Clinical Study Protocol

NCT Number: NCT03748953

Title: China Continuation: A Single-Arm, Open-Label Study of Oral Ixazomib Maintenance Therapy After Initial Therapy in Patients With Newly Diagnosed Multiple Myeloma Not Treated With Stem Cell Transplantation

Study Number: C16021 CCS

Document Version and Date: Amendment 10.0, 26 August 2022

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CLINICAL STUDY PROTOCOL C16021 AMENDMENT 10

Ixazomib

China Continuation: A Single-Arm, Open-Label Study of Oral Ixazomib Maintenance Therapy After Initial Therapy in Patients With Newly Diagnosed Multiple Myeloma Not Treated With Stem Cell Transplantation

Protocol Number:	C16021
Indication:	Multiple myeloma
Phase:	3
Sponsor:	Millennium Pharmaceuticals, Inc.
EudraCT Number:	2014-001394-13
Therapeutic Area:	Oncology

Protocol History

Original	Global	15 September 2014
Amendment 01	China	26 November 2014
Amendment 02	Global	14 June 2016
Amendment 03	China	07 September 2016
Amendment 04	China Continuation Study	02 November 2016
Amendment 05	Global, Substantial	28 September 2018
Amendment 06	China	28 September 2018
Amendment 07	Global (for use in all countries except China), Substantial	23 September 2020
Amendment 08	China Continuation Study	29 September 2020
Amendment 09	Global, Substantial	16 November 2021
Amendment 10	China Continuation Study	26 August 2022

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Rationale for Amendment 10

This document describes the changes to the protocol incorporating Amendment 10. The primary rationale for this amendment is to clarify aspects of study conduct.

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

For specific examples of changes in text and where the changes are located, see Section 15.23.

Purposes for Amendment 10

The purposes of this amendment are to:

1. Remove the reference to randomization throughout the protocol.
2. Remove reference to second progressive disease (PD2) throughout the protocol.
3. Clarify "vital signs" with a footnote in the Schedules of Events.
4. Clarify unblinding of patients off study.
5. Clarify language regarding procedures for reporting product complaints or medication errors.
6. Clarify language in study conduct regarding the coronavirus disease 2019 pandemic.
7. Clarify definitions of some of the populations for analysis.
8. Remove the Independent Review Committee section.
9. Update the management of transverse myelitis for ixazomib to reflect evolving data.
10. Clarify reporting of patient-reported outcome questionnaires.
11. Clarify the wording of some secondary and exploratory study objectives.

PROTOCOL SUMMARY

Study Title: China Continuation: A Single-Arm, Open-Label Study of Oral Ixazomib Maintenance Therapy After Initial Therapy in Patients With Newly Diagnosed Multiple Myeloma Not Treated With Stem Cell Transplantation

Number of Patients: Approximately 30 total patients from China with newly diagnosed multiple myeloma (NDMM) who had a major response to initial therapy and who have not undergone stem cell transplantation (SCT). Prior to implementation of Amendment 08, 10 patients have been randomized and treated in the China Continuation. An additional ~20 patients are to be enrolled upon implementation of Amendment 08.

Study Objectives

Primary

- To determine the long-term safety and tolerability of ixazomib maintenance therapy

Secondary

- To determine progression-free survival (PFS), defined as the time from date of first dose to progressive disease (PD) or death from any cause, in patients in China with NDMM who have had a major response—defined as complete response (CR), very good partial response (VGPR), or partial response (PR)—to initial therapy and who have not undergone SCT
- To determine overall survival (OS)
- To determine whether response at study entry is improved or maintained
- To determine time to progression
- To determine time to next-line therapy
- To assess the incidence of new primary malignancy in patients receiving ixazomib maintenance therapy
- To assess health-related quality of life (HRQL), as measured by the global health domain of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) in patients who receive ixazomib maintenance therapy
- To assess the correlation between frailty status and PFS and OS in patients receiving ixazomib maintenance therapy
- To collect pharmacokinetic (PK) data to contribute to population PK and exposure-response (safety/efficacy) analysis
- To evaluate the resolution and improvement of peripheral neuropathy, if it occurs, in patients receiving ixazomib maintenance therapy

Overview of Study Design: The China Continuation part of Study C16021 was originally designed as a randomized, double-blind, placebo-controlled, multicenter study in patients in China with NDMM who have not undergone SCT. Upon implementation of Amendment 08, the China Continuation will now be a single-arm, open-label study of ixazomib maintenance for patients in China with NDMM who have not undergone SCT. Patients who have not undergone SCT may not have done so because of frailty due to advanced age (eg, ≥65 years) or comorbidity or because they decline SCT for other reasons. Patients enrolled under Amendment 08 will be enrolled based on the same eligibility criteria; patients will be considered enrolled when they have been entered into the interactive voice/web response system (IXRS) and have received the first dose of study drug.

Patients must have received initial therapy, for 6 to 12 months, according to standard of care before study enrollment and have been treated to achieve a major response category (PR or better) that is judged to be their best response by the investigator/treating physician. Partial response, VGPR, or CR must be documented at screening, and patients must have met all additional inclusion/exclusion criteria. Upon implementation of Amendment 08, all patients will receive open-label ixazomib. New eligible and consenting patients are to be enrolled no later than 60 days after the last dose of initial therapy. For patients who were previously randomized to the placebo arm who reconsent and cross over to ixazomib, reconsenting more than 60 days after the last dose of initial therapy is permitted.

Patients will receive ixazomib capsules (hereafter referred to as "study drug") orally on Days 1, 8, and 15 of every 28-day cycle. The starting dose will be 3 mg of study drug, which—if tolerated during the first 4 cycles—will be escalated to 4 mg beginning with Cycle 5 Day 1. The Treatment period will be approximately 24 months (equivalent to 26 cycles [if no cycle delays], to the nearest complete cycle) or until patients experience PD or unacceptable toxicity, whichever occurs first.

Clinical, laboratory, and disease response assessments will be conducted, as will HRQL assessments with an emphasis on tolerability [redacted]. After documented PD, subsequent therapy will be determined by the investigator/treating physician. There will be 1 IA and a final analysis (FA) for the study. The IA is the primary analysis for this study and will be performed approximately 12 months after the additional ~20 patients have been enrolled under Amendment 8. The safety and efficacy endpoints will be assessed in the overall Chinese patient population (patients from China who were enrolled in the ixazomib arm of the C16021 global study, patients in the ixazomib arm of the China Continuation before implementation of Amendment 08, all patients enrolled in the China Continuation under Amendment 08, and patients who were randomized to the placebo arm before implementation of Amendment 08 and who crossed over to the ixazomib arm). The FA will be performed when all patients in the China Continuation are off treatment and have completed the End of Treatment (EOT) visit, or upon termination of the study by the sponsor, whichever occurs earlier. Descriptive statistics will be used to summarize patient data collected after the IA.

Study Population: Adult patients in China with NDMM who have had 6 to 12 months of initial therapy that is standard of care, during which the patient was treated to "best response" (in the investigator's judgment), with documented major response (PR, VGPR, or CR, according to International Myeloma Working Group criteria) and who have not undergone SCT.

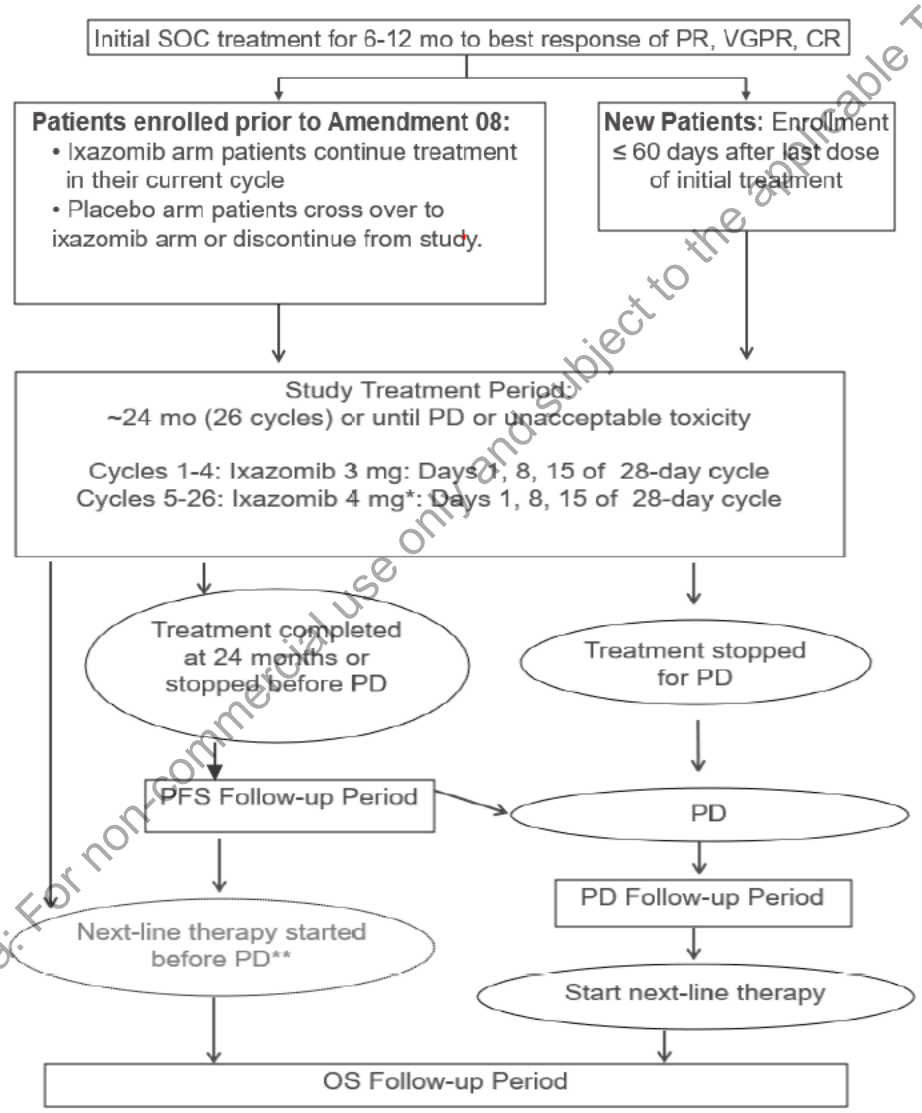
Duration of Study: Patients will be treated for a maximum duration of approximately 24 months (26 cycles [if there are no cycle delays], to the nearest complete cycle) or until documented PD or intolerable toxicity, whichever occurs first. Note, patients previously randomized to the placebo arm who reconsent and cross over to ixazomib may receive up to 24 months (26 cycles) of ixazomib treatment.

