORR) was 31% for the 4.0 mg arm and 54% for the 5.5 mg arm. Both arms had manageable toxicities. See Section 4.3.4 for more information.

4.2 Background Information on the Disease to Be Treated

MM is a clonal disease of plasma cells that is characterized by the accumulation of plasma cells in the bone marrow (and other organs) and sometimes results in bone marrow failure, bone destruction, hypercalcemia, anemia, infection, and renal failure. It is the second most common hematological malignancy, constituting approximately 1% of all reported neoplasms and approximately 13% of hematologic cancers worldwide [9]. The incidence of MM is expected to increase over the next decade, which highlights the need for more effective MM therapies [10]. Moreover, to a greater extent in the future than now, MM will be a disease that primarily affects older persons (those aged 64 to 84 years) [11], who generally have a worse prognosis than younger persons.

4.2.1 Current Medical Treatments for MM

Although MM is considered a fatal disease, duration of survival has improved dramatically over the last 2 decades because of advances in understanding the disease biology as well as improvements in treatment and supportive care strategies. Between 1990 and 2007, the cancer death rate for people with MM in the United States decreased by approximately 9% for men and 13% for women, owing to the introduction of stem cell transplantation and the novel agents bortezomib, thalidomide, and lenalidomide [12]. Correspondingly, 5-year survival improved from 25% in 1975 to 39% in 2006 [13]. Similar improvements in survival rates among European patients with MM have been shown, particularly among younger patients [14,15]. Moreover, newer agents continue to be introduced, including carfilzomib, pomalidomide, elotuzumab, and daratumumab. These newer agents have been shown to improve survival among older patients, with the 6-year OS among patients older than 65 years increasing from 31% among those diagnosed in 2001-2005 to 56% among those diagnosed in 2006-2010 ($p<0.001$) [16]. Nonetheless, responses to currently available therapies are temporary, and most patients receive multiple therapies and combination therapies over the course of their disease.

First-line treatment options are determined by a patient's eligibility, or lack thereof, for ASCT [17,18]. Regardless of whether the patient is transplant eligible, MM is sensitive to a number of cytotoxic drugs, including proteasome inhibitors such as bortezomib and carfilzomib, alkylating agents, immunomodulatory drugs (IMiDs) (eg, thalidomide and lenalidomide), corticosteroids, and monoclonal antibodies (eg, elotuzumab and daratumumab) [19-24]. However, even with such advances and risk-adapted approaches, nearly all patients eventually relapse or become refractory and require subsequent treatment [25,26]; thus, new treatment options are urgently needed. In particular, new therapies with less toxicity are needed for elderly patients to continue to improve the prognosis of this population that comprises most MM patients [16].

4.2.2 Unmet Medical Need Addressed by This Clinical Study

MM remains an incurable disease for most patients and development of RRMM is an inevitable reality for almost all patients. While there is no widely accepted standard of care for RRMM, patients typically receive several lines of therapy with combinations of drugs over the course of their disease. Further, MM is heterogeneous, and no single treatment regimen will be effective for all patients [27]. Consequently, treatment decisions are carefully based on patient and disease

characteristics. Historically, with each subsequent recurrence of MM, patients have a lower probability of responding to therapy [28-33]. Therefore, there is a need for regimens that are effective in later therapies. In addition, patients who require treatment after receiving 2 prior lines of therapy may experience long-term side effects as a consequence of being exposed to multiple cytotoxic drugs with varying toxicity profiles (eg, neuropathy, decreased bone marrow reserve).

Many patients in their third or later line of therapy are not able to tolerate the toxicity of a 3-drug regimen and would benefit from a less toxic doublet (see Section 4.3.3). (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 ASCT, followed by maintenance is considered 1 line of therapy [1]. Typically, each line of therapy is separated by progressive disease [PD]. Discussion with the medical monitor may help clarify the number of prior lines of therapy for each prospective study participant.)

As the incidence of MM in older patients increases, so does the need for therapy that is effective but also tolerable and that maintains quality of life (QOL) [34]. At first relapse, the goal of therapy is often similar to that for newly diagnosed patients, with a focus on a more aggressive treatment and a higher acceptance for toxicity, but at later stages and with older age, therapeutic goals may change significantly, toward an increased emphasis on QOL, safety, tolerability, and convenience, in addition to efficacy. Patients typically value spending time away from the hospital and clinic as their disease advances. Therefore, these patients may prefer an entirely oral treatment regimen. In addition, many elderly patients may also be unable to tolerate more-toxic 3-drug combinations and thus would benefit from an efficacious but less toxic doublet.

Real-world clinical practice data illustrate a significant correlation between duration of therapy and probability of survival. Recently, this was documented with real-world electronic medical record data from a US-based study showing that each additional month of treatment in second-line RRMM was associated with a reduced risk of death at 1 year after initiation of second-line therapy (HR=0.67; 95% CI] 0.59, 0.77) [35].

Further, currently available therapies have been associated with dose-limiting toxicities and added treatment burdens to patients and their caregivers. For example, proteasome inhibitors approved in the relapsed setting require frequent hospital visits for IV (bortezomib and carfilzomib) or subcutaneous (bortezomib) administration [2,36]. Similarly, newly approved monoclonal antibodies such as daratumumab require frequent, prolonged IV infusions [37]. IV infusions of anticancer agents, or any parenteral agents, require administration in a hospital or clinic setting and add more than drug costs to the health economic burden, including, but not limited to, the cost of the use of the facility and its staff plus the cost of transportation to the facility in addition to the overall costs associated with therapy. Moreover, AEs that are associated with currently available agents impact a patient's QOL and can lead to dose reductions and/or early treatment discontinuation, which in turn result in suboptimal treatment as well as potential loss of time able to perform work. Such AEs include peripheral neuropathy and hypotension (bortezomib), second primary malignancies (lenalidomide), neutropenia, allergic reactions, infusion-related reactions (daratumumab), vascular events (carfilzomib), thrombotic events (lenalidomide and

pomalidomide), and myelosuppression (pomalidomide) [2,17,36-42]. Finally, concern regarding the risk of teratogenicity of the IMiDs (including pomalidomide) has led to creation of the Pregnancy Prevention Programme in the European Union and the Risk Evaluation and Mitigation Strategies (REMS) programs in the United States. These programs increase the burdens placed on patients, health care providers, and health care clinics.

Consideration of the toxicity and the treatment burden to patients is important in this population because patients with relapsed MM are often sicker and carry with them some of the residual effects of their initial therapy [43]. Minimizing potential long-term adverse effects while maintaining efficacy is an important goal in the treatment of RRMM [43,44]. However, currently available therapies do not provide sustained improvements in disease control. For example, the median PFS for pomalidomide+dexamethasone (pom+dex) in patients in their third or later line of therapy in the registration-enabling MM-003 study (NIMBUS) [45] was 3.8 months (95% CI, 3.4-4.6 months) versus 1.9 months (95% CI 1.9-2.1 months) with high-dose dexamethasone. Although the 3.8 months was a clinically meaningful and statistically significant improvement over the 1.9 months, it was not a prolonged response. In that same study, pom+dex provided a 4.1-month improvement in OS. In addition, a study of single-agent daratumumab used to treat a similar population—US and EU patients with RRMM—showed a median PFS of 3.7 months and an ORR of 29.2% [46]. These survival and response findings support the observation that advanced MM continues to be an area of high unmet need, including a need for treatment approaches that prolong disease control while minimizing burden to patients (safety, oral convenience) and to the health care system.

The convenience of the all-oral ixazomib regimen benefits active working patients in addition to those elderly or frail patients who would prefer to avoid traveling for frequent long hospital visits. Furthermore, the nursing time involved with administration of IV regimens as compared with the all-oral ixazomib regimen is an important consideration, while the safety profile speaks to patients' ability to have a long-term regimen with maintenance of disease control.

4.2.3 Benefit/Risk Assessment

4.2.3.1 Benefits

Ixazomib in combination with LenDex has been approved by the US FDA and other agencies for the treatment of patients with MM who have received at least 1 prior therapy [3,4]. The exploration of ixazomib for other therapeutic areas is ongoing. To date, activity in MM has been seen with single-agent ixazomib and with ixazomib combined with established therapies. In addition, single-agent activity has been observed in relapsed amyloidosis and indolent non-Hodgkin lymphoma.

The pivotal phase 3 Study C16010 was the basis for the approval, involving 722 patients with RRMM [4]. The primary endpoint of PFS was met in the ITT population at the primary analysis, with a significant PFS benefit for patients receiving ixazomib+LenDex versus placebo+LenDex (HR=0.742, p=0.012; median PFS 20.6 vs 14.7 months). The PFS benefit in the ixazomib regimen was supported by improvements versus the placebo regimen in other efficacy data: ORR (78% vs 72%), time to progression (TTP) (median, 21.4 vs 15.7 months), and duration of response (median,

20.5 vs 15.0 months) at the primary analysis. At a median follow-up of approximately 23 months, the median OS had not been reached in either regimen; nevertheless, the 2-year OS rate was 77.5%, which is one of the largest achieved to date in phase 3 studies of RRMM.

The PFS benefit seen in global Study C16010 has been substantiated in the China Continuation study, a second double-blind, placebo-controlled study of similar design and the same inclusion criteria, with 115 patients with RRMM, all enrolled in China [5]. In this study, the primary endpoint of PFS was significantly improved in the ixazomib regimen as compared with the placebo regimen, with HR=0.598 and p=0.035 (with a median follow-up of approximately 8 months, the median PFS was 6.7 vs 4.0 months, respectively). The PFS benefit in the ixazomib regimen was supported by improvements with the ixazomib regimen versus the placebo regimen in ORR (56% vs 31%) and TTP (median 7.3 vs 4.1 months). The reasons for the shorter median PFS in the China Continuation population than in the Study C16010 ITT population are likely the fact that Chinese patients are diagnosed with MM when their disease is more advanced as compared with the global population [47,48] and that the China Continuation patients were more frequently refractory to thalidomide (54% vs 12%, respectively), which can cause reduced efficacy of subsequent lenalidomide-containing regimens [49]. At the final analysis, an OS benefit in favor of the ixazomib+LenDex combination was observed [6]. In summary, the data from the China Continuation study support Study C16010 data, showing a positive treatment effect with the ixazomib regimen.

The Study C16010 and China Continuation findings are supportive of the current study. In both studies, the addition of ixazomib to LenDex was associated with a survival benefit; notably, all patients had RRMM that could have been pretreated with, but not refractory to, IMiDs and proteasome inhibitors. In Study C16010 [4], the IMiD-pretreated population had a similar PFS benefit with ixazomib as did the IMiD-naïve population (HRs, 0.74 and 0.70), and the proteasome inhibitor-pretreated population had a similar PFS benefit as did the proteasome inhibitor-naive population (HRs, 0.74 and 0.75). Thus, there is randomized evidence of an ixazomib treatment effect in patients with at least 2 prior lines of therapy, including prior IMiD treatment and prior proteasome inhibitor treatment, similar to the patients who will be enrolled in the current study. On the basis of these findings, as well as support for doublet (rather than triplet) therapy (eg, [50], and the approval of pom+dex for RRMM), this study is being conducted to test the hypothesis that ixazomib in combination with a corticosteroid may be an effective treatment of RRMM.

Overall, ixazomib shows signs of antitumor activity, as evidenced by at least 50% reduction in disease burden in some patients, including patients that have been heavily pretreated as well as those with newly diagnosed MM, and prolongs stabilization of the underlying disease in other patients across all ongoing studies. Though additional data continue to be obtained to further establish the clinical benefit of this drug, the emerging data support the continued development of ixazomib for the treatment of patients with hematologic and solid tumor malignancies as well as ixazomib as part of doublet therapy for RRMM.

4.2.3.2 Risks

Safety data supporting the higher ixazomib dose (5.5 mg weekly for 3 weeks in each 28-day cycle) are available from PPD and colleagues at the Mayo Clinic [7,8]. The initial group of this study investigated single-agent oral ixazomib administered at 5.5 mg weekly for 3 weeks of a 28-day cycle with dexamethasone added if a patient had a suboptimal response (minimal response by end of Cycle 2 or lack of partial response [PR] at end of Cycle 4) or PD. Results observed in this initial experience with 5.5 mg ixazomib led to study modification, with the addition of a randomized portion, consisting of 2 treatment groups comparing oral ixazomib doses of 4 and 5.5 mg, each in combination with dexamethasone. These 2 groups inform the comparative safety, tolerability, and efficacy of ixazomib (4 or 5.5 mg) administered weekly for 3 weeks of a 28-day cycle plus oral dexamethasone (20 mg) administered on Days 1, 2, 8, 9, 15, and 16 of the 28-day cycle in adults with measurable MM who have received ≥1 prior lines of therapy and who are not refractory to proteasome inhibitor therapy.

Patients received a median of 7 cycles of therapy (range, 1-31 cycles) across the study; 53 (76%) and 34 (49%) patients received at least 4 and 8 cycles, respectively, and 21 (30%) patients continued in the study for >12 cycles. The median number of treatment cycles was similar for the 2 groups: 8 (range, 1-28) and 7 (range, 1-31) for the 4 mg and 5.5 mg dose groups, respectively. The total number of cycles delivered was similar between the 2 groups, with 347 cycles administered to the 4 mg dose group and 341 for the 5.5 mg dose group.

Dose modifications for ixazomib were required in a higher proportion of patients in the 5.5 mg dose group compared with the 4 mg dose group (43% vs 17%), while dose modifications for dexamethasone occurred in 34% and 23%, respectively. Thus, more than half the patients starting treatment at 5.5 mg ixazomib continued treatment without dose modification. Treatment delays were equivalent between the 2 ixazomib dose levels, with 26% and 29% of patients requiring dose delays in the 4 mg and 5.5 mg ixazomib groups, respectively. In terms of delivered dose, 95% of the intended dose of ixazomib was delivered in the 4 mg group compared with 85% of the intended dose in the 5.5 mg group.