Subsequent to the 24-month active Treatment period or removal from study therapy because of PD or toxicity, patients will be followed in the PFS, PD, and OS Follow-up periods for clinical status, disease status, HRQL, new primary malignancy, and survival.

The study will last until all patients in the China Continuation are off study treatment and have completed the EOT visit, or upon termination of the study by the sponsor, whichever occurs earlier.

STUDY OVERVIEW DIAGRAM—AMENDMENT 08 AND BEYOND

Upon implementation of Amendment 08, the China Continuation will now be a single-arm, open-label study of ixazomib maintenance for patients in China with newly diagnosed multiple myeloma (NDMM) who have not undergone SCT. The study objectives are now focused on long-term tolerability and efficacy of ixazomib in patients in China, so as to evaluate the consistency of the safety and efficacy of ixazomib maintenance between the China population and the C16021 global study population.



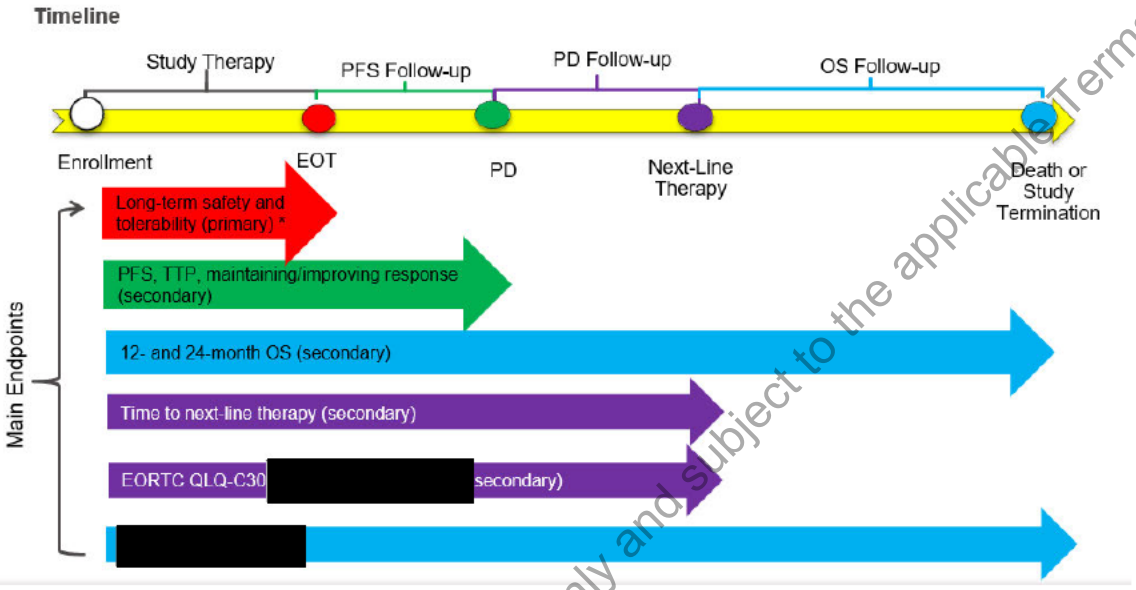
Abbreviations: CR=complete response; mo=months; OS=overall survival; PD=progressive disease (disease progression); PFS=progression-free survival, defined as time from date of first dose to PD or death from any cause; PR=partial response; SOC=standard of care; VGPR=very good partial response.

* After the first 4 cycles of treatment, eligible patients will have their dose of ixazomib escalated from 3 mg to 4 mg. See Section 6.5 for more information about eligibility criteria.

** If a physician chooses to start next-line therapy before PD, the patient will skip the PD Follow-up period and be entered directly into the OS Follow-up period.

STUDY ENDPOINT AND FOLLOW-UP PERIOD DIAGRAM—AMENDMENT 08 AND BEYOND

The timeline below shows the endpoints and follow-up periods for the revised study design.



Abbreviations: EOT=End of Treatment visit; OS=overall survival; PD=progressive disease (disease progression); PFS=progression-free survival, defined as time from date of first dose to PD or death from any cause; TTP=time to progression.

SCHEDULES OF EVENTS—AMENDMENT 08 AND BEYOND

Amendment 08 changes the China Continuation from a double-blind, placebo-controlled design to an open-label, single-arm design (ixazomib only). Given the positive results from the C16021 global study and the fact that the C16021 China Continuation is still open to enrollment, the sponsor does not believe it is appropriate to continue enrolling patients into a randomized, placebo-controlled maintenance study. The Center for Drug Evaluation (CDE), National Medical Products Administration (NMPA) acknowledged that it will be difficult to continue enrolling patients into the placebo arm of the C16021 China Continuation. The CDE suggested that the sponsor amend the study into a single arm study, so as to collect more efficacy and safety data from Chinese patients receiving ixazomib. This amendment describes modifications to the China Continuation study procedures for patients who are still on treatment, who are in 1 of the follow-up periods, or who will be enrolled after this amendment takes effect.

For ease of study conduct, the Schedule of Events has been modified to apply to the remainder of the study. Two separate schedules—the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients" and the "Schedule of Events for Crossover Patients"—have been created to clarify the procedures for different patients (as detailed in the bullets below). The Schedule of Events in effect prior to Amendment 08 has been moved to Section 15.13.

- ***Patients enrolled prior to implementation of Amendment 08:*** Prior to implementation of Amendment 08, 10 patients had been randomized and treated in the China Continuation. All patients continuing in the study under Amendment 08 must be reconsented.
    - ***Patients still on treatment:*** Patients who were randomized to study drug (ixazomib or placebo) prior to implementation of Amendment 08 and who are still on study treatment will complete their current cycle of treatment, following the previous Schedule of Events (see Section 15.13), and be unblinded.
        - Patients who are in the placebo arm who have not yet experienced disease progression will have the opportunity to cross over to ixazomib maintenance, based on the investigator's judgement and the patient's informed consent. Patients who cross over will follow the "Schedule of Events for Crossover Patients" starting at Crossover Cycle 1 Day 1. Patients in the placebo arm who do not cross over should complete an End of Treatment visit and discontinue the study.
        - Patients who are in the ixazomib arm will continue to receive ixazomib maintenance. Patients who reconsent will follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients" according to their current cycle of treatment.

- ***Patients in the progression-free survival (PFS) Follow-up Period:*** All patients will be unblinded.
    - Patients in the placebo arm who have discontinued study treatment but who have not yet experienced disease progression or started alternative therapy have the opportunity to cross over to ixazomib maintenance. The decision to cross over is based on the investigator's judgement and the patient's informed consent. Patients who cross over will follow the "Schedule of Events for Crossover Patients" starting at Crossover Cycle 1 Day 1. Patients in the placebo arm who do not cross over will discontinue the study.
    - Patients in the ixazomib arm who reconsent should continue on study and follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients" according to the PFS Follow-up Period schedule.
- ***Patients in the PFS2 or Overall Survival (OS) Follow-up Periods:*** All patients will be unblinded.
    - Patients in the placebo arm will discontinue the study. No crossover to the ixazomib arm is permitted in these patients who have experienced primary disease progression or who have initiated alternative therapy.
    - Patients in the ixazomib arm who reconsent will continue on study and follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients" according to the OS Follow-up Period schedule. Note, the PFS2 Follow-up period has been removed in Protocol Amendment 08; patients previously in PFS2 follow-up will be followed in the OS follow-up period.
- ***Patients Off Study:*** All these patients will be unblinded.

- ***Patients to be enrolled after implementation of Amendment 08:*** Approximately 20 additional patients with NDMM who responded to initial treatment will be enrolled in the C16021 China Continuation, for a total of approximately 30 patients overall. All newly enrolled patients will receive ixazomib maintenance and will follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients." For newly enrolled patients, ixazomib must be initiated within 5 days of the patient being entered into the IXRS system.

Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients—Amendment 08 and Beyond

Study Procedures	Screening	Treatment Period									EOT [a]	Follow-up [b]		
		28-Day Cycles [b]										PFS	PD	OS
Cycle		Cycle 1			Cycle 2		Cycle 3	Cycles 4–5	Cycle 5 [c]	Cycles 6-26		Every 4 Wk Until PD	Every 4 Wk After PD Until Next-Line Therapy	Every 12 Wk After PD on Next-Line Therapy
Days	-28 to -1	1	8	15	1	8	1	1	8	1				
Window		±2 days								±1 Wk	+1 Wk	±1 Wk	±1 Wk	±1 Wk
Informed consent (reconsent) [d]	X													
Inclusion/exclusion Criteria [e]	X													
Demographics	X													
Complete medical history and disease staging	X													
Complete physical examination, including for PN	X										X [f]			
Symptom-directed physical examination, including for PN [f]		X			X		X	X		X		X	X	
ECOG Performance Status [f]	X				X		X	X		X	X	X	X	
Frailty status [g]	X													
Vital signs [f]	X	X			X		X	X		X	X	X	X	
Height (cm)	X													
Weight (kg) [f]	X	X			X		X	X		X	X			

Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients—Amendment 08 and Beyond

Study Procedures	**Screening**	**Treatment Period**									**EOT** [a]	**Follow-up** [b]		
		28-Day Cycles [b]										**PFS**	**PD**	**OS**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3**	**Cycles 4–5**	**Cycle 5** [c]	**Cycles 6-26**		**Every 4 Wk Until PD**	**Every 4 Wk After PD Until Next-Line Therapy**	**Every 12 Wk After PD on Next-Line Therapy**
Days	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**1**	**1**	**8**	**1**				
Window		**±2 days**								**±1 Wk**	**+1 Wk**	**±1 Wk**	**±1 Wk**	**±1 Wk**
12-lead ECG	X													
EORTC QLQ-C30 [h]	X	X			X		X	X		X	X	X	X	
[redacted]														
Imaging disease assessment [i]	X													
Investigator assessment of disease response/status	X				X		X	X		X	X	X		

Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients—Amendment 08 and Beyond

Study Procedures	Screening	Treatment Period									EOT [a]	Follow-up [b]		
		28-Day Cycles [b]										PFS	PD	OS
Cycle		Cycle 1			Cycle 2		Cycle 3	Cycles 4–5	Cycle 5 [c]	Cycles 6-26		Every 4 Wk Until PD	Every 4 Wk After PD Until Next-Line Therapy	Every 12 Wk After PD on Next-Line Therapy
Days	-28 to -1	1	8	15	1	8	1	1	8	1				
Window		±2 days								±1 Wk	+1 Wk	±1 Wk	±1 Wk	±1 Wk
Ixazomib [j, k]		Single dose on Days 1, 8, and 15 of each cycle												
Determination of dose escalation [k]								X (Cycle 5)						
Adverse event reporting [l]		Recorded from the first dose of study drug through 30 days after last dose of study drug												
	Serious adverse events and serious pretreatment events will be collected from signing of the informed consent form through 30 days after the last dose of study drug													
Concomitant medications/procedures		Recorded from the first dose of study drug through 30 days after last dose of study drug												
New primary malignancy assessment		Continuous from start of study drug administration until death or termination of the study by sponsor												
Survival														X
Samples/Laboratory Assessments														
Pregnancy test (serum) [m]	X	X									X			
Hematology laboratory [f, n]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry laboratory [f, n]	X	X			X		X	X		X	X	X	X	
Urinalysis	X													

Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients—Amendment 08 and Beyond

Study Procedures	Screening	Treatment Period									EOT [a]	Follow-up [b]		
		28-Day Cycles [b]										PFS	PD	OS
Cycle		Cycle 1			Cycle 2		Cycle 3	Cycles 4–5	Cycle 5 [c]	Cycles 6-26		Every 4 Wk Until PD	Every 4 Wk After PD Until Next-Line Therapy	Every 12 Wk After PD on Next-Line Therapy
Days	-28 to -1	1	8	15	1	8	1	1	8	1				
Window		±2 days								±1 Wk	+1 Wk	±1 Wk	±1 Wk	±1 Wk
[redacted]														
M-protein (SPEP) [f]	X	X [p]			X		X	X		X	X	X	X	
M-protein (UPEP [24-hr urine]) [f]	X	X [p]			X		X	X		X	X	X	X	
SFLC assay [f]	X	X [p]			X		X	X		X	X	X	X	
Immunofixation: serum and urine [f, q]	X	X [p]			X		X	X		X	X	X	X	
Quantification of Ig [f, r]	X	X [p]			X		X	X		X	X	X	X	
Bone marrow aspiration (BMA)														
Disease assessment BMA (local lab) [s]	X													
Progressive disease BMA (local lab) [t]		Progressive disease BMA specimen is requested at any time of progressive disease confirmation												

Abbreviations: BMA=bone marrow aspirate; COVID-19: coronavirus disease 2019; CT=computed tomography; EC: ethics committee; ECG=electrocardiography; ECOG=Eastern Cooperative Oncology Group; EORTC=European Organization for Research and Treatment of Cancer; EOT=End of Treatment; [redacted]; GCP: Good Clinical Practice; [redacted] Ig=immunoglobulins; IRB: institutional review board; IXRS: interactive voice/web response system; MRD=minimal residual disease; MRI=magnetic resonance imaging; N/A=not available; OS=overall survival; PD=progressive disease (disease progression); PET=positron emission tomography; PFS=progression-free survival, defined as time from date of first dose to PD or death from any cause; PFS2=progression-free survival 2, defined as time from date of first dose to objective disease progression on next-line treatment or death from any cause; PN=peripheral neuropathy; QLQ-C30=Quality of Life Questionnaire Core 30 (questions); [redacted] SFLC=serum free light chain; SPEP=serum protein electrophoresis; UPEP=urine protein electrophoresis.

Tests and procedures should be performed on schedule but, unless otherwise specified, occasional changes are allowable within a 2-day window during Cycles 1-5 and within a 7-day window during Cycle 6 and beyond for holidays, vacations, and other administrative reasons; a longer window is allowable after discussion with the Millennium Pharmaceuticals, Inc. (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. These windows are also permissible for study days not specified in this Schedule of Events, including Cycle 2 Day 15 and Day 8 and Day 15 of Cycle 3 and beyond.

a Before an investigator discontinues a patient from treatment for PD, the pertinent data must be confirmed by a Millennium project clinician or designee.

b For Cycle 4 and 5 and Cycle 6 through 26 procedures, all cycles are meant unless numbers are given in parentheses, indicating the specific cycles meant. For PFS and PD follow-up, exceptions to the follow-up interval of every 4 weeks are given in parentheses.

c Cycle 5 Day 8 assessments should be done only for patients who have the dose escalated after Cycle 4.

d 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. For patients enrolled prior to implementation of Amendment 08 and still on study treatment, before dosing on Day 1 of the next full treatment cycle, all patients must be reconsented. Patients randomized to the ixazomib arm prior to implementation of Amendment 08 who are in 1 of the follow-up periods must also be reconsented. Consenting/reconsenting should be done in person. Remote consenting/reconsenting is permitted as long as the process adheres to site, IRB/EC, and GCP standards and local regulations.

e Confirmation of patient eligibility by the Millennium project clinician or designee is required before enrollment.

f Patients must present to the study site for all visits shown in the Schedule of Events during Cycles 1-5 to ensure proper safety, efficacy, and PK monitoring. Alternative methods for administering study procedures/assessments may be considered for Cycle 6 and beyond 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 lab assessment performed at a facility closer to the patient's home, etc). If an in-clinic visit is not possible, the permitted alternatives are as follows. These assessments/procedures may be waived: symptom-directed physical examination, ECOG performance status, vital signs, weight, whole blood, [redacted]. These assessments/procedures may be deferred until the next in-clinic visit: SPEP, UPEP, serum free light-chain assay, immunofixation, quantification of immunoglobulins, BMA, and biopsy. These assessments/procedures may be performed locally if possible and, if not, may be deferred until the next in-clinic visit: hematology and chemistry laboratory tests.

g Patients' frailty status is classified as fit, unfit, or frail on the basis of 4 components: age, the Katz Index of Independence in Activities of Daily Living, the Lawton Instrumental Activities of Daily Living Scale, and the Charlson Comorbidity Scoring System [1-3].

h Patient-reported outcomes [redacted] should be completed before any other study procedures are performed or study drug is administered. Patient-reported outcome questionnaires are preferred to be completed by patients in the clinic, but if needed due the COVID-19 pandemic, the EORTC QLQ-C30 [redacted] questionnaires may be completed at the patient's home using paper versions of the questionnaires. At time points when a clinic visit is not required, or if needed due the COVID-19 pandemic, [redacted]

i A skeletal survey to assess status of bone disease and extramedullary disease will be done at screening (within 8 weeks before date of first dose) for all patients. Additional assessments can be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD). At the discretion of the investigator, a CT scan, a PET-CT scan, or whole body MRI may be done at screening in place of a skeletal survey, provided that the same modality for assessment is used throughout the study.

j Upon implementation of Amendment 08, all patients will receive open-label oral ixazomib. Patients will receive ixazomib on Days 1, 8, and 15 of every 28-day cycle.