An AE of any grade that was considered at least possibly related was reported in 100% of the patients in both groups. There were no treatment-related deaths in either group; 2 patients died on study in the 4 mg ixazomib group (respiratory syncytial virus and multiorgan failure approximately 10 months after first dose; pancreatic cancer approximately 2 years after first dose; all were assessed as unrelated to study medication). Grade 3 or 4 AEs considered at least possibly related to study treatment were reported for 9 (26%) and 2 (6%) patients in the lower-dose group and in 19 (54%) and 2 (6%) patients in the higher-dose group, respectively. Both of the Grade 4 events reported in the 5.5 mg ixazomib group were considered related to study treatment. The most common Grade ≥2 AEs included fatigue, neutropenia, thrombocytopenia, and diarrhea. Peripheral neuropathy that was considered at least possibly related to study treatment was seen in 33 patients (Grade 1), 8 patients (Grade 2), and 2 patients (Grade 3; both in the 5.5 mg dose group). No cumulative hematological toxicity was observed in either group of the study, and the reported thrombocytopenia AEs usually resolved before the next cycle. Overall, the majority of AEs were Grade 3 or less in both the 4 mg and 5.5 mg ixazomib dose groups. Five patients discontinued the

study because of an AE (2 in the 4 mg ixazomib group; 3 in the 5.5 mg ixazomib group); these events included continued Grade 2 neuropathy and heart failure.

These data indicate that there is a subpopulation of patients who are able to tolerate 5.5 mg ixa+dex. In the current study design, the intent is to identify this subpopulation based on excellent tolerability of ixazomib 4 mg in the first cycle and have the potential to dose escalate.

The investigators in the PPD study recommended that careful attention be given to the toxicity associated with the higher dose and that timely dose reductions be considered to mitigate the adverse effects [7,8]. Indeed, to mitigate the inherent risks in clinical studies of ixazomib, patients are monitored closely for anticipated toxicities. Guidance for the management of AEs (see Section 8.8) and procedures for reducing doses (see Section 8.4) are provided, and drug dosage can be reduced either by decreasing the dose administered or by holding of the scheduled treatment. Further information is provided in the IB.

4.3 Rationale for the Proposed Study

4.3.1 Need for Non-IMiD, Cost-Effective Combination Therapies in RRMM

With the recent approval of lenalidomide in front-line MM both in the United States and the European Union, the use of this IMiD as primary therapy will become increasingly prevalent. Because all patients with MM will ultimately relapse and most will develop lenalidomide-resistant disease, alternatives to lenalidomide will be required in later lines of therapy. Also, use of a non-IMiD combination in this setting will lower the burdens placed on patients, health care providers, and health care clinics, because a Pregnancy Prevention Programme (European Union) or a REMS program (United States) will no longer be required.

Although the typical later-line therapy for patients with RRMM is triplet therapy, some triplet combinations have not shown superior efficacy over doublets involving dexamethasone (eg, bortezomib, melphalan, and prednisone [VMP] or bortezomib, thalidomide, and dexamethasone [VTD] vs bortezomib with dexamethasone [VD])—even among elderly patients being treated in community practices [50]. Dexamethasone-based doublets like VD have also been shown as effective and tolerable for elderly patients with RRMM [51]. Ixa+dex is a new potentially beneficial doublet therapy for RRMM patients. Furthermore, many elderly and/or heavily pretreated patients may not be able to tolerate the toxicity of a triplet drug combination.

4.3.2 Need for All-Oral Combination Therapies in Patients With RRMM at Later Lines of Therapy

Both ixa+dex and the comparator, pom+dex, are particularly compelling options for third-line RRMM patients because many of these heavily pretreated patients, who are in the later stages of their disease, may prefer an all-oral regimen. Such a regimen will benefit patients who are not able or do not wish to travel to treatment clinics for weekly or more-frequent IV infusions. An entirely oral treatment option may therefore afford patients a better QOL. Furthermore, because the investigational regimen is an entirely oral therapy, an all-oral, standard-of-care comparator, pom+dex, provides a balanced treatment burden between the 2 regimens.

A recently published study [52] summarizes cross-sectional data from >7000 patients with MM who were being treated across 7 European countries in 2014. In that study, bortezomib-based therapies were the most commonly used induction regimens, and 61% of patients who received bortezomib at first line went on to receive lenalidomide at second line. Third-line therapy was more variable, with the therapies divided among pomalidomide, other agents (eg, bendamustine), and bortezomib retreatment (used in 43% of patients who had received it at first line). In the third-line setting, salvage therapy with either regimen in Study C16029—that is, an entirely oral combination of either pom+dex or ixa+dex—may be preferred by some patients to retreatment with bortezomib (either IV or subcutaneous) or treatment with another IV therapy, such as daratumumab, recently approved by both the FDA and European Medicines Agency in the salvage setting after treatment with a proteasome inhibitor and an IMiD [37,53].

Furthermore, the efficacy of available therapies could be improved upon for this patient population. As noted above, in the NIMBUS study, use of pom+low-dose dex resulted in a median PFS of only 4.0 months (95% CI, 3.6-4.7 months). Similarly, the median PFS with daratumumab was 4.0 months (95% CI, 2.8-5.6 months) [54]. For this study, daratumumab was considered as a potential comparator; however, given that treatment with daratumumab requires travel to a clinic for IV infusion and premedication, an entirely oral combination was determined to be a more appropriate control for this study. In addition, a comparison of ixa+dex to daratumumab single agent would not allow for the characterization of the ixazomib contribution to the observed treatment effect, unlike a comparison of ixa+dex to pom+dex, in which the dexamethasone contribution would be similar in both treatment groups. For this reason, this study will compare an experimental regimen including ixazomib, which typically has been studied in combination with LenDex, but here will be combined with dexamethasone only. As a control regimen, pomalidomide will be used in combination with dexamethasone.

4.3.3 Possible Benefit-Risk of Ixa+Dex versus Pom+Dex

Preliminary data suggest that, under some circumstances, ixa+dex may have favorable efficacy as compared with pom+dex. PPD and colleagues at the Mayo Clinic have conducted an investigator-initiated phase 2 study of ixazomib in patients with RRMM who were considered not refractory to bortezomib [7,8]. The preliminary data suggested that greater clinical benefit may be achieved with the use of ixa+dex, with 4 mg and 5.5 mg doses of ixazomib, compared with historical data with pom+dex (described in Section 4.2.2 above). Therefore, this company-sponsored study is intended to provide further assessment on the feasibility and safety of the dose escalation of 4 mg to 5.5 mg ixazomib after the first cycle.

Pomalidomide is indicated for use in combination with dexamethasone in adults with RRMM who have received ≥2 prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated PD on the last therapy. In this study, pom+dex will be administered to patients who have received ≥2 prior lines of therapy, have been exposed but are not refractory to a proteasome inhibitor, and are refractory to lenalidomide. This is a subgroup of the population of patients for whom pomalidomide is currently approved and who may derive particular benefit from a proteasome inhibitor. Pomalidomide given with dexamethasone is an accepted standard of care for this patient population.

The risks of both pomalidomide and ixazomib in the patient population eligible for this study appear manageable with appropriate prophylaxis, dose holds, and/or dose modification. In summary, patients receiving pomalidomide are likely to have greater risks of thromboembolic events and neutropenia, while those receiving ixazomib are more at risk of experiencing thrombocytopenia and gastrointestinal events—all of which appear to be largely manageable with appropriate monitoring, prophylaxis, dose holds, and/or dose modifications.

4.3.4 Ixazomib Dose Rationale

The ixazomib dosing regimen for this study was informed by the phase 2 Mayo Clinic study (conducted by PPD and colleagues [7,8] and described in Section 4.2.3.2) of ixazomib in combination with dexamethasone conducted in patients with relapsed MM who were not refractory to bortezomib. In the randomized portion of the study with 2 treatment groups, patients received ixazomib at either 4 mg or 5.5 mg on Days 1, 8, and 15 of each 28-day cycle, in combination with 20 mg dexamethasone on Days 1, 2, 8, 9, 15, and 16 of each cycle. Thirty-five patients were randomized to each group.

The ORR for patients randomized to receive ixazomib at 5.5 mg was found to be higher (54%) than that for the 4 mg patients (31%). Additionally, a trend was observed between the average ixazomib dose (calculated to first best response [PR or better]) and the probability of ≥PR (p=0.0795, N=70), suggesting that higher doses of ixazomib may result in higher ORR. Event-free survival was similar across the tertiles of average ixazomib dose; however, it should be noted that this small study was not powered to detect a statistically significant difference in event-free survival.

As noted in Section 4.2.3.2, a higher frequency of Grade ≥3 AEs that were considered at least possibly related to study therapy was observed in the 5.5 mg ixazomib group than in the 4 mg ixazomib group (54% vs 26%). Dose reductions for ixazomib were also required for a higher percentage of patients in the 5.5 mg ixazomib group (43%, vs 17% in the 4 mg ixazomib group).

Collectively, the available data from the randomized phase 2 study [7,8] indicate that both the 4 mg and 5.5 mg doses of ixazomib are active, with the 5.5 mg dose being associated with a higher ORR, although it is not yet known whether this dose will result in longer PFS. The 5.5 mg dose was associated with a higher frequency of AEs and more dose modifications.

As a result, in an effort to provide an opportunity for maximum clinical benefit without excessive toxicity, a 4 mg starting dose for ixazomib will be used in this study, with escalation to 5.5 mg at the start of Cycle 2 for those patients who tolerate the 4 mg dose in Cycle 1 (as specified in Section 8.4.1). Because the study population is patients with advanced disease in later-line therapy, the timing of dose escalation at the start of Cycle 2 was selected so that patients who appear to be tolerating ixazomib can escalate quickly to a higher dose and potentially improve their chance of achieving disease control before experiencing PD. Also, the main potential AEs (eg, thrombocytopenia, gastrointestinal events, rash) are acute AEs that are expected to be seen early in the treatment course, further providing a rationale for an intrapatient dose escalation decision after Cycle 1.

4.3.5 Summary of Rationale

A typical patient eligible for this study will have received a proteasome inhibitor other than ixazomib in the first or second line without having developed resistance and will have developed resistance to lenalidomide in the second or later line. This study is designed to determine whether there is a subpopulation of patients for whom pom+dex is clinically indicated but who may preferentially benefit from ixa+dex.

The sponsor expects there to be a significant number of patients in the United States and European Union who would qualify for third-line salvage therapy in this study and would potentially benefit from either of these all-oral, doublet study therapies.

5.0 STUDY OBJECTIVES AND ENDPOINTS

As of Amendment 06, the objective and endpoint are to continue to collect long-term safety data from patients who are continuing on ixazomib and dexamethasone or pomalidomide and dexamethasone because of continuing clinical benefit. Data collection for all other study objectives and endpoints is complete and no further formal analyses will be conducted. However, the original lists of objectives and endpoints are retained below for reference only.

5.1 Objectives

5.1.1 Primary Objective

The primary objective is to compare the effect of ixa+dex versus pom+dex on PFS in patients with RRMM who have received at least 2 prior lines of therapy, including lenalidomide and a proteasome inhibitor, and are refractory to lenalidomide but not refractory to proteasome inhibitors.

5.1.2 Secondary Objectives

Secondary objectives are:

- To compare OS in patients treated with ixa+dex versus pom+dex.
- To compare duration of response, ORR, time to response, and time to progression with ixa+dex versus pom+dex.
- To obtain health-related QOL data related to physical functioning of patients treated with ixa+dex versus pom+dex.
- To assess health-related QOL by additional function and symptom domains of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) instrument and by the EORTC Quality of Life Questionnaire–multiple myeloma module (EORTC QLQ-MY20) and 5-level classification system of the EuroQol 5-Dimensional Health Questionnaire (EQ-5D-5L) instruments in patients receiving ixa+dex versus those receiving pom+dex.
- To evaluate HU by patients receiving ixa+dex versus those receiving pom+dex.
- To collect plasma concentration-time data for ixazomib to contribute to population PK characterization of ixazomib and to conduct exposure-response analyses for patients receiving ixa+dex.

5.1.3 Safety Objective

The safety objective is to compare the safety/tolerability of ixa+dex to that of pom+dex.

5.1.4 Exploratory Objective

PPD

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint is PFS, defined as the time from randomization to the first occurrence of confirmed PD, as evaluated by the investigator, according to International Myeloma Working Group (IMWG) criteria [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

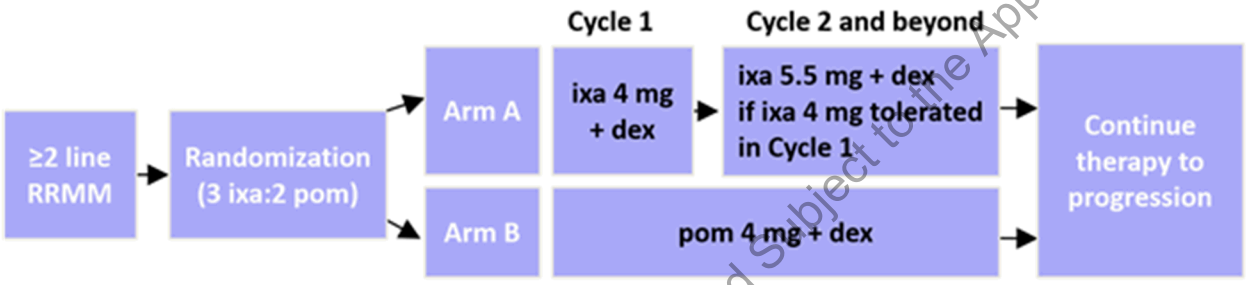
PPD

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 ≥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 ≥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 ≥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 ≥2 nonhematologic or Grade ≥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 ≥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.

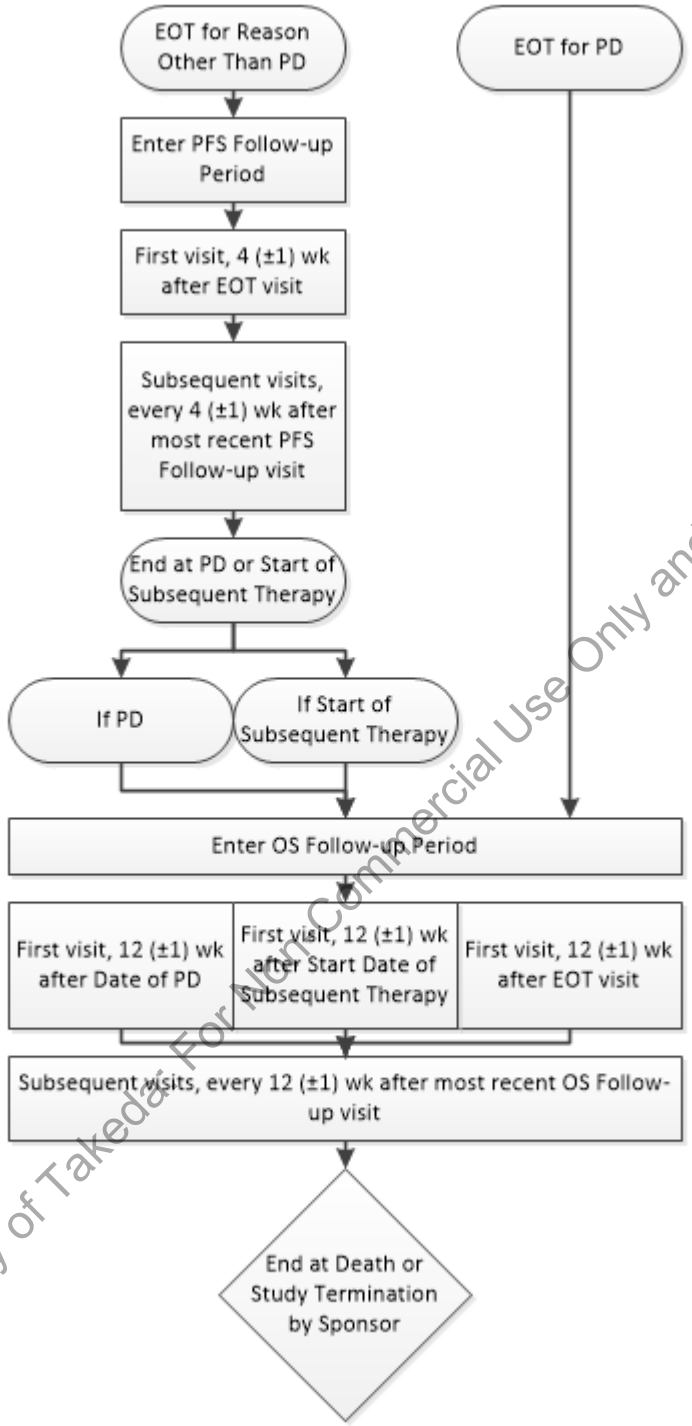
Figure 6.b provides more detail about both follow-up periods.

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)



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.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
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.

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 ≥1 g/dL (≥10 g/L), OR
   - Urine M-protein ≥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) ≥1000/mm^3 and platelet count ≥75,000/mm^3, without growth factor or transfusion support.
   - Total bilirubin ≤1.5 times the upper limit of normal (ULN).

- Alanine aminotransferase and aspartate aminotransferase ≤3×ULN.
- Calculated creatinine clearance ≥30 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 ≤1 nonhematologic toxicity) from the reversible effects of prior anticancer therapy.

15. Patients must be willing and able to adhere to pomalidomide-related risk mitigation activities if randomized to the pom+dex arm (eg, REMS, pregnancy prevention programs).

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Patients must not have received prior ixazomib or pomalidomide and must not have been a participant in a previous ixazomib clinical study.
2. Prior allogenic bone marrow transplantation in any prior line of therapy or prior autologous SCT in the last prior line of therapy—unless the autologous SCT was performed a year or more before disease progression.
3. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the Screening period.
4. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol, such as life-threatening illness unrelated to cancer.
5. Diagnosed with or treated for another malignancy within 2 years before randomization, or previously diagnosed with another malignancy and have any evidence of residual, persistent, or recurrent disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
6. Diagnosis of smoldering MM (see Appendix D), Waldenström's macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, plasma cell leukemia, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome.
7. Known allergy to any of the study medications or their analogues, or excipients in the various formulations.
8. Peripheral neuropathy Grade 1 with pain or Grade 2 or higher peripheral neuropathy of any cause on clinical examination during the Screening period.
9. Treatment with any investigational products or with chimeric or fully human monoclonal antibodies within 30 days before randomization, systemic anticancer therapy or radiotherapy within 14 days before randomization (Note: "spot" radiation for areas of pain is permitted), and major surgery within 14 days before randomization.
10. Known gastrointestinal disease or gastrointestinal procedure that could interfere with the oral absorption or tolerance of study therapy, including difficulty swallowing.
11. Serious infection requiring parenteral antibiotic therapy or any other serious infection within 14 days before randomization.
12. Central nervous system involvement with MM (by clinical symptoms and signs).

13. Ongoing or active systemic infection, known human immunodeficiency virus-RNA positive, known hepatitis B surface antigen seropositive, or known hepatitis C virus-RNA positive. Note: Patients who have positive hepatitis B core antibody can be enrolled but must have hepatitis B virus-DNA negative. Patients who have positive hepatitis C antibody can be enrolled but must have hepatitis C virus-RNA negative.
14. Systemic treatment with strong cytochrome P-450 3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital) or use of St. John's wort within 14 days before randomization.
15. Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.
16. History of severe cutaneous reactions, including hypersensitivity reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), in the context of treatment with lenalidomide or thalidomide (see Section 8.7 for more information).

8.0 STUDY THERAPY

All protocol-specific criteria for administration of study therapy must be met and documented before drug administration. Study therapy will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s). One cycle of study therapy at a time will be dispensed for oral dosing at home as directed in the Schedule of Events (Appendix A). Patients may take study therapy at home as directed. The date and time of each dose of study therapy should be recorded by the patient in the patient diary. Refer to the Study Manual for additional instructions regarding study therapy administration.

Patients should be monitored for toxicity as necessary and doses of the appropriate study therapy should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose holds, and adjustments of the dose.

Each AE should be attributed to a specific drug (ie, ixazomib, pomalidomide, or dexamethasone), if possible, so that dose modifications can be made accordingly. Only 1 dose adjustment per cycle will be performed for a given agent when toxicity is suspected to be related primarily to that agent. Reduction of 1 agent and not the other is appropriate if the toxicity is suspected to be related primarily to that 1 agent.

8.1 Investigational Therapy: Ixazomib Administration (Arm A)

Ixazomib capsules will be supplied by the sponsor as single capsules at 4 different dose strengths, containing 5.5, 4.0, 3.0, and 2.3 mg of ixazomib. The dose strengths will allow for delivery of the unit starting dose (4.0 mg), dose escalation to 5.5 mg, or dose reductions (2.3, 3.0 mg) as needed during treatment.

In patients randomized to Arm A, ixazomib will be given as a single, oral dose weekly (Days 1, 8, and 15) for 3 weeks, followed by 1 week without ixazomib in a 28-day cycle. Day 1 dosing in Cycle 1 through Cycle 6 must be administered in the clinic, as must the first cycle of dose escalation to 5.5 mg of ixazomib; other cycle doses may be taken at home. Refer to Section 8.10.1.3 and the Study Manual for additional instructions regarding study therapy administration.

The starting dose for ixazomib is 4 mg, with escalation to 5.5 mg at the start of Cycle 2 for patients who tolerate the 4 mg dose in Cycle 1 (specifically, patients who do not experience any new Grade 1 peripheral neuropathy with pain or other ixazomib-related Grade ≥2 nonhematologic or Grade ≥3 neutropenia or thrombocytopenia in Cycle 1). 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 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. The capsule should be swallowed with a sip of water. A total of approximately 240 mL of water should be taken with the capsules. Missed doses can be taken as soon as the patient remembers as long as the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a

dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

It is recommended that dexamethasone be taken at least 2 hours before the ixazomib dose on the ixazomib dosing days (see Section 8.3).

8.2 Reference/Control Therapy: Pomalidomide Administration (Arm B)

Patients randomized to Arm B will be dosed with pomalidomide per local prescribing information [41,42]: oral pomalidomide at a dose of 4 mg daily on Days 1 to 21 of each 28-day cycle. Thromboprophylaxis is recommended (see Section 8.8.2). Also see local prescribing information [41,42] for further dosing instructions.

8.3 Standard of Care Therapy: Dexamethasone Administration (Both Arms)

Each treatment arm will receive 40 mg of dexamethasone per week, with a difference in dosing schedule across study arms. Patients in Arm A will receive a total of 40 mg dexamethasone split across 2 consecutive days (to maximize the prophylactic anti-emetic effect around the ixazomib dosing) and patients in Arm B will receive a 40 mg dexamethasone dose in 1 day (as per the pomalidomide prescribing information), as detailed below.

Patients randomized to Arm A will receive 20 mg oral dexamethasone (or 10 mg if patient is aged ≥75 years) on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 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 ≥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.

Patients randomized to Arm B will receive 40 mg oral dexamethasone (or 20 mg if patient is aged ≥75 years) on Days 1, 8, 15, and 22 of each 28-day cycle, per the pomalidomide local prescribing information that specifies dexamethasone dosing when used in combination with pomalidomide [41,42].

The dexamethasone dose will be determined by the patient's age at time of randomization. In the event that a patient is aged 74 years or younger at randomization and turns 75 or older while taking part in the study, the patient's dexamethasone dose will only be changed from the dose at randomization in the event of dexamethasone-related AEs.

Dexamethasone should be taken at approximately the same time each dosing day. If a dose of dexamethasone is missed, the dose should be taken as soon as the patient remembers it. If enough time has elapsed that it is almost time for the next dose (within 6 hours), the missed dose should be skipped and the next dose taken according to the regular dosing schedule. 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.

In patients randomized to Arm A, it is recommended that dexamethasone be administered at least 2 hours before the ixazomib dose on the ixazomib dosing days (to maximize the potential antiemetic effect).

8.4 Dose Modification Guidelines

In general, if ixazomib, pomalidomide, or dexamethasone are delayed or held due to AEs or other safety findings, then the corresponding study therapy should also be delayed or held, given that study treatment is combination therapy. Therefore, if ixazomib is held, dexamethasone should also be held. Likewise, if pomalidomide is held, dexamethasone should be held. If dexamethasone is held, either ixazomib or pomalidomide should be held, based on the patient's treatment group determined at randomization.

8.4.1 Intrapatient Dose Escalation of Ixazomib (Arm A)

A starting dose of 4 mg of ixazomib will be used at Cycle 1 for all patients in Arm A. Patients who do not experience any new Grade 1 peripheral neuropathy with pain or other ixazomib-related Grade ≥2 nonhematologic or Grade ≥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.

8.4.2 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

8.4.2.1 Criteria for Beginning the Next Treatment Cycle With Ixa+Dex (Arm A)

Treatment with ixazomib will be repeated every 28 days in Arm A. The criteria for toxicity recovery before the patient can begin the next cycle of treatment are as follows:

- ANC ≥1000/mm^3.
- Platelet count ≥75,000/mm^3.
- All nonhematologic toxicity considered to be related to treatment with study therapy must have resolved to Grade ≤1 or to the patient's baseline values or to a severity level considered stable and tolerable by the investigator/patient (eg, Grade 2 chronic kidney disease due to underlying MM).

If the patient does not meet the above-cited criteria for retreatment, initiation of the next cycle of ixa+dex should be delayed for 1 week. After 1 week, the patient should be re-evaluated to determine whether the criteria for retreatment have been met. If the patient continues to not meet the previously cited criteria, delay ixa+dex and continue to re-evaluate. Should the start of the next cycle need to be delayed ≥2 weeks because of incomplete recovery from treatment-related toxicity, the ixa+dex doses will be reduced by 1 dose level when therapy resumes. Should ixa+dex need to be delayed for 4 weeks because of incomplete recovery from treatment-related toxicity, ixa+dex should be discontinued or dose reduction of 1 or more than 1 dose levels should be considered if, in the investigator's view, therapy still has a reasonable probability of providing a benefit. Resumption of cycles after 4 weeks must be discussed with the Millennium project clinician or designee.

8.4.2.2 Criteria for Beginning the Next Treatment Cycle With Pom+Dex (Arm B)

Treatment with pom+dex will be repeated every 28 days in Arm B. The criteria for toxicity recovery before the patient can begin the next cycle are outlined in the pom+dex local prescribing information [41,42].

8.4.3 Ixazomib Treatment Modification (Arm A)

Patients experiencing AEs attributed to ixazomib may continue in the study but may have doses of ixazomib held or reduced by at least 1 dose level as shown in Table 8.a. When a dose reduction of ixazomib is required because of toxicity, no dose re-escalation will be permitted.

Treatment modifications because of to ixazomib-related AEs are outlined in Table 8.b for hematologic toxicities and in Table 8.c for nonhematologic toxicities. Table 8.d provides the criteria for retreatment and cycle delays.