- **Patients enrolled prior to implementation of Amendment 08:** Prior to implementation of Amendment 08, 10 patients had been randomized and treated in the China Continuation. All patients continuing in the study under Amendment 08 must reconsent.
  - ***Patients still on treatment:*** Patients who were randomized to study drug (ixazomib or placebo) prior to implementation of Amendment 08 and who are still on study treatment will complete their current cycle of treatment, following the previous Schedule of Events (see Section 15.13), and be unblinded.
    - Patients who are in the placebo arm and who have not yet experienced disease progression will have the opportunity to cross over to ixazomib maintenance, based on the investigator's judgement and the patient's informed consent. Patients who cross over will follow the "Schedule of Events for Crossover Patients" starting at Crossover Cycle 1 Day 1. Patients in the placebo arm who do not cross over should complete an EOT visit and discontinue the study.
    - Patients who are in the ixazomib arm will continue to receive ixazomib maintenance. Patients who reconsent will follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients" according to their current cycle of treatment.
  - ***Patients in the PFS Follow-up Period:*** All patients will be unblinded.
    - Patients in the placebo arm who have discontinued study treatment but who have not yet experienced disease progression or started alternative therapy have the opportunity to cross over to ixazomib maintenance. The decision to cross over is based on the investigator's judgement and the patient's informed consent. Patients who cross over will follow the "Schedule of Events for Crossover Patients" starting at Crossover Cycle 1 Day 1. Patients in the placebo arm who do not cross over will discontinue the study.
    - Patients in the ixazomib arm who reconsent should continue on study and follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients" according to the PFS Follow-up period schedule.
  - ***Patients in the PFS2 or OS Follow-up periods:*** All patients will be unblinded.
    - Patients in the placebo arm will discontinue the study. No crossover to the ixazomib arm is permitted in these patients who have experienced primary disease progression or who have initiated alternative therapy.
    - Patients in the ixazomib arm who reconsent will continue on study and follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients" according to the OS Follow-up period schedule. Note, the PFS2 Follow-up period has been removed in Protocol Amendment 08; patients previously in PFS2 follow-up will be followed in the OS Follow-up period.
  - ***Patients Off Study:*** All these patients will be unblinded.
- ***Patients to be enrolled after implementation of Amendment 08:*** Approximately 20 additional patients with NDMM who responded to initial treatment will be enrolled in the China Continuation, for a total of approximately 30 patients overall. All newly enrolled patients will receive ixazomib maintenance and will follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients." For newly enrolled patients, ixazomib must be initiated within 5 days of the patient being entered into the IXRS system.

k A starting dose of 3 mg of ixazomib will be given to all patients through Cycle 4. Upon evaluation of toxicities at Cycle 4, and on the basis of the dose escalation criteria detailed in Section 6.5, the dose will be escalated to 4 mg on Cycle 5 Day 1 and administered on the same schedule for the duration of the study to provide maximum possible clinical benefit for patients who tolerated the first 4 cycles of treatment (see Section 6.5). If dose escalation was inadvertently missed at Cycle 5,

escalation at a later cycle may be performed with permission from the Millennium project clinician or designee.

l When PN occurs, each subsequent monthly evaluation will record the grade of PN at that visit. (This is in contrast to other adverse events 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 the PN, 2) the start of a second-line alternative antineoplastic treatment, or 3) 6 months after PD has occurred—whichever occurs first.

m A serum pregnancy test will be performed for women of childbearing potential during screening, predose on Cycle 1 Day 1, and at the EOT visit, or more frequently as required per local regulations. The Cycle 1 Day 1 pregnancy test may be collected up to 3 days before dosing. The results must be available and negative before the study drug is administered.

n Clinical laboratory evaluations will be performed by a central laboratory (see Section 7.4.13 and the Laboratory Manual). For dosing decisions, local hematology and chemistry laboratory results may be used; however, samples must still be sent to the central laboratory also. Hematology and chemistry panels may be collected up to 3 days before Day 1 dosing and 24 hours before Day 8 and Day 15 dosing, where required. Local laboratory evaluations may be done more frequently at the investigator's discretion (ie, for acute management of treatment-emergent adverse events).

[redacted]

p If the screening test was performed more than 14 days before the first dose, the test will be repeated at baseline.

q Immunofixation is also to be done to confirm CR (if the M-protein level is undetectable by protein electrophoresis in both serum and urine, the central laboratory will perform immunofixation testing in both serum and urine).

r Blood samples for IgM, IgG, and IgA will be obtained throughout the study at the time points specified. Quantitative IgD and IgE measurement will be done at screening (and baseline if needed) only, except for the rare patient who has IgD or IgE multiple myeloma, for whom quantitative measurement for that antibody will be done at the same time points as, and in addition to, IgM, IgG, and IgA measurements.

s BMA for disease assessment is to be evaluated at a local laboratory at screening. BMA with local assessment should be repeated if the patient has reduction of serum and urine M-protein consistent with possible CR or when indicated to investigate suspected PD.

t An additional BMA for patients who have PD is optional but highly recommended and should be collected at any time PD is suspected or before starting a new therapy. This marrow will be evaluated locally.

Schedule of Events for Crossover Patients—Amendment 08 and Beyond

Study Procedures	Treatment Period									EOT [a]	Follow-up [b]		
	28-Day Cycles [b]										PFS	PD	OS
	Crossover Cycle Number												
Cycle	Cycle 1			Cycle 2		Cycle 3	Cycles 4–5	Cycle 5 [c]	Cycles 6-26		Every 4 Wk Until PD	Every 4 Wk After PD Until Next-Line Therapy	Every 12 Wk After PD on Next-Line Therapy
Days	1	8	15	1	8	1	1	8	1				
Window	±2 days								±1 Wk	+1 Wk	±1 Wk	±1 Wk	±1 Wk
Informed consent (reconsent) [d, e]	X												
Complete physical examination, including for PN										X [f]			
Symptom-directed physical examination, including for PN [f]	X			X		X	X		X		X	X	
ECOG Performance Status [f]				X		X	X		X	X	X	X	
Frailty status [g]													
Vital signs [f]	X			X		X	X		X	X	X	X	
Height (cm)													
Weight (kg) [f]	X			X		X	X		X	X			
12-lead ECG													
EORTC QLQ-C30 [h]	X			X		X	X		X	X	X	X	

Schedule of Events for Crossover Patients—Amendment 08 and Beyond

Study Procedures	Treatment Period									EOT [a]	Follow-up [b]		
	28-Day Cycles [b]										PFS	PD	OS
	Crossover Cycle Number												
Cycle	Cycle 1			Cycle 2		Cycle 3	Cycles 4–5	Cycle 5 [c]	Cycles 6-26		Every 4 Wk Until PD	Every 4 Wk After PD Until Next-Line Therapy	Every 12 Wk After PD on Next-Line Therapy
Days	1	8	15	1	8	1	1	8	1				
Window	±2 days								±1 Wk	+1 Wk	±1 Wk	±1 Wk	±1 Wk
[redacted]													
Imaging disease assessment [i]													
Investigator assessment of disease response/status				X		X	X		X	X	X		
Ixazomib [j, k]	Single dose on Days 1, 8, and 15 of each cycle												
Determination of dose escalation [k]							X (Cycle 5)						

Schedule of Events for Crossover Patients—Amendment 08 and Beyond

Study Procedures	Treatment Period									EOT [a]	Follow-up [b]		
	28-Day Cycles [b]										PFS	PD	OS
	Crossover Cycle Number												
Cycle	Cycle 1			Cycle 2		Cycle 3	Cycles 4–5	Cycle 5 [c]	Cycles 6-26		Every 4 Wk Until PD	Every 4 Wk After PD Until Next-Line Therapy	Every 12 Wk After PD on Next-Line Therapy
Days	1	8	15	1	8	1	1	8	1				
Window	±2 days								±1 Wk	+1 Wk	±1 Wk	±1 Wk	±1 Wk
Adverse event reporting [l]	Recorded from the first dose of study drug through 30 days after last dose of study drug												
	Serious adverse events will be collected from re-signing of the informed consent form through 30 days after the last dose of study drug												
Concomitant medications/procedures	Recorded from the first dose of study drug through 30 days after last dose of study drug												
New primary malignancy assessment	Continuous from start of study drug administration until death or termination of the study by sponsor												
Survival													X
Samples/Laboratory Assessments													
Pregnancy test (serum) [m]	X									X			
Hematology laboratory [f, n]	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry laboratory [f, n]	X			X		X	X		X	X	X	X	
Urinalysis	X												
[redacted]													
M-protein (SPEP) [f]	X			X		X	X		X	X	X	X	

Schedule of Events for Crossover Patients—Amendment 08 and Beyond

Study Procedures	**Treatment Period**									**EOT** [a]	**Follow-up** [b]		
	28-Day Cycles [b]										**PFS**	**PD**	**OS**
	Crossover Cycle Number												
Cycle	**Cycle 1**			**Cycle 2**		**Cycle 3**	**Cycles 4–5**	**Cycle 5** [c]	**Cycles 6-26**		**Every 4 Wk Until PD**	**Every 4 Wk After PD Until Next-Line Therapy**	**Every 12 Wk After PD on Next-Line Therapy**
Days	**1**	**8**	**15**	**1**	**8**	**1**	**1**	**8**	**1**				
Window	**±2 days**								**±1 Wk**	**+1 Wk**	**±1 Wk**	**±1 Wk**	**±1 Wk**
M-protein (UPEP [24-hr urine]) [f]	X			X		X	X		X	X	X	X	
SFLC assay [f]	X			X		X	X		X	X	X	X	
Immunofixation: serum and urine [f, p]	X			X		X	X		X	X	X	X	
Quantification of Ig [f, q]	X			X		X	X		X	X	X	X	
Bone marrow aspiration (BMA)													
Disease assessment BMA (local lab) [r]	Disease assessment BMA specimen is requested when patient has reduction of serum and urine M-protein consistent with possible CR or when indicated to investigate suspected PD												
Progressive disease BMA (local lab) [s]	Progressive disease BMA specimen is requested at any time of progressive disease confirmation												

Schedule of Events for Crossover Patients—Amendment 08 and Beyond

Study Procedures	Treatment Period									EOT [a]	Follow-up [b]		
	28-Day Cycles [b]										PFS	PD	OS
	Crossover Cycle Number												
Cycle	Cycle 1			Cycle 2		Cycle 3	Cycles 4–5	Cycle 5 [c]	Cycles 6-26		Every 4 Wk Until PD	Every 4 Wk After PD Until Next-Line Therapy	Every 12 Wk After PD on Next-Line Therapy
Days	1	8	15	1	8	1	1	8	1				
Window	±2 days								±1 Wk	+1 Wk	±1 Wk	±1 Wk	±1 Wk

Abbreviations: BMA=bone marrow aspirate; COVID-19: coronavirus disease 2019; CT=computed tomography; EC: ethics committee; ECG=electrocardiography; ECOG=Eastern Cooperative Oncology Group; EORTC=European Organization for Research and Treatment of Cancer; EOT=End of Treatment; [redacted]; GCP: Good Clinical Practice; [redacted]; Ig=immunoglobulins; IRB: institutional review board; IXRS: interactive voice/web response system; MRD=minimal residual disease; MRI=magnetic resonance imaging; N/A=not available; OS=overall survival; PD=progressive disease (disease progression); PET=positron emission tomography; PFS=progression-free survival, defined as time from date of first dose to PD or death from any cause; PFS2=progression-free survival 2, defined as time from date of first dose to objective disease progression on next-line treatment or death from any cause; PN=peripheral neuropathy; QLQ-C30=Quality of Life Questionnaire Core 30 (questions); [redacted] SFLC=serum free light chain; SPEP=serum protein electrophoresis; UPEP=urine protein electrophoresis.

Tests and procedures should be performed on schedule but, unless otherwise specified, occasional changes are allowable within a 2-day window during Cycles 1-5 and within a 7-day window during Cycle 6 and beyond for holidays, vacations, and other administrative reasons; a longer window is allowable after discussion with the Millennium Pharmaceuticals, Inc. (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. These windows are also permissible for study days not specified in this Schedule of Events, including Cycle 2 Day 15 and Day 8 and Day 15 of Cycle 3 and beyond.

a Before an investigator discontinues a patient from treatment for PD, the pertinent data must be confirmed by a Millennium project clinician or designee.

b For Cycle 4 and 5 and Cycle 6 through 26 procedures, all cycles are meant unless numbers are given in parentheses, indicating the specific cycles meant. For PFS and PD follow-up, exceptions to the follow-up interval of every 4 weeks are given in parentheses.

c Cycle 5 Day 8 assessments should be done only for patients who have the dose escalated after Cycle 4.

d Patients randomized to the placebo arm prior to implementation of Amendment 08 who crossover to receive ixazomib must be reconsented prior to receiving the first dose of ixazomib on Crossover Cycle 1 Day 1.

e Reconsenting should be done in person. Remote reconsenting is permitted as long as the process adheres to site, IRB/EC, and Good Clinical Practice (GCP) standards and local regulations.

f Patients must present to the study site for all visits shown in the Schedule of Events during Cycles 1-5 to ensure proper safety, efficacy, and PK monitoring. Alternative methods for administering study procedures/assessments may be considered for Cycle 6 and beyond when it is not possible for the patient to come to the study site due to the COVID-19 pandemic. Alternative methods should be considered for performing the assessments by other means than the

Schedule of Events for Crossover Patients—Amendment 08 and Beyond

Study Procedures	Treatment Period								EOT [a]	Follow-up [b]		
	28-Day Cycles [b]									PFS	PD	OS
	Crossover Cycle Number											
Cycle	Cycle 1			Cycle 2		Cycle 3	Cycles 4–5	Cycle 5 [c]	Cycles 6-26		Every 4 Wk After PD Until Next-Line Therapy	Every 12 Wk After PD on Next-Line Therapy
										Every 4 Wk Until PD		
Days	1	8	15	1	8	1	1	8	1			
Window	±2 days								±1 Wk	+1 Wk	±1 Wk	±1 Wk	±1 Wk	±1 Wk

patient presenting to the clinic (eg, remote assessment, having lab assessment performed at a facility closer to the patient's home, etc). If an in-clinic visit is not possible, the permitted alternatives are as follows. These assessments/procedures may be waived: symptom-directed physical examination, ECOG performance status, vital signs, weight, whole blood, [redacted]. These assessments/procedures may be deferred until the next in-clinic visit: SPEP, UPEP, serum free light-chain assay, immunofixation, quantification of immunoglobulins, BMA, and biopsy. These assessments/procedures may be performed locally if possible and, if not, may be deferred until the next in-clinic visit: hematology and chemistry laboratory tests.

g Patients' frailty status is classified as fit, unfit, or frail on the basis of 4 components: age, the Katz Index of Independence in Activities of Daily Living, the Lawton Instrumental Activities of Daily Living Scale, and the Charlson Comorbidity Scoring System [1-3].

h Patient-reported outcomes [redacted] should be completed before any other study procedures are performed or study drug is administered. Patient-reported outcome questionnaires are preferred to be completed by patients in the clinic, but if needed due the COVID-19 pandemic, the EORTC QLQ-C30 [redacted] questionnaires may be completed at the patient's home using paper versions of the questionnaires. At time points when a clinic visit is not required, or if needed due to the COVID-19 pandemic, [redacted].

i A skeletal survey to assess status of bone disease and extramedullary disease will be done at screening (within 8 weeks before date of first dose) for all patients. Additional assessments can be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD). At the discretion of the investigator, a CT scan, a PET-CT scan, or whole body MRI may be done at screening in place of a skeletal survey, provided that the same modality for assessment is used throughout the study.

j Upon implementation of Amendment 08, all patients will receive open-label oral ixazomib. Patients will receive ixazomib on Days 1, 8, and 15 of every 28-day cycle.

- **Patients enrolled prior to implementation of Amendment 08:** Prior to implementation of Amendment 08, 10 patients had been randomized and treated in the China Continuation. All patients continuing in the study under Amendment 08 must reconsent.
  - ***Patients still on treatment:*** Patients who were randomized to study drug (ixazomib or placebo) prior to implementation of Amendment 08 and who are still on study treatment will complete their current cycle of treatment, following the previous Schedule of Events (see Section 15.13), and be unblinded.
    - Patients who are in the placebo arm and who have not yet experienced disease progression will have the opportunity to cross over to ixazomib maintenance, based on the investigator's judgement and the patient's informed consent. Patients who cross over will follow

Schedule of Events for Crossover Patients—Amendment 08 and Beyond

Study Procedures	Treatment Period									EOT [a]	Follow-up [b]		
	28-Day Cycles [b]										PFS	PD	OS
	Crossover Cycle Number												
Cycle	Cycle 1			Cycle 2		Cycle 3	Cycles 4–5	Cycle 5 [c]	Cycles 6-26		Every 4 Wk Until PD	Every 4 Wk After PD Until Next-Line Therapy	Every 12 Wk After PD on Next-Line Therapy
Days	1	8	15	1	8	1	1	8	1				
Window	±2 days								±1 Wk	+1 Wk	±1 Wk	±1 Wk	±1 Wk

the "Schedule of Events for Crossover Patients" starting at Crossover Cycle 1 Day 1. Patients in the placebo arm who do not cross over should complete an EOT visit and discontinue the study.

- Patients who are in the ixazomib arm will continue to receive ixazomib maintenance. Patients who reconsent will follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients" according to their current cycle of treatment.