Table 8.a Dose Reduction Steps for Ixazomib

Current Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction	Fourth Dose Reduction
4 mg	3 mg	2.3 mg	Discontinue ixazomib	--
5.5 mg	4 mg	3 mg	2.3 mg	Discontinue ixazomib

Table 8.b Ixazomib Dose Modification for Hematologic Toxicities

Criteria	Action
Within-Cycle Dose Modifications	
If platelet count $\leq 50\times10^9$/L or ANC $\leq 0.75\times10^9$/L on an ixazomib dosing day (other than Day 1)	Ixazomib dose should be withheld. Complete blood count with differential should be repeated at least weekly or more frequently until the ANC and/or platelet counts have exceeded the prespecified values (ANC $\geq 1.0\times10^9$/L; platelet count $\geq 75\times10^9$/L). Upon recovery, ixazomib may be reinitiated and reduced by 1 dose level in accordance with reductions outlined in Table 8.a.
Dose Modifications for Subsequent Treatment Cycles	
Delay of ≥2 weeks at the start of a subsequent cycle because of lack of toxicity recovery as defined in Section 8.4.2: ANC $<1.0\times10^9$/L; platelet count $<75\times10^9$/L (Or other nonhematologic toxicities Grade >1 or not to the patient's baseline condition)	Hold ixazomib until resolution per criteria. Reduce ixazomib by 1 dose level as outlined in Table 8.a. The maximum delay before treatment should be discontinued will be 4 weeks (except in the case of investigator-determined clinical benefit and discussion with the project clinician or designee, at which time a reduction of 1 or more dose levels should be made).
All hematologic toxicities	For hematologic toxicity that occurs during a cycle but recovers in time for the start of the next cycle: If dose was reduced within the cycle, start the next cycle at that same dose. If because of timing–ie, a toxicity after Day 15 dosing such that a dose reduction was not required at that point in the cycle–then reduce ixazomib by 1 dose level at the start of the cycle. Do not reduce the dose both within a cycle and at the start of the cycle for the same most severe toxicity.

Table 8.c Ixazomib Dose Modification for Nonhematologic Toxicities

Criteria		Action
Peripheral Neuropathy		
Grade 1 peripheral neuropathy	No action	Grade 1 signs and symptoms: asymptomatic, without pain or loss of function, clinical or diagnostic observations only
Worsening Grade 1 peripheral neuropathy (ie, Grade 1 with pain) or Grade 2	Hold ixazomib until resolution to Grade ≤1 without pain or baseline.	Grade 2 signs and symptoms: moderate symptoms, limiting instrumental activities of daily living
New or worsening Grade 2 peripheral neuropathy with pain or Grade 3	Hold ixazomib until resolution to Grade ≤1 or baseline. Reduce ixazomib to next lower dose upon recovery as outlined in Table 8.a.	Grade 3 signs and symptoms: severe symptoms, limiting self-care activities of daily living, assistive device indicated
New or worsening Grade 4 peripheral neuropathy	Discontinue ixazomib.	
Grade 2 Rash	Symptomatic recommendations per Section 8.8. The investigator and project clinician or designee may discuss considerations for dose modifications and symptom management.	
All other Grade ≥2 nonhematologic toxicities	Hold ixazomib until resolution to Grade ≤1 or baseline. Reduce ixazomib by 1 dose level as outlined in Table 8.a. Note: A dose level reduction will be made either on the basis of within-cycle criteria or subsequent cycle criteria but not both for the same cycle.	
Grade 4 nonhematologic toxicities	Consider permanently discontinuing ixazomib, except in the case where the investigator determines that the patient is obtaining a clinical benefit and has discussed this with the project clinician or designee. If ixazomib is continued, the dose should be reduced by at least 1 level.	

ANC: absolute neutrophil count.

Table 8.d Criteria for Ixazomib Retreatment and Cycle Delays Subsequent to Hematologic and Nonhematologic Toxicities

Criteria	Action
Both hematologic and nonhematologic events	Delay ixazomib for 1 week. Re-evaluate patient; if still not resolved, delay ixazomib for 1 additional week.
Hematologic and nonhematologic events not resolved after 1-week treatment delay	If initiation of subsequent therapy needs to be delayed for more than 2 weeks because of incomplete recovery from treatment-related toxicity, the dose of ixazomib will be reduced by 1 dose level as outlined in Table 8.a when treatment resumes. The maximum delay before treatment should be discontinued will be 4 weeks (except in the case of investigator-determined clinical benefit and discussion with the project clinician or designee at which time dose reduction by at least 1 dose level should be considered).

8.4.4 Pomalidomide Treatment Modification (Arm B)

All pomalidomide treatment modifications are according to the local prescribing information [41,42].

Patients experiencing AEs attributed to pomalidomide may have doses of pomalidomide held or reduced by at least 1 dose level as noted in the local prescribing information [41,42]. When a dose reduction of pomalidomide is required because of toxicity, no dose re-escalation will be permitted. If a patient experiences angioedema, skin exfoliation, bullae, or any other severe cutaneous reaction such as SJS, TEN, or DRESS, treatment with pomalidomide should be immediately and permanently discontinued. The patient should additionally discontinue treatment with dexamethasone and remain on study for PFS and OS follow-up.

8.4.5 Dexamethasone Treatment Modification (Both Arms)

Patients experiencing AEs attributed to dexamethasone may have doses of dexamethasone held or reduced by at least 1 dose level as shown in Table 8.e. When a dose reduction of dexamethasone is required because of toxicity, no dose re-escalation will be permitted.

Treatment modifications because of dexamethasone-related AEs are outlined in Table 8.f.

Table 8.e Dose Reduction Steps for Dexamethasone

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
Arm A			
For patients aged <75 yr 20 mg on Days 1, 2, 8, 9, 15, 16, 22, and 23	20 mg on Days 1, 8, 15, and 22	10 mg on Days 1, 8, 15, and 22 *OR, if only 4 mg tablets are available* 12 mg on Day 1, 8 mg on Day 8, 12 mg on Day 15, and 8 mg on Day 22	Discontinue dexamethasone
For patients aged ≥75 yr 10 mg on Days 1, 2, 8, 9, 15, 16, 22, and 23 *OR, if only 4 mg tablets are available* 12 mg on Days 1, 8, 15, and 22 8 mg on Days 2, 9, 16, and 23	12 mg on Days 1, 8, 15, and 22	8 mg on Days 1, 8, 15, and 22	Discontinue dexamethasone
Arm B (per pomalidomide local prescribing information)			
For patients aged <75 yr 40 mg on Days 1, 8, 15, and 22	20 mg on Days 1, 8, 15, and 22	10 mg on Days 1, 8, 15, and 22 *OR, if only 4 mg tablets are available* 12 mg on Day 1, 8 mg on Day 8, 12 mg on Day 15, and 8 mg on Day 22	Discontinue dexamethasone
For patients aged ≥75 yr 20 mg on Days 1, 8, 15, and 22	12 mg on Days 1, 8, 15, and 22	8 mg on Days 1, 8, 15, and 22	Discontinue dexamethasone

Table 8.f Dexamethasone-Related Treatment Modification (Delays, Reductions, and Discontinuations) Guidelines Because of AEs [56]

AE (Severity)		Action on Dexamethasone [a]
Gastrointestinal	Dyspepsia, gastric, or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)	Treat with histamine-2 blockers, sucralfate, or omeprazole. If symptoms persist despite these measures, decrease dexamethasone by 1 dose level.
	Grade ≥3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart and decrease 1 dose level of current dose along with concurrent therapy with histamine-2 blockers, sucralfate, or omeprazole. If symptoms persist despite these measures, discontinue dexamethasone and do not resume.
	Acute pancreatitis	Discontinue dexamethasone and do not resume.
Cardiovascular	Edema Grade >2 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed and decrease dexamethasone by 1 dose level. If edema persists despite these measures, decrease dose another level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Neurological	Confusion or mood alteration Grade >2	Hold dexamethasone until symptoms resolve. Restart with 1 dose level reduction. If symptoms persist despite these measures, discontinue dexamethasone and do not resume.
Musculoskeletal	Muscle weakness Grade >2 (interfering with function ± interfering with activities of daily living)	Decrease dexamethasone dose by 1 dose level. If weakness persists despite these measures, decrease dose by 1 dose level. Discontinue dexamethasone and do not resume if symptoms persist.
Metabolic	Hyperglycemia Grade ≥3	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite these measures, decrease dose by 1 dose level until levels are satisfactory.
Other: Grade ≥3 dexamethasone-related events		Hold dexamethasone until symptoms resolve to Grade ≤2; then resume with dose reduced by 1 dose level.

AE: adverse event.
[a] If recovery from toxicities does not occur within 14 days, then the dose of dexamethasone will be decreased by 1 dose level.

8.4.6 Criteria for Discontinuation of Study Drug

Grade 4 nonhematologic toxicities (considered related to treatment) will, in general, require that treatment with study therapy be permanently discontinued. If, in the opinion of the investigator and the project clinician or designee, it is in the patient's best interest to continue treatment with study therapy, then the dose of study therapy will be reduced by at least 1 dose level in subsequent cycles of treatment after recovery of the toxicity or toxicities in question to Grade 1 or to baseline values.

8.5 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

Systemic treatment with any of the following drug-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 cytochrome P-450 3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital, and St John's wort.

Refer to the local prescribing information for drug-drug interaction information for pomalidomide [41,42].

The following procedures are prohibited during the treatment period of the study:

- Any antineoplastic treatment with activity against MM, other than study therapy.
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates PD).

8.6 Permitted Concomitant Medications and Procedures

All necessary supportive care consistent with optimal patient care will be available to patients, as necessary. All blood products and concomitant medications received from the signing of the informed consent form until 30 days after the final dose of study therapy will be recorded in the eCRFs.

The following medications and procedures are permitted during the study:

- Myeloid growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor) are permitted. Their use should follow the local prescribing information, published guidelines, and/or institutional practice; however, alternative usage may be reviewed with the Millennium project clinician or designee. Long-acting growth factors (eg, pegylated G-CSF) are not permitted, however. Myeloid growth factors may not be used during the Screening period to meet the neutrophil eligibility requirements.
- Erythropoietin will be allowed in this study. The use of erythropoietic agents carries a risk of thrombotic events including thromboembolism. Therefore, erythropoietic agents, as well as other agents that may increase the risk of thromboembolic events, should be used with caution in combination with pomalidomide therapy (Arm B).
- Patients should be transfused with red cells and platelets as clinically indicated. Platelet transfusions may not be used during the Screening period to meet the platelet eligibility requirements.
- Patients who are receiving bone-healing agents, such as bisphosphonates or denosumab, for previously identified lytic destruction of bone or with osteopenia may continue treatment according to the American Society of Clinical Oncology Clinical Practice Guidelines or

institutional practice in accordance with the local prescribing information, unless specifically contraindicated. If bone-healing–agent therapy was not started before the study start, initiation of treatment should be discussed with the Millennium project clinician or designee.

- Supportive measures consistent with optimal patient care may be given throughout the study.

8.7 Precautions and Restrictions

Fluid deficit should be promptly corrected before initiation of, and during treatment with, ixazomib (in Arm A).

Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

Caution should be used when administering contrast materials for imaging.

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

Female patients 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 one 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 who are randomized to Arm B (pom+dex), 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.

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.

Special warnings and precautions for use of pomalidomide were added in Amendment 05 on the basis of the updated Summary of Product Characteristics (SmPC) of pomalidomide (Imnovid) [57]. Management of current study patients and enrollment of future study patients who have a history of severe cutaneous reactions, including hypersensitivity reactions, in the context of treatment with pomalidomide, lenalidomide, or thalidomide, is required as follows:

a. For all patients assigned to pomalidomide+dexamethasone treatment and who were enrolled prior to the C16029 protocol amendment 05 effective date:
    i. Inform patients of the newly identified safety risk and document this step clearly within the patient's source documentation.
    ii. Obtain medical history regarding severe cutaneous reactions to lenalidomide, thalidomide, or pomalidomide (on-study) and immediately discontinue treatment with pomalidomide in those patients with a positive history of skin reactions consistent with angioedema, skin exfoliation, bullae, or any other severe cutaneous reactions such as SJS, TEN, or DRESS; do not resume therapy.
b. For all patients currently in screening and all future screened patients after the C16029 protocol amendment 05 effective date:
    i. Inform patients of this newly identified safety risk and document this step clearly within the patient's source documentation.
    ii. If a patient has experienced a severe cutaneous reaction as part of prior treatment with lenalidomide or thalidomide, the patient must be excluded from Study C16029.

8.8 Management of Clinical Events

AEs associated with an overdose will be documented on AE eCRF according to Section 10.0. SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.

8.8.1 Ixazomib

Prophylaxis Against Risk of Reactivation of Herpes Infection

Patients may be at an increased risk of infection, including reactivation of herpes zoster and herpes simplex viruses. Prophylactic antiviral therapy, such as acyclovir, valacyclovir, or other antivirals, are recommended unless clinically contraindicated.

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 ≤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

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.

Transverse Myelitis

Transverse myelitis has been reported with ixazomib. It is not known whether ixazomib causes transverse myelitis; however, because transverse myelitis happened to a patient receiving ixazomib, the possibility that ixazomib may have contributed to the transverse myelitis cannot be excluded. Transverse myelitis should be managed according to standard medical practice.

Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. If overdose occurs, consider close observation including hospitalization for hemodynamic support. Gastric lavage may be considered if instituted within 1 hour of ingestion of ixazomib overdose.

8.8.2 Pomalidomide

See the pomalidomide local prescribing information for more information [41,57].

Arterial and Venous Thromboembolism

Venous thromboembolic events (deep venous thrombosis and pulmonary embolism) and arterial thromboembolic events (myocardial infarction and stroke) have been observed in patients treated with pomalidomide. Patients with known risk factors, including prior thrombosis, may be at greater risk, and actions should be taken to try to minimize all modifiable factors (eg, hyperlipidemia, hypertension, smoking).

Thromboprophylaxis is recommended, and the choice of regimen should be based on assessment of the patient's underlying risk factors and local practice guidelines. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. Anticoagulation therapy (eg, acetylsalicylic acid, warfarin, heparin or clopidogrel) is recommended unless contraindicated, especially in patients with additional thrombotic risk factors.

The use of erythropoietic agents carries a risk of thrombotic events including thromboembolism. Therefore, erythropoietic agents, as well as other agents that may increase the risk of thromboembolic events, should be used with caution.

Erythematous Rash With or Without Pruritus

Pomalidomide hold or discontinuation should be considered for Grade 2 to 3 skin rash. Pomalidomide must be discontinued permanently for any Grade 4 rash.

Severe Cutaneous Reactions

Pomalidomide administration should be immediately and permanently discontinued for angioedema, skin exfoliation, bullae, or any other severe cutaneous reaction such as SJS, TEN, or DRESS.

Thrombocytopenia

Pomalidomide administration should be modified according to dose modification recommendations in the protocol when thrombocytopenia occurs (see Section 8.4.4).

Neutropenia

Pomalidomide administration should be modified according to dose modification recommendations in the protocol when neutropenia occurs (see Section 8.4.4). Therapy can be reinitiated at a reduced level upon recovery of ANC. In case of neutropenia, growth factor use should be considered.

8.8.3 Dexamethasone

See the dexamethasone local prescribing information for management of any dexamethasone-related clinical events [58].

8.9 Blinding and Unblinding

This is an open-label study.

8.10 Description of Investigational Agents

8.10.1 Ixazomib

The ixazomib capsule formulation consists of the drug substance (ixazomib citrate), microcrystalline cellulose, talc, and magnesium stearate. There are 4 capsule strengths: 2.3, 3.0, 4.0, and 5.5 mg. Each strength is differentiated by a unique capsule color. Dosage strength is stated as ixazomib. Ixazomib capsules are individually packaged in blisters.

For additional details, please see the ixazomib IB and Pharmacy Manual.

8.10.1.1 Preparation, Reconstitution, and Dispensation

Ixazomib is dispensed in a blister pack in a child-resistant carton. For the 2.3, 3.0, 4.0, and 5.5 mg capsule strengths, there are 3 capsules in each wallet/carton.

Ixazomib is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised during handling. See the Pharmacy Manual for more information.

8.10.1.2 Packaging and Labeling

Ixazomib will be provided by Millennium. The ixazomib local prescribing information will fulfill all requirements specified by governing regulations.

8.10.1.3 Storage, Handling, and Accountability

On receipt at the investigative site, ixazomib should remain in the blister pack and carton provided until use or dispensation. For storage conditions, refer to the Pharmacy Manual or equivalent. All excursions from the temperature storage guidelines should immediately be brought to the

sponsor's attention for assessment and authorization for continued use. Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life. In case of extenuating circumstances that prevent a patient from attending the study site (eg, the COVID-19 pandemic), sites may use alternative strategies to deliver study drug to patients (eg, via courier or site staff), per local standard practice and regulations and with prior approval from the investigator and the sponsor's project clinician/designee.

Ixazomib dispensed to the patient for take-home dosing should remain in the blister packaging and carton and stored as directed until the point of use. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time. Comprehensive instructions should be provided to the patient to ensure compliance with dosing procedures. Patients should be instructed to store the medication as indicated in the Pharmacy Manual or equivalent. Patients should be instructed to return their empty or partially used cartons to the investigative site at their next visit, rather than discarding them, as permitted by site policy. Reconciliation will occur accordingly when the patient returns at their next visit for take-home medication. In case of extenuating circumstances that prevent a patient from attending the study site (eg, the COVID-19 pandemic), drug packs and dosing diaries should be returned at the next available on-site clinic visit. Any excursions in temperature should be reported and dealt with on a case-by-case basis.

Ixazomib is an anticancer drug and, as with other potentially toxic compounds, caution should be exercised during handling. Patients should be instructed not to chew, break, or open capsules. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during clean-up and during return of broken capsules and powder to minimize skin contact. The area should be ventilated and the site washed with soap and water after material pick up is complete. The material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations.

In case of contact with the powder (eg, from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified.

Patients are to be instructed on proper storage, accountability, and administration of ixazomib, including that study drug is to be taken as intact capsules.

Refer to the Pharmacy Manual for this study for additional instructions.

8.10.2 Pomalidomide (Control Therapy)

8.10.2.1 Preparation, Reconstitution, and Dispensation

Pomalidomide is dispensed as a capsule as described in the local prescribing information [41,42].

Pomalidomide is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised during handling.

8.10.2.2 Packaging and Labeling

Pomalidomide will be supplied from commercial sources.

8.10.2.3 Storage, Handling, and Accountability

Pomalidomide capsules should be stored according to the instructions provided in the manufacturer's package insert.

8.10.3 Dexamethasone

8.10.3.1 Preparation, Reconstitution, and Dispensation

Dexamethasone is dispensed as a tablet as described in the local prescribing information [58].

8.10.3.2 Packaging and Labeling

Dexamethasone will be supplied from commercial sources.

8.10.3.3 Storage, Handling, and Accountability

Dexamethasone tablets should be stored according to the instructions provided in the manufacturer's package insert.

8.11 Other Protocol-Specified Materials

No other drugs or ancillary material are supplied for use in this study.

9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

9.1 Study Personnel and Organizations

The contact information for the project clinician for this study, the central laboratory, any additional clinical laboratories, the coordinating investigator, and any other vendors may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/independent ethics committee (IEC). It is not envisioned that prisoners (or other populations that might be subject to coercion or exploitation) will be enrolled into this study.

9.3 Treatment Group Assignments

After written informed consent has been obtained, the patient will be randomized to a treatment arm using IRT. Patient eligibility will be confirmed by a Millennium project clinician or designee before randomization into the study. Centralized randomization via IRT will be used.

9.4 Study Procedures

Tests and procedures should be performed on schedule, but unless otherwise specified, occasional changes are allowable within a 2-day window for holidays, vacations, and other administrative reasons or a longer window after discussion with the Millennium project clinician or designee. If the study schedule is shifted, assessments must be shifted to ensure that collection of assessments is completed before dosing.

Refer to the Schedule of Events (Appendix A) for timing of assessments. Additional details are provided as necessary in the sections that follow. (For the timing of assessments performed before implementation of Amendment 06, please refer to the previous, full Schedule of Events and Pharmacokinetic Sampling Schedule in Appendix L.)

In acknowledgement of hospital, local, state, or national government restrictions, or other site-related factors caused by unavoidable circumstances (eg, the COVID-19 pandemic) that may prevent investigators from conducting the study according to the Schedule of Events at the clinical study site, investigators may continue patients in the study despite departure from the Schedule of Events. Investigators are expected to evaluate the impact to the safety of the study participants and site personnel for patients to continue. In evaluating such requests, the investigator/study site staff will give the highest priority to the safety and welfare of the patients. Patients must be willing and able to continue taking study medication and remain compliant with the protocol. For patients who

are impacted by these unavoidable circumstances, any procedures not conducted per the study protocol will be documented in the eCRF.

If a patient misses an in-person study visit, the investigator/study team staff will speak directly with the patient by telephone or other medium (eg, a computer-based video communication) during each visit window to assess subject safety and overall clinical status. During this contact with the patient, the study site physician or other qualified site staff should at minimum conduct AE collection and an assessment of clinical symptoms. Other study assessments may be collected remotely as is feasible and may involve audio or video recording. Assessments/procedures that cannot be completed during the protocol-specified window because a site visit is done remotely (ie, symptom-directed physical examination, hematology, clinical chemistry) are waived.

9.4.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

As of Amendment 06, patients remaining on study treatment will need to 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.

9.4.2 Enrollment

A patient is considered to be enrolled in the study when he/she has been randomized to a study therapy. Procedures for completion of the enrollment information are described in the Study Manual.

9.4.3 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during Screening.

9.4.4 Physical Examinations

A complete physical examination and symptom-directed physical examination, including examination for rash, performance status, and peripheral neuropathy, will be conducted at the time points specified in the Schedule of Events (Appendix A). Please refer to the previous, full Schedule of Events (Appendix L) for the timing of assessments before implementation of Amendment 06.

9.4.5 Medical History and Disease Staging

During the Screening period, a complete medical history will be compiled for each patient including the diagnosis and initial staging; a review of all current medications, prior radiation, and/or antineoplastic therapy; and the patient's current smoking status.

- Diagnosis of MM (Appendix D) and initial ISS staging (based on serum albumin and β_2-microglobulin levels; Appendix F), myeloma isotyping (IgG, IgA, IgM, IgD, IgE, light chain kappa or lambda), and initial cytogenetic information, if known. Note: Cycle 1 Day 1

dosing may proceed if MM isotype testing has been submitted to, but not yet analyzed at, the central laboratory.

- MM-directed therapy including initial and subsequent therapies, responses, dates and clinically significant toxicities.
- Review of all current medications, prior radiation (as permitted >14 days before randomization for symptomatic bone lesion or >5 years before randomization for another malignancy), and the patient's current smoking status.

9.4.6 ECOG Performance Status

Performance status will be assessed using the ECOG Performance Scale (see Appendix E) at every cycle, as well as other times, as indicated in the previous, full Schedule of Events (Appendix L). Upon implementation of Amendment 06, ECOG data will no longer be collected.

9.4.7 Vital Signs

Measurements of temperature and respiratory rate are to be performed at Screening, and thereafter, only as clinically indicated. Measurements of blood pressure and heart rate are to be performed at Screening and during the Treatment period as indicated in the previous, full Schedule of Events (Appendix L). Upon implementation of Amendment 06, vital signs data will no longer be collected.

9.4.8 Height and Weight

Height will be measured only during Screening. Weight will be measured during Screening as well as other times, as indicated in the previous, full Schedule of Events (Appendix L). Upon implementation of Amendment 06, weight data will no longer be collected.

9.4.9 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be conducted at Screening. It may be repeated as clinically indicated during the study at the discretion of the investigator. ECG data to be obtained include PR interval, QRS interval, and QT interval.

9.4.10 QOL and HU Assessments

QOL and HU assessments will be performed per the previous, full Schedule of Events (Appendix L), also described in this section. All QOL and HU assessments will be completed before any other study procedures are performed or study therapy is administered. The order of assessments will be the EORTC QLQ-C30 (Appendix H), EORTC QLQ-MY20 (Appendix I), and EQ-5D-5L (Appendix J), followed by the HU assessment (Appendix K). Upon implementation of Amendment 06, PRO data will no longer be collected.

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 (±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 (±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.

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 (±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.

9.4.12 Disease Response Assessment by Investigator

Patients will be assessed for disease response according to the IMWG uniform response criteria, version 2011 (see Appendix G), until the data cutoff date for the study analysis (including for PFS) has occurred. At that time, all central efficacy and investigator assessments of disease response for protocol purposes will be stopped. Details of the clinical laboratory evaluations for disease assessment are given in Section 9.4.15.2.

Response categories are in Table 9.a.

Table 9.a Response Assessment

Complete response	CR
Subcategory: stringent complete response	*sCR*
Very good partial response	VGPR
Partial response	PR
Stable disease	SD
Progressive disease	PD

CR must be confirmed with follow-up assessments of serum protein electrophoresis, urine protein electrophoresis, immunofixation of blood and urine, and serum free light chains as outlined in Section 9.4.15.2. One bone marrow assessment must occur to document CR; no second bone marrow confirmation of CR is needed.

Note: To determine a response of stringent CR, bone marrow immunohistochemistry or immunofluorescence for kappa/lambda ratio should be performed for all patients suspected to be in CR to meet this response category's requirements.

The duration of stable disease should be collected.

At any point during treatment, patients suspected of having PD will have response assessments repeated to confirm PD. Per IMWG criteria, 2 consecutive response assessments are required to document PD. These assessments must be performed at the central laboratory in order to document PD. Before an investigator discontinues a patient from treatment for PD, the Progressive Disease Review form must be completed and sent as soon as possible, permitting pertinent data to be confirmed by a Millennium project clinician or designee.

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. The reason for treatment discontinuation must be recorded in the eCRF but no approval is required.

CCI

[redacted]

CCI

[redacted]

9.4.14 Pregnancy Test

In Arm A, 3 serum pregnancy tests must be performed for women of childbearing potential: one at Screening, one at Cycle 1 Day 1, and one at the EOT visit. 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 serum tests) 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.

9.4.15 Clinical Laboratory Evaluations

If the Screening laboratory tests were performed more than 14 days before the first dose (Cycle 1 Day 1), the tests will be repeated before dosing. The test closest to the first dose will be considered Baseline.

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, the laboratory samples may be collected 24 hours prior to dosing on Day 15 for Arm A (ixa+dex) or before dosing on Day 15. For Arm B (pom+dex); hematology samples only 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 may be done more frequently at the investigator's discretion (ie, for acute management of TEAEs).

9.4.15.1 Clinical Chemistry and Hematology

Upon implementation of Amendment 06, centralized clinical laboratory evaluations are no longer required and local laboratories are to be used. Local laboratory evaluations should be entered into the eCRF only if required to understand a TEAE. For dosing decisions and all other safety assessments for the patient, local hematology and chemistry laboratory results should be used and do not need to be entered into the eCRF. These laboratory evaluations may be done more frequently at the investigator's discretion (ie, for acute management of TEAEs), per the investigator's judgement of standard of care.

Blood samples for analysis of the clinical chemistry and hematological parameters shown in 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	Gamma glutamyl transferase
Leukocytes with differential	Alkaline phosphatase	Lactate dehydrogenase (at Screening only)
Neutrophils ANC	Alanine aminotransferase	Magnesium
Platelet (count)	Aspartate aminotransferase	Potassium
	β2-microglobulin (at Screening only)	Urate
	Bilirubin (total)	C-reactive protein
	Blood urea nitrogen	
	Calcium	
	Creatinine	

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:

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

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 β_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.

- 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.

Within 90 days of the end of the study, the sponsor will notify the competent authorities and the IECs in all member states where the study is being carried out that the study has ended.

Within 1 year after the end of the study, a summary of the clinical study results will be submitted to the competent authorities and IECs in all member states involved in the study.