- ***Patients in the PFS Follow-up Period:*** All patients will be unblinded.
  - Patients in the placebo arm who have discontinued study treatment but who have not yet experienced disease progression or started alternative therapy have the opportunity to cross over to ixazomib maintenance. The decision to cross over is based on the investigator's judgement and the patient's informed consent. Patients who cross over will follow the "Schedule of Events for Crossover Patients" starting at Crossover Cycle 1 Day 1. Patients in the placebo arm who do not cross over will discontinue the study.
  - Patients in the ixazomib arm who reconsent should continue on study and follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients" according to the PFS Follow-up Period schedule.
- ***Patients in the PFS2 or OS Follow-up Periods:*** All patients will be unblinded.
  - Patients in the placebo arm will discontinue the study. No crossover to the ixazomib arm is permitted in these patients who have experienced primary disease progression or who have initiated alternative therapy.
  - Patients in the ixazomib arm who reconsent will continue on study and follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients" according to the OS Follow-up period schedule. Note, the PFS2 Follow-up period has been removed in Protocol Amendment 08; patients previously in PFS2 follow-up will be followed in the OS follow-up period.
- ***Patients Off Study:*** All these patients will be unblinded.

- ***Patients to be enrolled after implementation of Amendment 08:*** Approximately 20 additional patients with NDMM who responded to initial treatment will be enrolled in the China Continuation, for a total of approximately 30 patients overall. All newly enrolled patients will receive ixazomib maintenance and will follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients." For newly enrolled patients, ixazomib must be initiated within 5 days of the patient being entered into the IXRS system.

k A starting dose of 3 mg of ixazomib will be given to all patients through Cycle 4. Upon evaluation of toxicities at Cycle 4, and on the basis of the dose

Schedule of Events for Crossover Patients—Amendment 08 and Beyond

Study Procedures	Treatment Period								EOT [a]	Follow-up [b]		
	28-Day Cycles [b]									PFS	PD	OS
	Crossover Cycle Number											
Cycle	Cycle 1			Cycle 2		Cycle 3	Cycles 4–5	Cycle 5 [c]	Cycles 6-26		Every 4 Wk After PD Until Next-Line Therapy	Every 12 Wk After PD on Next-Line Therapy
										Every 4 Wk Until PD		
Days	1	8	15	1	8	1	1	8	1			
Window	±2 days								±1 Wk	+1 Wk	±1 Wk	±1 Wk	±1 Wk	±1 Wk

escalation criteria detailed in Section 6.5, the dose will be escalated to 4 mg on Cycle 5 Day 1 and administered on the same schedule for the duration of the study to provide maximum possible clinical benefit for patients who tolerated the first 4 cycles of treatment (see Section 6.5). If dose escalation was inadvertently missed at Cycle 5, escalation at a later cycle may be performed with permission from the Millennium project clinician or designee.

l When PN occurs, each subsequent monthly evaluation will record the grade of PN at that visit. (This is in contrast to other adverse events 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 the PN, 2) the start of a second-line alternative antineoplastic treatment, or 3) 6 months after PD has occurred—whichever occurs first.

m A serum pregnancy test will be performed for women of childbearing potential during screening, predose on Cycle 1 Day 1, and at the EOT visit, or more frequently as required per local regulations. The Cycle 1 Day 1 pregnancy test may be collected up to 3 days before dosing. The results must be available and negative before the study drug is administered.

n Clinical laboratory evaluations will be performed by a central laboratory (see Section 7.4.13 and the Laboratory Manual). For dosing decisions, local hematology and chemistry laboratory results may be used; however, samples must still be sent to the central laboratory also. Hematology and chemistry panels may be collected up to 3 days before Day 1 dosing and 24 hours before Day 8 and Day 15 dosing, where required. Local laboratory evaluations may be done more frequently at the investigator's discretion (ie, for acute management of treatment-emergent adverse events).

[redacted]

p Immunofixation is also to be done to confirm CR (if the M-protein level is undetectable by protein electrophoresis in both serum and urine, the central laboratory will perform immunofixation testing in both serum and urine).

q Blood samples for IgM, IgG, and IgA will be obtained throughout the study at the time points specified. Quantitative IgD and IgE measurement will be done at screening (and baseline if needed) only, except for the rare patient who has IgD or IgE multiple myeloma, for whom quantitative measurement for that antibody will be done at the same time points as, and in addition to, IgM, IgG, and IgA measurements.

r BMA with local assessment should be performed if the patient has reduction of serum and urine M-protein consistent with possible CR or when indicated to investigate suspected PD.

s An additional BMA for patients who have PD is optional but highly recommended and should be collected at any time PD is suspected or before starting a new therapy. This marrow will be evaluated locally.

IXAZOMIB PHARMACOKINETIC SAMPLING SCHEDULE

Upon implementation of Amendment 08, PK sampling will be performed only for patients receiving ixazomib.

- Patients who were randomized to ixazomib prior to implementation of Amendment 08 and who are still on study treatment will continue to follow this PK sampling schedule according to their current cycle of treatment.
- Patients who were randomized to placebo prior to implementation of Amendment 08 and who cross over to the ixazomib arm after their current cycle will follow this PK sampling schedule starting at Crossover Cycle 1 Day 1 (first dose of ixazomib after crossover).
- Patients who enroll after implementation of Amendment 08 will follow this PK sampling schedule starting at Cycle 1 Day 1 (first dose of ixazomib).

Cycle 1				Cycle 2		Cycles 3-5	Cycle 5 [a]	Cycles 6-10
Day 1		Day 8	Day 15	Day 1	Day 8	Day 1	Day 8	Day 1
1 Hour Postdose (± 15 Minutes)	4 Hours Postdose (± 45 Minutes)	Predose [b]	Predose [b]	Predose [b]	Predose [b]	Predose [b]	Predose [b]	Predose [b]
X	X	X	X	X	X	X	X	X

a The Cycle 5 Day 8 sample should be obtained only for patients who have dose escalated after Cycle 4.

b All predose pharmacokinetic 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.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
AE	adverse event
AL amyloidosis	(amyloid) light-chain amyloidosis
ANC	absolute neutrophil count
ASCT	autologous stem cell transplantation
AUC	area under the curve
BCRP	breast cancer resistance protein
best response	the best response to initial therapy maintained for 2 cycles after the M-protein nadir is reached (enrollment criterion for this study)
BMA	bone marrow aspirate
CDE	Center for Drug Evaluation
C_{max}	maximum observed concentration
COVID-19	coronavirus disease 2019
CR	complete response
CT	computed tomography
CYP	cytochrome P450
DDI	drug-drug interaction
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
[redacted]	[redacted]
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOT	End of Treatment (visit)
[redacted]	[redacted]
ESMO	European Society for Medical Oncology
FA	final analysis
FIRST	Study to Determine Efficacy and Safety of Lenalidomide Plus Low-dose Dexamethasone Versus Melphalan, Prednisone, Thalidomide in Patients With Previously Untreated Multiple Myeloma
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GI	gastrointestinal

Abbreviation	Term
GIMEMA	Italian Group for Hematologic Diseases in Adults
HRQL	health-related quality of life
[redacted]	[redacted]
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IMiD	immunomodulatory drugs
IMWG	International Myeloma Working Group
IRB	institutional review board
IRC	independent review committee
ISS	International Staging System
ITT	intent-to-treat
IV	intravenous(ly)
IXRS	interactive voice/web response system
K-M	Kaplan-Meier
len/dex	lenalidomide and dexamethasone
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MP	melphalan and prednisone
MPT	melphalan/prednisone/thalidomide
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRP2	multidrug resistance–associated protein
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDMM	newly diagnosed multiple myeloma
NGS	next generation sequencing
NMPA	National Medical Products Administration
[redacted]	[redacted]
OS	overall survival
PAD	bortezomib, Adriamycin, and dexamethasone

Abbreviation	Term
PD	progressive disease (disease progression)
PET	positron emission tomography
PFS	progression-free survival, defined as the time from date of first dose to progressive disease or death from any cause
PFS2	progression-free survival 2, defined as the time from date of first dose to objective disease progression on next-line treatment or death from any cause
Pgp	P-glycoprotein
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PN	peripheral neuropathy
PR	partial response
Rd	Revlimid (lenalidomide) and dexamethasone
RP2D	recommended phase 2 dose
RRMM	relapsed and/or refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
SCT	stem-cell transplantation
SD	stable disease
SDV	source data verification
Millennium	Millennium Pharmaceuticals, Inc.
TEAE	treatment-emergent adverse event
TTNT	time to next line therapy
TTP	time to progression
ULN	upper limit of the normal range
US	United States
VGPR	very good partial response
[redacted]	[redacted]

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

Multiple myeloma (MM) is a B-cell tumor of malignant plasma cells within the bone marrow, which accumulate in the bone marrow and result in bone marrow failure, bone destruction, hypercalcemia, and renal failure. Multiple myeloma constitutes approximately 1% of all reported neoplasms and approximately 13% of hematologic cancers worldwide [4]. In the Americas and Western European countries, approximately 5 to 7 new cases of MM are diagnosed per 100,000 people each year [4-6]. Although less common in Asian countries, incidences of MM there have increased almost 4-fold in the past 25 years and are characterized by younger age of onset, more invasive disease, and a less favorable prognosis [7,8].