Study participation by individual sites or the entire study may be prematurely terminated if, in the opinion of the investigator or Millennium, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Millennium by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients.
- Failure to enter patients at an acceptable rate.
- Insufficient adherence to protocol requirements.
- Insufficient, incomplete, and/or unevaluable data.
- Determination of efficacy based on the study analysis.
- Plans to modify, suspend, or discontinue the development of the study drug.

Should the study be closed prematurely, the site will no longer be able to access the electronic data capture (EDC) application, will not have a right to use the EDC application, and will cease using the password or access materials once its participation in the study has concluded. In the event that any access devices for the EDC application have been provided, these will be returned to Millennium once the site's participation in the study has concluded.

Within 15 days after premature closure, Millennium must notify the competent authorities and IECs of any member state where the study is being conducted, providing the reasons for study closure.

9.10 Study Compliance

Study therapy will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study therapy receipt and dispensing.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event is defined as any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AE Definition

AE means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study therapy.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

10.1.3 SAE Definition

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 in Section 10.2 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.

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^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 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.

SAE Reporting Contact Information

US and Canada

CCI

[redacted]

CCI

[redacted]

Japan

Emergency Center for Safety Information (available 24 hours a day, 365 days a year)

CCI

[redacted]

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?"

10.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the signing of informed consent through 30 days after administration of the last dose of study therapy regardless of whether a patient starts a new line of therapy and recorded in the eCRFs. AEs should be monitored until they are resolved or return to Baseline or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es); the exception is peripheral neuropathy, which 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.
- SAEs
  - Serious pretreatment events will be reported to the Millennium Global Pharmacovigilance department or designee from the time of the signing of the informed consent form up to first dose of study therapy, and will also be recorded in the eCRF.
  - Related and unrelated treatment-emergent SAEs will be reported to the Millennium Global Pharmacovigilance department or designee from the first dose of study therapy through 30 days after administration of the last dose of study therapy regardless of whether a patient starts a new line of therapy and recorded in the eCRF. After this period, only related SAEs must be reported to the Millennium Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or return to baseline or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es); the exception is peripheral neuropathy, which 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.

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study therapy. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Global Pharmacovigilance department or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Global Pharmacovigilance department or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

A product complaint is defined as 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 report this via the phone numbers or email addresses provided below.

A medication error is defined as a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the phone number or email address provided below.

Product	Call center	Phone number	Email	Fax
NINLARO (ixazomib)	CCI [redacted]			

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 CCI [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.

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.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. If selected for coding, AEs, pretreatment events, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an informed consent form.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, contract research organization (CRO) partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Millennium personnel (or designees) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The following procedure is applied for the countries except for Japan. The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor, or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in

the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

The following procedure is applied for Japanese sites only. The investigator and the head of the institution agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copies of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator and the head of the institution to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and/or the head of the institution and sponsor. Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

In general, summary tabulations will be presented by treatment arm and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage per category for categorical data. The Kaplan-Meier (KM) survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 95% CIs for time-to-event data.

Deviations from the statistical analyses outlined in this protocol will be indicated in the statistical analysis plan; any further modifications will be noted in the clinical study report.

Study C16029 is a phase 2 study with PFS as the primary endpoint. The preliminary data from the phase 2 study by PPD et al., an investigator-initiated study, demonstrated that greater clinical benefit (eg, ORR) may be achieved with the use of ixa+dex, with 4 mg and 5.5 mg doses of ixazomib, compared with pom+dex [7,8]. Therefore, this company-sponsored study is intended to provide further assessment on 1) the feasibility and safety of the dose escalation of 4 mg to 5.5 mg ixazomib after the first cycle, and 2) the efficacy of ixa+dex.

13.1.1 Analysis Sets

The populations used for analysis will include the following:

- **Safety population**: The safety population is defined as all patients who receive at least 1 dose of any study therapy. Patients will be analyzed according to the treatment actually received. That is, those patients who are randomized to the active arm but receive the regimen in the control arm will be included in the control arm; those patients who are randomized to the control arm but receive the regimen in the active arm will be included in the active arm for safety analyses.
- **ITT population:** The ITT population is defined as all patients who are randomized. Patients will be analyzed according to the treatment they are randomized to receive, regardless of any errors of dosing.

13.1.2 Analysis of Demographics and Other Baseline Disease Characteristics

The demographic and baseline characteristics will be summarized in a descriptive fashion. Data to be evaluated will include age, sex, race or ethnic group, weight, baseline disease characteristics, and other parameters, as appropriate.

13.1.3 Efficacy Analysis

All available efficacy 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. In general, missing data will be treated as missing, and no data imputation will be applied, unless otherwise specified.

13.1.3.1 Analyses for Primary Efficacy Endpoint

The analysis of the primary endpoint, PFS, will be based on the ITT population using investigator-assessed PD data. PFS is defined as the time from randomization to the first occurrence of confirmed PD or death from any cause, whichever occurs first. Patients without documentation of PD will be censored at the date of the last response assessment that is SD or better.

PFS will be analyzed after approximately 81 PFS events have been observed. Unstratified analyses of PFS will be conducted.

A 2-sided, unstratified log-rank test will be used to compare the treatment groups with respect to PFS at a 2-sided alpha level of 0.20. In addition, an unadjusted unstratified Cox model will be used to estimate the HR and its 80% and 95% CIs for the treatment effect. The KM survival curves and KM medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

Sensitivity analyses for PFS will include:

- PFS assessed by stratified analyses in the ITT population.

Subgroup analyses will be performed for PFS relative to baseline stratification factors and demographic data such as sex, race or ethnic group, and age, as appropriate.

13.1.3.2 Analyses of Secondary Efficacy

The primary endpoint of PFS will be supported by prespecified evidence of clinical benefit as measured by other secondary endpoints. Other secondary efficacy parameters are OS, ORR, duration of response, time to response, and TTP. Disease response–related endpoints will be analyzed using investigator-assessed response rate for the ITT population.

OS will be analyzed on the basis of the ITT population and is defined as the time from randomization to death from any cause. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive. A 2-sided, unstratified log-rank test will be used to compare the treatment and control groups with respect to OS. In addition, an unadjusted unstratified Cox model will be used to estimate the HR and its 80% and 95% CIs for the treatment effect. OS will be also tested at 2-sided alpha=0.2. The KM survival curves and KM medians (if estimable), along with their 95% CIs, will also be provided for each study group.

ORR is defined as the rates of PR, VGPR, or CR, as evaluated by an investigator on the basis of central laboratory results according to IMWG criteria [55]. The percentage of each response category (CR, VGPR, and PR) and of the combination CR + VGPR will be determined.

Duration of response is defined as the time from the first documentation of PR or better to the first documentation of PD. Responders without documentation of PD will be censored at the date of the last assessed response of PR or better. Duration of CR will be summarized descriptively using the KM method.

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.

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 ≥10% of all patients).
- All SAEs.
- Grade ≥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.

13.1.6.1 New Primary Malignancy

Two types of incidence rates will be calculated for the safety population based on the new primary malignancy assessment:

- Incidence proportions, defined as the percentage of patients reporting any new primary malignancy in the safety population with available information.
- Incidence rates, defined as the number of patients reporting any new primary malignancy divided by the total duration of follow-up in the safety population with available information up to the onset of new primary malignancies.

For incidence proportions, the relative risks, defined as the ratio of incidence proportions between the 2 randomized treatment groups, will be provided along with their 95% CIs. For incidence rates, the relative risks, along with their 95% CIs, will be calculated using an exponential regression model for lifetime data (assuming constant hazards).

Because of the distinct nature of hematologic and nonhematologic neoplasms, and the emerging signals of new primary malignancies for IMiDs, analyses of new primary malignancies may be performed separately for hematologic and nonhematologic malignancies.

13.1.7 Control of Overall Type I Error for the Primary Endpoint of PFS

Type I error is controlled by the primary endpoint, because only 1 test is planned for primary endpoint of PFS at a 2-sided level of 0.20.

13.2 Determination of Sample Size

Approximately 120 patients will be enrolled. The primary endpoint is PFS with assumption of an HR of 0.62 (median PFS, 7.3 months for ixa+dex vs 4.5 months for pom+dex). The analysis of PFS will be performed on the basis of approximately 81 PFS events in total (for 80% power at a 2-sided 0.20 level of significance).

The PFS assumption for pom+dex is based on the PFS of 3.9 months (with a 95% CI of 3.5-4.6) for the subgroup of patients in the NIMBUS study with 2 prior lines who were lenalidomide refractory [45], with a higher value of 4.5 months chosen to be on the conservative side. The PFS assumption for ixa+dex is based on the PFS of 9.6 months in a similar population (2 prior lines, lenalidomide refractory), calculated on the basis of data from the PPD study as discussed above. Because this latter study had a smaller population and the PFS had a wider 95% CI (4.6-16.3) than the NIMBUS study, a more conservative value of 7.3 months was chosen.

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.

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

addition, approval must be obtained from the Competent Regulatory Authority before commencement of the study and, in the case of a substantial amendment, before implementation of the amendment. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the

subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and before subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's [e]CRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Millennium will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined in Millennium Policy/Standard. Millennium contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed Millennium and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Millennium may assist participants or potential participants to find a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Millennium providing this information to callers must provide Millennium with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Millennium will post the results of clinical trials on ClinicalTrials.gov and www.clinicaltrialsregister.eu, as well as other publicly accessible websites (including the Millennium corporate site) and registries, as required by Millennium Policy/Standard, applicable laws, and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Updated Schedule of Events

The previous, full Schedule of Events in effect before Amendment 06 and the PK Sampling Schedule completed as of Amendment 06 are no longer followed and have been moved to Appendix L for reference only.

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, ± 1 week	**Window, + 1 week**
Informed consent (reconsent)	X (b)	
Complete physical examination, including for PN (c,d)		X
Symptom-directed physical examination, including for PN (c,d)	X	
Pregnancy test, Arm A (e)		X
Pregnancy test, Arm B (e) (increased frequency required per pomalidomide PI)	X	X
Hematology laboratory tests, Arm A (d,f,g)	X	X
Hematology laboratory tests, Arm B (d,f,g) (increased frequency required per pomalidomide SmPC)	X	X
Chemistry laboratory tests (d,f,g)	X	X
Arm A: ixazomib	Single dose of 5.5 mg on Days 1, 8, 15 (if Cycle 1 dose tolerated)	
Arm A: dexamethasone 20 mg (10 mg if aged ≥75 yr)	Days 1, 2, 8, 9, 15, 16, 22, 23	
Arm A: dexamethasone, if 4 mg dexamethasone is the only dosage available and patient is aged ≥75 yr	12 mg on Days 1, 8, 15, and 22; and 8 mg on Days 2, 9, 16, and 23	
Arm B: pomalidomide	Days 1-21	
Arm B: dexamethasone 40 mg (20 mg if aged ≥75 yr)	Days 1, 8, 15, 22	
AE reporting (h)	Recorded from the signing of informed consent form through 30 days after last dose of study therapy	
	SAEs and serious pretreatment events collected from the signing of informed consent form through 30 days after last dose of study therapy	

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, ± 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

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.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH, and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should

contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor. This responsibility lies on the appropriate individual, designated by the site in Japan.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Investigator Consent to Use of Personal Information

Millennium will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Millennium, its affiliates, and licensing partners.
- Business partners assisting Millennium, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Millennium and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Millennium, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Millennium and other parties for the purposes described above.

Appendix D Revised IMWG Diagnostic Criteria for MM

Definition of multiple myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 µmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
  - Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved:uninvolved serum free light chain ratio§ ≥100
    - >1 focal lesions on MRI studies¶

Definition of smouldering multiple myeloma

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%
- Absence of myeloma defining events or amyloidosis

PET-CT=^{18}F-fluorodeoxyglucose PET with CT. *Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used. †Measured or estimated by validated equations. ‡If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement. §These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L. ¶Each focal lesion must be 5 mm or more in size.

Source: Rajkumar et al 2014 [55].

Appendix E ECOG Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Source: Oken et al 1982 [67].

Appendix F ISS Staging Criteria

ISS	
Stage	**Criteria**
Stage I	Serum β_2-microglobulin <3.5 mg/L Serum albumin ≥3.5 g/dL
Stage II	Neither stage I nor stage III (a)
Stage III	Serum β_2-microglobulin ≥5.5 mg/L

Source: Greipp et al 2005 [68].
(a) There are 2 categories for stage II: serum ß$_2$-microglobulin <3.5 mg/L but serum albumin <3.5 g/dL; or serum β_2-microglobulin 3.5 to <5.5 mg/L irrespective of the serum albumin level.

Appendix G IMWG Uniform Response Criteria for MM

CR*	Stringent complete response (sCR)†	VGPR*	PR	SD	PD†
Negative immunofixation of serum and urine, *and*	CR as defined, *plus*	Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or*	≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours	Not meeting criteria for CR, VGPR, PR, or PD	Increase of 25% from lowest-response value in any of the following:
Disappearance of any soft tissue plasmacytomas, *and*	Normal FLC ratio *and*	≥ 90% reduction in serum M-component plus urine M-component < 100 mg/24 h	If the serum and urine M-protein are not measurable, a decrease ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria		Serum M-component (absolute increase must be ≥ 0.5 g/dL), *and/or*
< 5% PCs in bone marrow	Absence of clonal PCs by immunohistochemistry or 2- to 4-color flow cytometry		If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥ 50% reduction in bone marrow PCs is required in place of M-protein, provided baseline percentage was ≥ 30%		Urine M-component (absolute increase must be ≥ 200 mg/24 h), *and/or*
			In addition to the above criteria, if present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also		Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be

	required	> 10 mg/dL)
		Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥ 10%)
		Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
		Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the PC proliferative disorder

Adapted from Durie et al[7] and Kyle et al[13] with permission. All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

PCs indicate plasma cells.