Information on cancer incidence in China is rather sparse, with population-based cancer registries covering only a small proportion of the total population [9]. The estimated age-specific MM incidence rates per 100,000 people in China in 2005 are as follows for men versus women, respectively: 45 to 54 years, 1.2 vs. 0.5; 55 to 64 years, 1.7 vs. 1.1; 65 to 74 years, 3.1 vs. 2.4; and 75 years or older, 2.9 vs. 1.1 [9]. The GLOBOCAN 2012 age-standardized incidence of MM in China is 0.6/100,000 people. The 5-year prevalence of MM in China is 1.5/100,000 men and 1.0/100,000 women [10]. Death from MM accounts for 0.4% of deaths from cancer in China, and the age-standardized death rate from MM is 0.5/100,000 deaths [10].

Multiple myeloma is sensitive to many cytotoxic drugs, including alkylating agents, anthracyclines, and corticosteroids, for both initial treatment and relapsed disease. Over the past 2 decades, significant achievements have been made in expanding treatment options for MM with novel therapies such as thalidomide, bortezomib, and lenalidomide and stem cell transplantation (SCT). These regimens have extended progression-free survival (PFS) and time to progression (TTP) [11-15].

Although autologous SCT has been shown to be associated with improved survival, historically this therapy has been limited to the younger (< 65 years) MM population (because the risk of morbidity/mortality increases with increasing age) or those without significant comorbidities. However, as a result of improvements in SCT procedures and supportive care, and the recognition that some elderly patients are sufficiently vigorous to

tolerate autologous SCT, it is increasingly common to provide autologous SCT to patients 65 years of age or older. Nonetheless, because of the advanced age of MM patients (in the United States [US], the median age at diagnosis is 69 years), or because of significant comorbidities, the majority of patients are not considered candidates for autologous SCT and therefore do not benefit from the survival-prolonging transplant.

Despite advances in therapy and the advent of a newer generation of agents such as carfilzomib and pomalidomide, in almost all circumstances, this disease remains incurable, and there remains a need for new and better agents. When patients relapse after their initial therapy, they demonstrate variable responses to subsequent treatments with decreasing likelihood and duration of response. The disease ultimately becomes refractory to approved therapies, leaving patients with no alternative treatment options. In an effort to expand the therapeutic armamentarium against MM with agents that target the proteasome, Millennium Pharmaceuticals, Inc. (Millennium) has developed ixazomib, a small molecule 20S proteasome inhibitor.

1.1.2 Ixazomib: Millennium's Next-Generation Proteasome Inhibitor

The proteasome was validated as an effective oncology target with the clinical success of intravenous (IV) and subcutaneous VELCADE® (bortezomib) for Injection, the first-in-class, small molecule proteasome inhibitor developed by Millennium. Building on the efficacy seen with bortezomib in MM and other hematologic malignancies, Millennium has subsequently developed oral ixazomib to improve the pharmacology of the agent and provide a more convenient mode of drug administration.

Like VELCADE, ixazomib is a modified peptide boronic acid; specifically, ixazomib citrate is the citrate ester of the biologically active dipeptide boronic acid, ixazomib. Formulated to improve the chemical properties of ixazomib for clinical delivery, in physiological conditions, ixazomib citrate rapidly hydrolyzes to ixazomib, the active form that potently, reversibly, and selectively inhibits the proteasome. Ixazomib preferentially binds the β5 site of the 20S proteasome, similar to VELCADE; at higher concentrations, ixazomib also inhibits the activity of the β1 and β2 sites. Ixazomib demonstrates a faster dissociation rate from the proteasome than VELCADE, which may result in enhanced tumor penetration. Ixazomib exhibits antitumor activity in a broader range of tumor xenografts than VELCADE.

1.2 Nonclinical Experience

Detailed information regarding the nonclinical pharmacology, absorption, distribution, metabolism, excretion, pharmacokinetics (PK), and toxicology of ixazomib may be found in the Investigator's Brochure (IB).

1.3 Clinical Experience

Ixazomib is the first oral proteasome inhibitor in clinical trials and is under evaluation for safety, tolerability, PK, pharmacodynamics, and efficacy. The clinical benefit of ixazomib continues to be studied in a comprehensive and global development plan that involves multiple company-sponsored clinical studies in several indications.

Although 2 studies of IV ixazomib have been performed, the rest of the studies of ixazomib have used the oral formulation, which is the formulation planned for commercialization. Throughout this section and the remainder of this protocol, the ixazomib formulation described will be the oral formulation.

As of 27 March 2014, 1287 patients have been enrolled in clinical trials of oral ixazomib and have safety data. A total of 491 patients have received ixazomib in open-label, phase 1/2 studies, and 796 patients have been treated in the phase 3, pivotal studies (with ixazomib or placebo in Study C16010 in relapsed/refractory multiple myeloma [RRMM] and Study C16014 in newly diagnosed multiple myeloma [NDMM], and counting the ixazomib arm only in Study C16011 in light chain [AL] amyloidosis).

1.3.1 Ongoing Studies of Ixazomib

Eighteen clinical studies of ixazomib are ongoing, including the 4 pivotal, phase 3 studies. To date, the development of ixazomib has focused on MM (RRMM and NDMM), with additional trials in a different yet related orphan disease, AL amyloidosis. These indications are currently being studied in ongoing, phase 3 clinical studies. Additionally, multiple research paths are being considered or are advancing to evaluate this drug across a number of treatment settings, in combination with commonly used agents, and in other therapeutic areas in oncology (solid tumors, lymphomas) and non-oncology (lupus nephritis). The strategy for later-stage development of ixazomib in solid tumors and advanced lymphomas will be influenced by the antitumor activity and pharmacodynamic response observed during phase 1 development of ixazomib and other VELCADE lymphoma studies. Patient selection strategies may also be explored to maximize the efficacy of ixazomib in selected patient populations.

The primary focus of each of the phase 1 clinical studies was the characterization of the safety and tolerability of the oral formulation of the drug, determination of the maximum tolerated dose (MTD) and a recommended phase 2 dose (RP2D), and establishment of the PK and pharmacodynamic properties. The ongoing clinical studies are exploring twice-weekly dosing in a 21-day cycle and weekly dosing in a 28-day cycle.

Three studies (C16003, C16004, and C16007) included specific expansion cohorts to further evaluate antitumor activity and safety at the MTD/RP2D. The expansion cohorts in the 2 MM studies (C16003 and C16004) were conducted in patients with RRMM who represent the highly heterogeneous population seen in current clinical practice in an attempt to understand the possible activity of ixazomib in patients with MM that have been previously exposed to several lines of agents, including agents also targeting the proteasome. The expansion phase in the AL amyloidosis study (C16007) was open to cohorts of patients who were either naïve to, or had been previously exposed to, proteasome inhibitors to better understand activity and safety. Two phase 1 studies are exploring the PK and safety of ixazomib in patients with RRMM in Asia (Study C16013, a PK study of ixazomib in combination with lenalidomide/dexamethasone [len/dex] after 1-3 prior lines of therapy) and Japan (Study TB-MC010034, 2 cohorts, of ixazomib single agent and in combination with len/dex).

Three of the clinical studies in frontline MM (Studies C16005, C16006, and C16008) were designed with a phase 2 portion to explore relevant combinations with ixazomib such as len/dex or melphalan and prednisone (MP); the main purposes of the phase 2 portions of these studies are to characterize preliminary efficacy and safety profiles. The phase 2 portions also explore quality of life, the documentation of minimal residual disease (MRD) in patients with a complete response (CR), and response in the subset of high-risk patients as determined by cytogenetics.

Another phase 2 study is C16020, an open-label study of ixazomib, cyclophosphamide, and dexamethasone in adult patients with NDMM or RRMM requiring systemic treatment; the patients with NDMM must be treatment naïve and must not have undergone high-dose therapy followed by SCT because of age (≥ 65 years) or comorbidities (or they have declined for other reasons). The primary objective of this study is combined response rate. It is anticipated that approximately 70 patients will enroll in more than 20 sites worldwide.

Four phase 3, randomized, controlled, multicenter studies are ongoing:

- Study C16010 is a placebo-controlled, double-blind study in which ixazomib is used in combination with len/dex in patients with RRMM who are enrolled in the treatment arm of the study. The study is being conducted at approximately 150 sites worldwide with an anticipated enrollment of approximately 703 patients. The primary endpoint is PFS.

- Study C16011 is an open-label, safety and efficacy study of dexamethasone plus ixazomib versus physician's choice of a currently available treatment regimen administered to patients with relapsed or refractory AL amyloidosis. The study is being conducted at approximately 65 sites worldwide with an anticipated enrollment of approximately 248 patients. There are 2 primary objectives in this study: hematologic response (partial response [PR] + very good partial response [VGPR] + CR) and 2-year rate of vital organ deterioration or death.