*Clarifications to IMWG criteria for coding CR and VGPR 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 to 1.65 in addition to CR criteria listed above. VGPR in such patients requires a > 90% decrease in the difference between involved and uninvolved FLC levels.

†Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels; "25% increase" refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the "lowest response value" does not need to be a confirmed value.

Source: Rajkumar et al 2011 **[69]** (adapted from Durie et al **[70]** and Kyle et al **[71]** with permission).

Appendix H EORTC QLQ-C30 (version 3)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): _____

	Not at all	A little	Quite a bit	Very much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A little	Quite a bit	Very much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at all	A little	Quite a bit	Very much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix I EORTC QLQ-MY20

EORTC Multiple Myeloma Module (QLQ-MY20)

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

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

Please turn to next page

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

Appendix J EQ-5D-5L

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about	☐
I have slight problems in walking about	☐
I have moderate problems in walking about	☐
I have severe problems in walking about	☐
I am unable to walk about	☐

SELF-CARE

I have no problems washing or dressing myself	☐
I have slight problems washing or dressing myself	☐
I have moderate problems washing or dressing myself	☐
I have severe problems washing or dressing myself	☐
I am unable to wash or dress myself	☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities	☐
I have slight problems doing my usual activities	☐
I have moderate problems doing my usual activities	☐
I have severe problems doing my usual activities	☐
I am unable to do my usual activities	☐

PAIN / DISCOMFORT

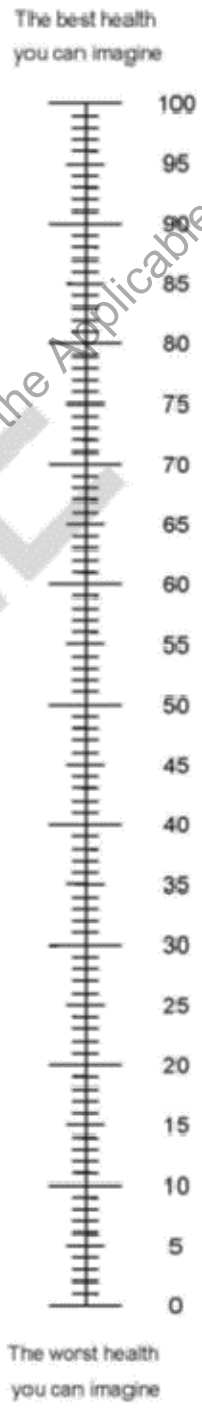
I have no pain or discomfort	☐
I have slight pain or discomfort	☐
I have moderate pain or discomfort	☐
I have severe pain or discomfort	☐
I have extreme pain or discomfort	☐

ANXIETY / DEPRESSION

I am not anxious or depressed	☐
I am slightly anxious or depressed	☐
I am moderately anxious or depressed	☐
I am severely anxious or depressed	☐
I am extremely anxious or depressed	☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix K Site HU Data Collection Form

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

Appendix L Previous, Full Schedule of Events and PK Sampling Schedule (Schedules Before Implementation of Amendment 06)

Previous Schedule of Events

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**
Informed consent	X													
Inclusion/exclusion criteria (e)	X													
Demographics	X													
Complete medical history and disease staging	X													
Complete physical examination, including for PN	X											X		
Symptom-directed physical examination, including for PN		X				X				X	X		X	
ECOG performance status	X					X				X	X	X	X	
Vital signs (f)	X	X				X				X	X	X		
Height (cm)	X													
Weight (kg)	X	X				X				X	X	X		
12-Lead ECG	X													

Footnotes are on last table page.

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	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	X
Determination of dose escalation						X (d)								

Footnotes are on last table page.

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**
Samples/Laboratory Assessments														
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	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	X	X	
Chemistry laboratory tests (k)	X	X				X				X	X	X	X	
LDH and β_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.

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**
Study Therapy Administration														
Arm A: ixazomib		Single dose of 4 mg on Days 1, 8, 15				Single dose of 5.5 mg on Days 1, 8, 15 (if Cycle 1 dose tolerated)								
Arm A: dexamethasone 20 mg (10 mg if aged ≥75 yr)		Days 1, 2, 8, 9, 15, 16, 22, 23 of each 28-day cycle												
Arm A: dexamethasone, if 4 mg dexamethasone is the only dosage available and patient is aged ≥75 yr		12 mg dexamethasone on Days 1, 8, 15, and 22 of every 28-day cycle; and 8 mg dexamethasone on Days 2, 9, 16, and 23 of every 28-day cycle												
Arm B: pomalidomide		Days 1-21 of each 28-day cycle												
Arm B: dexamethasone 40 mg (20 mg if aged ≥75 yr)		Days 1, 8, 15, 22 of each cycle												
AE reporting (r)	Recorded from the signing of informed consent form through 30 days after last dose of study therapy													
	SAEs and serious pretreatment events collected from the signing of informed consent form through 30 days after last dose of study therapy													
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												
Survival														X
Subsequent therapy														X

Footnotes are on following page.

BMA: bone marrow aspirate; C: study cycle; LDH: lactate dehydrogenase; NPM: new primary malignancy; PI: package insert; PN: peripheral neuropathy; SmPC: Summary of Product Characteristics.

(a) Tests and procedures should be performed on schedule, within a 2-day 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 k below), all required tests and procedures for a specific visit should be done on the same day as the study visit.

(b) Before discontinuing a patient from treatment for PD, the Progressive Disease Review form must be completed as soon as possible, permitting pertinent data to be confirmed by a Millennium project clinician or designee.

(c) Patients who have stopped treatment for any reason other than PD will first enter the PFS Follow-up period. Patients who have PD while on study therapy, during the Treatment period, 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 will end PFS Follow-up and will enter into the OS Follow-up period. See Figure 6.b for a detailed flow chart for both follow-up periods.

(d) All Arm A patients who tolerated the 4 mg dose of ixazomib in Cycle 1 (see Section 6.1.2) should dose escalate to 5.5 mg on Cycle 2 Day 1. If the patient qualified for escalation but escalation was inadvertently missed at Cycle 2 Day 1, escalation at a later cycle may be allowed after consultation with the Millennium project clinician or designee; in that case, the patient must have Day 15 hematology samples collected in addition to Day 1 hematology samples. Patients who dose escalate to 5.5 mg must receive the first cycle of the 5.5 mg dose in the clinic rather than taking it at home.

(e) Confirmation of patient eligibility by a Millennium project clinician or designee is required before randomization. Cycle 1 Day 1 should be no later than 7 days after the date of randomization.

(f) Measurement of blood pressure and heart rate is to be performed at screening, along with temperature and respiratory rate. During the Treatment period, measurement of blood pressure and heart rate is to be performed; temperature and respiratory rate are collected only as clinically indicated.

(g) Patient-reported outcomes and HU assessment (eg, number of medical encounters) should be completed on the same day as the study visit, before any other study procedures are performed or study therapy is administered. At any time point when a clinic visit is not otherwise required (ie, during the OS Follow-up period), the EQ-5D-5L questionnaire may be administered over the telephone by trained site staff.

(h) Imaging to assess status of bone disease will be done at Screening (within 8 weeks before randomization) for all patients by means of skeletal survey, CT, MRI, or PET-CT. Additional assessments for bone disease 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.

(i) 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 prior to Cycle 1 Day 1; then the next assessment can be on Cycle 3 Day 1.

(j) 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.

(k) 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 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). Clinical laboratory evaluations for disease assessments (SPEP, UPEP, serum free light chain, immunofixation, and immunoglobulin) must be sent to the

central laboratory for evaluation until the data cutoff date for the study analysis has occurred. At that time, all central efficacy and investigator assessments for protocol purposes will be stopped and not recorded in the eCRF—namely, PK, SPEP, UPEP, serum free light chain, CCI , serology, C-reactive protein, immunofixation, immunoglobulin, and LDH/albumin/β_2-microglobulin at screening.

(l) If the screening test was performed more than 14 days before the first dose (Cycle 1 Day 1), the test will be repeated before dosing. The test closest to the first dose will be considered Baseline. Note that 24-hour urine collection is permitted before screening if it is part of standard clinical practice at the site.

(m) Note that Cycle 1 Day 1 dosing may proceed if MM isotype testing has been submitted to, but not yet analyzed at, the central laboratory. Immunofixation to 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). Note that 24-hour urine collection is permitted before screening if it is part of standard clinical practice at the site.

(n) Blood samples for IgM, IgG, and IgA will be obtained at Screening and throughout the study at the time points specified. If the screening test was performed more than 14 days before the first dose (Cycle 1 Day1), the test will be repeated before dosing. The test closest to the first dose will be considered Baseline. 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 for IgG and IgA.

(o) To be performed at a local laboratory to assess disease status at Baseline 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.

(p) CCI

(q) CCI .

(r) 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.

Table A Previous PK Sampling Schedule: Arm A (ixa+dex) Only (completed as of Amendment 06)

Cycle 1			Cycle 2				Cycles 3-4
Day 1		Day 15	Day 1			Day 15	Day 1
1 Hour Postdose (±15 Minutes)	4 Hours Postdose (±45 Minutes)	Any Time During Clinic Visit	Predose (a)	1 Hour Postdose (±15 Minutes)	4 Hours Postdose (±45 Minutes)	Any Time During Clinic Visit	Predose (a)
X	X	X	X	X	X	X	X

(a) All predose PK assessments should occur within 4 hours of dosing. If a predose sample is drawn from a patient and the patient does not receive a dose on that protocol visit day, a second predose sample does not need to be drawn on the subsequent visit where the dose is administered. All future visits should be done per the protocol. The exact date and time of each PK sample collection should be recorded in the source documents and eCRF.

Appendix M Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment 06 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: To note that the data cutoff date for the study analysis, which is the only planned formal analysis for this study, has now occurred.

The change occurs in Section 6.1.4 Statistical Analyses:

Initial wording:	Upon completion of this study, approximately 120 patients will have been enrolled globally. The PFS analysis 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 the PFS analysis; no further analyses are planned.
Amended or new wording:	Upon completion of this study, approximately 120 patients will have been enrolled globally. The ~~PFS~~**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 ~~the PFS~~**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.**

Rationale for Change: To clarify aspects of the study analysis.

Change 2: To note that, now that the data cutoff date for the study analysis has occurred, all central efficacy and investigator assessments of response for protocol purposes are now discontinued.

The primary change occurs in Section 9.4.12 Disease Response Assessment by Investigator:

Initial wording:	Patients will be assessed for disease response according to the IMWG uniform response criteria, version 2011 (see Appendix G), until the PFS endpoint has been met for this study. At that time, all central efficacy and investigator assessments of disease response for protocol purposes will be stopped.
Amended or new wording:	After the ~~primary endpoint of~~**data cutoff date for the study analysis (including for** PFS**)** has ~~been met~~**occurred**, all central efficacy and investigator assessments of response for protocol purposes will be discontinued~~; patients will be followed for survival and the appropriate data collected.~~**.**

Rationale for Change: To note that the data cutoff date for the study analysis has now occurred.

Section 2.0 STUDY SUMMARY also contains this change.

Change 3: To note that, now that the data cutoff date for the study analysis has occurred, the objective and endpoint of the study has changed to solely continue to collect long-term safety data.

The primary change occurs in Section 5.0 STUDY OBJECTIVES AND ENDPOINTS and Section 6.1.3 Study Assessments:

Added text:	**[Section 5.0]** **As of Amendment 06, the objective and endpoint are to continue to collect long-term safety data from patients who are continuing on ixazomib and dexamethasone or pomalidomide and dexamethasone because of continuing clinical benefit. Data collection for all other study objectives and endpoints is complete and no further formal analyses will be conducted. However, the original lists of objectives and endpoints are retained below for reference only.**
Added text:	**[Section 6.1.3]** **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.**

Rationale for Change: To clarify the study objective and endpoint at this point in the study.

The changes also occur in the following sections:

- Section 2.0 STUDY SUMMARY

Change 4: To note that as of the current amendment, now that the data cutoff date for the study analysis has occurred, only patients who continue to demonstrate clinical benefit but have no access to study drugs other than staying in the study may stay in the study.

The primary change occurs in Section 6.1.3 Study Assessments, Section 9.8 Withdrawal of Patients From Study, and Section 9.9 Study Closure:

Added text:	**[Section 6.1.3]** **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.
Initial wording:	**[Section 9.8]** 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. However, every effort will be made to follow all patients for safety.
Amended or new wording:	**[Section 9.8]** **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. ~~However, every effort will be made to follow all patients for safety.~~
Deleted wording:	**[Section 9.7 and Section 9.9]** ~~Patients remaining on study drug at the time of study closure (whether after completion of the study analysis or any other reason) will be provided continued access to study drug by the sponsor as long as they are receiving clinical benefit, either through commercial drug supply or through continued treatment in another extension or rollover study.~~ **[Section 9.7]** ~~Once study therapy has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the Schedule of Events (Appendix A). The primary reason for study therapy discontinuation will be recorded on the eCRF.~~ ~~Note that some patients may discontinue study therapy for reasons other than PD before completing the full treatment course; these will remain in the study for posttreatment assessments as outlined in the Schedule of Events (Appendix A) until PD occurs.~~
Rationale for Change: To clarify which patients may remain on study at this point.	
The following sections also contain this change: • Section 2.0 STUDY SUMMARY • Section 9.4.12 Disease Response Assessment by Investigator • Section 9.5 Completion of Study Treatment (for Individual Patients) • Section 9.7 Discontinuation of Treatment With Study Therapy • Section 9.9 Study Closure	

Change 5: To clarify that, as of the current amendment, the reason for a patient's treatment discontinuation must be recorded in the eCRF but no approval by the sponsor is required to discontinue treatment.

The primary change occurs in Section 9.7 Discontinuation of Treatment With Study Therapy:

Initial wording:	Discontinuation of treatment with study therapy is to be reviewed and confirmed by the Millennium project clinician or designee.
Amended or new wording:	**The reason for treatment discontinuation must be recorded in the eCRF but no approval is required.** ~~Discontinuation of treatment with study therapy is to be reviewed and confirmed by the Millennium project clinician or designee.~~

Rationale for Change: To clarify aspects of deciding to discontinue a patient's treatment at this point in the study.

The following sections also contain this change:

- Section 9.4.12 Disease Response Assessment by Investigator
- Section 9.5 Completion of Study Treatment (for Individual Patients)

Change 6: To clarify that local laboratory evaluations are to be used henceforth.

The primary change occurs in Section 9.4.15.1 Clinical Chemistry and Hematology:

Added text:	**Upon implementation of Amendment 06, centralized clinical laboratory evaluations are no longer required and local laboratories are to be used. Local laboratory evaluations should be entered into the eCRF only if required to understand a TEAE. For dosing decisions and all other safety assessments for the patient, local hematology and chemistry laboratory results should be used and do not need to be entered into the eCRF. These laboratory evaluations may be done more frequently at the investigator's discretion (ie, for acute management of TEAEs), per the investigator's judgement of standard of care.**

Rationale for Change: To clarify that central laboratory assessments are discontinued at this point in the study.

Section 9.4.15.2 Clinical Laboratory Evaluations for Disease Assessments also contains this change.

Change 7: To simplify the Schedule of Events to reflect the other changes noted.

The change occurs in Appendix A Updated Schedule of Events:

Description of changes:	SOE changed to retain only the following rows: • Informed consent (reconsent). • Complete physical examination.

- Symptom-directed physical examination.
- Pregnancy tests.
- Hematology and chemistry laboratory tests.
- Study drug dosing.
- AE reporting.
- Concomitant medications/procedures reporting.
- NPM assessment.

SOE changed to retain only the following columns:

- Cycle X Day 1; window now changed from ± 2 days to ± 1 week.
- EOT; window remains the same at +1 week.

Rationale for Change: To describe simplification of the Schedule of Events at this point in the study.

Change 8: To clarify that PK sample collection is now complete.

The change occurs in Section 9.4.18 PK Samples and Measurements:

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

Rationale for Change: To clarify that PK sample collection is complete at this point in the study.

Change 9: To clarify that the previous, full Schedule of Events and the now-completed PK sampling schedule have been moved to a new appendix (Appendix L) for reference only.

The primary change occurs in a new Appendix L Previous, Full Schedule of Events and PK Sampling Schedule (Schedules Before Implementation of Amendment 06):

Added text: [SOE and Table A in Appendix A now moved to a new Appendix L and labeled "Previous"]

Appendix L Previous, Full Schedule of Events and PK Sampling Schedule (Schedules Before Implementation of Amendment 06)

…

Previous Schedule of Events

…

Table A Previous PK Sampling Schedule: Arm A (ixa+dex) Only (completed as of Amendment 06)

…

Rationale for Change: To retain previous study conduct information for reference.

The following sections also contain this change:

- Section 6.1.3 Study Assessments
- Section 9.4 Study Procedures
- Section 9.4.4 Physical Examinations
- Section 9.4.6 ECOG Performance Status
- Section 9.4.7 Vital Signs
- Section 9.4.8 Height and Weight
- Section 9.4.10 QOL and HU Assessments
- Section 9.4.10.1 QOL
- Section 9.4.10.2 HU
- Section 9.4.15.1 Clinical Chemistry and Hematology
- Section 9.4.15.2 Clinical Laboratory Evaluations for Disease Assessments
- Section 9.4.18 PK Samples and Measurements

Change 10: Identify, as needed, text in the protocol that is no longer applicable as of the current amendment, now that the data cutoff date for the study analysis has occurred.

The primary change occurs in Section 6.1.3.1 Assessments During the Treatment Period and Section 6.1.3.2 Assessments During the Follow-up Periods: PFS and OS

Added text:

[Section 6.1.3.1]

Assessments Effective Only Before Amendment 06

…

Assessments Still in Effect as of Amendment 06

…

[Section 6.1.3.2]

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.

…

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

…

Rationale for Change: To clarify protocol text that is no longer relevant at this point in the study.

The following sections also contain this change:

- Section 9.4.6 ECOG Performance Status
- Section 9.4.7 Vital Signs
- Section 9.4.8 Height and Weight
- Section 9.4.10 QOL and HU Assessments
- Section 9.4.10.1 QOL
- Section 9.4.10.2 HU
- Section 9.4.11 Imaging Disease Assessment
- CCI [redacted]

Change 11: To add flexibility in study conduct in unavoidable circumstances (eg, the COVID-19 pandemic).

The primary change occurs in Section 8.10.1.3 Storage, Handling, and Accountability, 9.4 Study Procedures, and 14.1 Study-Site Monitoring Visits:

Added text:

[Section 8.10.1.3]

In case of extenuating circumstances that prevent a patient from attending the study site (eg, the COVID-19 pandemic), sites may use alternative strategies to deliver study drug to patients (eg, via courier or site staff), per local standard practice and regulations and with prior approval from the investigator and the sponsor's project clinician/designee.

…

In case of extenuating circumstances that prevent a patient from attending the study site (eg, the COVID-19 pandemic), drug packs and dosing diaries should be returned at the next available on-site clinic visit.

…

[Section 9.4]

In acknowledgement of hospital, local, state, or national government restrictions, or other site-related factors caused by unavoidable circumstances (eg, the COVID-19 pandemic) that may prevent investigators from conducting the study according to the Schedule of Events at the clinical study site, investigators may continue patients in the study despite departure from the Schedule of Events. Investigators are expected to evaluate the impact to the safety of the study participants and site personnel for patients to continue. In

evaluating such requests, the investigator/study site staff will give the highest priority to the safety and welfare of the patients. Patients must be willing and able to continue taking study medication and remain compliant with the protocol. For patients who are impacted by these unavoidable circumstances, any procedures not conducted per the study protocol will be documented in the eCRF.

If a patient misses an in-person study visit, the investigator/study team staff will speak directly with the patient by telephone or other medium (eg, a computer-based video communication) during each visit window to assess subject safety and overall clinical status. During this contact with the patient, the study site physician or other qualified site staff should at minimum conduct AE collection and an assessment of clinical symptoms. Other study assessments may be collected remotely as is feasible and may involve audio or video recording. Assessments/procedures that cannot be completed during the protocol-specified window because a site visit is done remotely (ie, symptom-directed physical examination, hematology, clinical chemistry) are waived.

…

[Section 14.1]

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.

…

Rationale for Change: To account for unavoidable circumstances affecting study conduct.

This change also occurs in Appendix A Updated Schedule of Events.

Change 12: To indicate that, given the changes in the current amendment, patients remaining on study will need to be reconsented.

The change occurs in Section 9.4.1 Informed Consent:

Added text: **As of Amendment 06, patients remaining on study treatment will need to 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.**

Rationale for Change: To clarify the need for reconsenting.

Change 13: Update language about management of clinical events in patients receiving ixazomib.

The change occurs in Section 8.8.1 Ixazomib:

Initial wording:

Erythematous Rash With or Without Pruritus

…

The rare risks of Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), and pemphigus vulgaris have been reported in oncology studies when ixazomib 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 according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib administration should be modified 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. A rare risk is thrombotic thrombocytopenic purpura, 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. Thrombotic thrombocytopenic purpura should be managed symptomatically according to standard medical practice.

…

Transverse Myelitis

One case of transverse myelitis has been reported in a patient receiving ixazomib+LenDex twice weekly, given for 16 cycles, followed by 4 complete cycles of ixazomib only in the maintenance phase (the patient received 2 additional doses beyond the 4 full cycles). During a break in therapy (Oct-Dec 2013) the patient experienced progressive neurologic deterioration. The event of transverse myelitis was diagnosed 1 day after the 22nd cycle of ixazomib maintenance was initiated. It is not known whether ixazomib causes transverse myelitis; however, because transverse myelitis happened to a patient receiving ixazomib, the possibility that ixazomib may have contributed to the transverse myelitis cannot be excluded. Transverse myelitis should be managed according to standard medical practice.

…

Amended or new wording:

Erythematous Rash With or Without Pruritus

…

The rare risks of Stevens-Johnson syndrome, ~~toxic epidermal necrolysis~~**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 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. ~~A rare risk is~~**Thrombotic microangiopathy (TMA), including** thrombotic ~~thrombocytopenic~~**thrombocytopenia** purpura **(TTP)**~~,~~ ~~a~~ **and hemolytic uremic syndrome (HUS), are** rare**, serious** blood ~~disorder where~~**disorders that cause low levels of platelets and red blood cells and result in** blood clots ~~form~~ in small blood vessels ~~throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. Thrombotic thrombocytopenic purpura~~**. 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 ~~symptomatically~~ according to standard medical practice.

…

Transverse Myelitis

~~One case of transverse myelitis has been reported in a patient receiving ixazomib+LenDex twice weekly, given for 16 cycles, followed by 4 complete cycles of ixazomib only in the maintenance phase (the patient received 2 additional doses beyond the 4 full cycles). During a break in therapy (Oct-Dec 2013) the patient experienced progressive neurologic deterioration. The event of transverse myelitis was diagnosed 1 day after the 22nd cycle of ixazomib maintenance was initiated~~ **Transverse myelitis has been reported with ixazomib**. It is not known whether ixazomib causes transverse myelitis; however, because transverse myelitis happened to a patient receiving ixazomib, the possibility that ixazomib may have contributed to

	the transverse myelitis cannot be excluded. Transverse myelitis should be managed according to standard medical practice. …
Rationale for Change: To add information currently available around clinical events.	
Change 14: To clarify details about ixazomib packaging, handling, and storage guidelines.	
The primary change occurs in Section 8.1 Investigational Therapy: Ixazomib Administration (Arm A), Section 8.10.1.3 Storage, Handling, and Accountability, and Section 8.10.1.1 Preparation, Reconstitution, and Dispensation:	
Added text:	**[Section 8.1]** … **Refer to Section 8.10.1.3 and the Study Manual for additional instructions regarding study therapy administration.** … **Section 8.10.1.3** On receipt at the investigative site, ixazomib should remain in the blister **pack** and carton provided until use or dispensation. For storage conditions, refer to the Pharmacy Manual or equivalent. All excursions from the temperature storage guidelines should **immediately** be brought to the sponsor's attention for assessment and authorization for continued use. Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life. …
Initial wording:	**[Section 8.10.1.1]** Ixazomib is dispensed in blisters in a child-resistant carton. For the 2.3, 3.0, 4.0, and 5.5 mg capsule strengths, there are 3 capsules in each wallet/carton. Ixazomib is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised during handling. …
Amended or new wording:	**[Section 8.10.1.1]** Ixazomib is dispensed in ~~blisters~~**a blister pack** in a child-resistant carton. For the 2.3, 3.0, 4.0, and 5.5 mg capsule strengths, there are 3 capsules in each wallet/carton. Ixazomib is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised during handling. **See the Pharmacy Manual for more**

information.

…

Rationale for Change: To add clarification to this protocol.

Change 15: To clarify that PFS and OS data will be analyzed using unstratified tests, among others.

The change occurs in Section 13.1.3.1 Analyses for Primary Efficacy Endpoint and 13.1.3.2 Analyses of Secondary Efficacy:

Initial wording:

[Section 13.1.3.1]

…

A 2-sided, stratified log-rank test will be used to compare the treatment groups with respect to PFS at a 2-sided alpha level of 0.20. In addition, an unadjusted stratified Cox model will be used to estimate the HR and its 80% and 95% CIs for the treatment effect. The KM survival curves and KM medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

[Section 13.1.3.2]

OS will be analyzed on the basis of the ITT population and is defined as the time from randomization to death from any cause. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive. A 2-sided, unstratified log-rank test will be used to compare the treatment and control groups with respect to OS. In addition, an unadjusted stratified Cox model will be used to estimate the HR and its 80% and 95% CIs for the treatment effect. OS will be also tested at 2-sided alpha=0.2. The KM survival curves and KM medians (if estimable), along with their 95% CIs, will also be provided for each study group.

…

Amended or new wording:

[Section 13.1.3.1]

…

A 2-sided, ~~stratified~~**unstratified** log-rank test will be used to compare the treatment groups with respect to PFS at a 2-sided alpha level of 0.20. In addition, an unadjusted ~~stratified~~**unstratified** Cox model will be used to estimate the HR and its 80% and 95% CIs for the treatment effect. The KM survival curves and KM medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

[Section 13.1.3.2]

	OS will be analyzed on the basis of the ITT population and is defined as the time from randomization to death from any cause. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive. A 2-sided, unstratified log-rank test will be used to compare the treatment and control groups with respect to OS. In addition, an unadjusted ~~stratified~~**unstratified** Cox model will be used to estimate the HR and its 80% and 95% CIs for the treatment effect. OS will be also tested at 2-sided alpha=0.2. The KM survival curves and KM medians (if estimable), along with their 95% CIs, will also be provided for each study group.
Rationale for Change: To provide correct information about statistical testing for this study.	
Change 16: To add information about submitting SAE reports.	
The primary change occurs in Section 10.2 Procedures for Recording and Reporting AEs and SAEs:	
Added text:	**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.**
Rationale for Change: To assist in timely submission of SAE reports.	
Change 17: To correct a typographical error and clarify that there is only 1 study analysis planned (and as such, no interim analyses).	
The change occurs in Section 9.9 Study Closure:	
Initial wording:	• Determination of efficacy based on IA.
Amended or new wording:	• Determination of efficacy based on ~~IA~~**the study analysis**.
Rationale for Change: To correct a typographical error.	

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	01-Sep-2020 16:53 UTC
	Biostatistics Approval	01-Sep-2020 17:56 UTC
	Clinical Science Approval	01-Sep-2020 18:08 UTC
	Pharmacovigilance Approval	01-Sep-2020 22:48 UTC