- Study C16014 is a double-blind study of len/dex plus ixazomib or placebo in patients with NDMM who are treatment naïve and who have not undergone high-dose therapy followed by SCT because of age (≥ 65 years) or comorbidities (or they have declined for other reasons). The primary objective of this study is PFS. This study is being conducted at 155 sites worldwide with anticipated enrollment of approximately 701 patients.

- Study C16019 is a phase 3, randomized, placebo-controlled, double-blind study in adult patients with NDMM who have had a major response (PR or better) to standard-of-care induction therapy followed by autologous SCT. The primary endpoint of this study is PFS, with overall survival (OS) as the key secondary endpoint. The study is being conducted at more than 200 sites worldwide with an anticipated enrollment of approximately 652 patients.

All 4 studies also explore the impact of treatment on quality of life.

To further investigate the clinical pharmacology of ixazomib, 4 additional phase 1 clinical pharmacology studies are ongoing, 2 in special populations. Study C16009 was a 5-arm study designed to assess drug-drug interactions (cytochrome P450 [CYP] 3A strong inducers and inhibitors), food effect, and relative bioavailability (and safety and tolerability). This study was conducted in patients with advanced nonhematologic malignancy or lymphoma for which no effective standard treatment is available. Study C16016 is a study of

absorption, distribution, metabolism, and excretion in patients with advanced solid tumors or lymphoma. The study is designed to assess mass balance, PK, total radioactivity, metabolism, and elimination. The 2 clinical pharmacology studies in special populations aim specifically to evaluate the effects of severe renal impairment/end-stage renal disease necessitating dialysis (C16015) or moderate/severe hepatic impairment (C16018) on the PK of ixazomib in patients with cancer. These studies have been designed with the overall strategic objective of providing PK data to inform development of scientifically guided ixazomib dosing guidelines for physicians treating these special patient populations.

The current Study C16021 is the fifth global, phase 3 trial of ixazomib and the second exploring single-agent ixazomib in a maintenance setting.

1.3.2 Overall Clinical Experience

Clinical safety data include experience from patients who received multiple ixazomib treatment cycles followed by treatment-free periods and from patients who reduced or discontinued treatment. The emerging safety profile indicates that the adverse events (AEs) associated with ixazomib administration are generally manageable and reversible with dose modification and supportive care. Although some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention. The weekly schedule that will be evaluated in this trial has been determined to be tolerable in other trials of ixazomib in MM.

Ixazomib shows early signs of antitumor activity, as evidenced by at least a 50% reduction in disease burden in some MM patients, including patients who have been heavily pretreated and those who have been newly diagnosed with MM, and prolongs stabilization of the underlying disease in others, across all ongoing trials. The preliminary findings are favorable when considering historical and currently available therapies for the patient populations evaluated. Though additional data are needed to characterize the clinical benefit of this drug, the emerging data support expanded development of ixazomib for the treatment of patients with advanced malignancy. Weekly dosing appears to enable delivery of higher ixazomib doses for a longer period of time as compared with twice-weekly dosing.

As of 27 March 2014, the most common treatment-emergent AEs (TEAEs) in the Overall Safety population receiving ixazomib are shown in Table 1.a.

Table 1.a Most Common Treatment-Emergent Adverse Events in Ixazomib Studies, as of 27 March 2014

Treatment-Emergent Adverse Event	Overall Safety Population (n=1287)	Phase 1 or 2 (n=491)[a]			Phase 3 Studies (n=796)[b]		
		All	Single Agent (n=221)	Combination Agent (n=220)	C16010 (Ixazomib or Placebo) n=683	C16011 (Ixazomib Arm) n=21	C16014 (Ixazomib or Placebo) n=92
	Number (%) of Patients						
Diarrhea	423 (33)	230 (47)	95 (43)	116 (53)	179 (26)	2 (10)	12 (13)
Nausea	379 (29)	230 (47)	117 (53)	93 (42)	128 (19)	1 (5)	20 (22)
Fatigue	395 (31)	223 (45)	114 (52)	99 (45)	152 (22)	4 (19)	16 (17)
Rash (all rash terms)[c]	349 (27)	197 (40)	73 (33)	117 (53)	126 (18)	3 (14)	23 (25)
Constipation	324 (25)	134 (27)	50 (23)	76 (35)	164 (24)	3 (14)	23 (25)
Vomiting	277 (29)	181 (37)	90 (41)	73 (33)	80 (12)	2 (10)	14 (15)
Anemia	262 (20)	161 (33)	72 (33)	78 (35)	92 (13)	2 (10)	5 (5)
Thrombocytopenia	260 (20)	114 (23)	48 (22)	57 (26)	129 (19)	0	19 (21)

a For phase 1 or 2 studies, single agent studies consist of C16003, C16004, C16007, and C16009; combination studies consist of C16005, C16006, C16008, C16013, and C16020; and "all" consists of single agent and combination studies and C16015, C16017, C16018, and TB_MC010034.

b For phase 3 studies, in C16010 and C16014, all patients also receive lenalidomide and dexamethasone; in C16011, ixazomib patients also receive dexamethasone.

c There is some variety in the characterization and causality of reported rash, resulting in different Preferred Terms to describe it; the data here refer to all rash Preferred Terms. Not included here are cases classified as pruritus, erythemas, papulosquamous conditions, or exfoliative conditions. When these other terms are included, rash is generally reported in approximately 50% of patients in combination trials and is more common when ixazomib is given in combination with lenalidomide, where rash is an overlapping toxicity.

The dose escalation phases of most trials reported in the IB have now completed enrollment, and gastrointestinal (GI) symptoms were found to be the common dose-limiting toxicities when the use of prophylactic anti-emetics was not permitted per protocol. In the expansion cohorts or phase 2 cohorts (per each study), the incidence and severity of GI symptoms is expected to be mitigated by the use of the RP2D, the ixazomib dose that was 1 dose level lower than the MTD (per each study), and standard clinical use of anti-emetics and antidiarrheal medications as deemed appropriate. Prophylactic anti-emetics have not been required as with other agents but (as outlined in Section 6.9) have been used according to standard practice and are effective.

Additional detailed information regarding the clinical experience of ixazomib may be found in the IB.

1.3.3 Pharmacokinetics and Drug Metabolism

Clinical PK data show that ixazomib has multi-exponential disposition with a rapid initial phase that is largely over by 4 hours. Ixazomib is rapidly absorbed with a median single-dose first time of occurrence of maximum (peak) ixazomib concentration of approximately 0.5 to 2.0 hours and a terminal disposition half-life after multiple dosing of approximately 5 to 7 days [16]. Results of a population PK analysis (N=137) show that there is no relationship between body surface area or body weight and clearance. Also, on the basis of stochastic simulations for fixed dose, exposures are independent of the individual patient's body surface area [17]. On the basis of these data, a recommendation was made for fixed dosing in clinical trials. Also, an absolute bioavailability of 67% was determined for ixazomib using the population PK analysis.

Metabolism appears to be the major route of elimination for ixazomib, and urinary excretion of the parent drug is negligible (< 5% of dose). In vitro studies indicate that ixazomib is metabolized by multiple CYPs and non-CYP enzymes/proteins. At clinically relevant concentrations of ixazomib, in vitro studies using human cDNA-expressed CYP isozymes showed that no specific CYP isozyme predominantly contributes to ixazomib clearance. At concentrations exceeding those observed clinically (10 µM), ixazomib was metabolized by multiple CYP isoforms with estimated relative contributions of 3A4 (42.3%), 1A2 (26.1%), 2B6 (16.0%), 2C8 (6.0%), 2D6 (4.8%), 2C19 (4.8%) and 2C9 (<1%). In contrast, at 0.1 µM and 0.5 µM substrate concentrations, which are closer to clinical concentrations of ixazomib following oral administration of 4 mg ixazomib, non-CYP–mediated clearance was observed and seemed to play a major role in ixazomib clearance in vitro. These data indicate that at clinically relevant concentrations of ixazomib, minimal CYP-mediated drug-drug interactions (DDIs) with a selective CYP inhibitor would be expected. In addition, ixazomib is neither a reversible nor a time-dependent inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5.

In a recently concluded, phase 1 DDI study, the PK of ixazomib (maximum observed concentration [C_{max}] and $AUC_{0\text{-}last}$) was similar with and without co-administration of clarithromycin, a strong CYP3A inhibitor (Study C16009, Arm 5) [18]; hence, no dose adjustment is necessary when ixazomib is administered with strong CYP3A inhibitors. These findings are explained by the in vitro metabolism data indicating the lack of a discernible contribution of CYP-mediated metabolism at clinically relevant ixazomib concentrations. As discussed earlier, no CYP isoforms have been identified to contribute meaningfully to ixazomib metabolism at clinically relevant concentrations, and CYP3A

contribution to total metabolism was highest across all CYP isoforms when characterized at a supratherapeutic concentration of 10 µM. Therefore, based on the totality of information from the clinical clarithromycin DDI study and the in vitro CYP phenotyping data, it can be concluded that ixazomib PK is not likely to be altered upon co-administration with any CYP isoform-selective inhibitor, including strong CYP1A2 inhibitors. Consistently in the population PK analysis, co-administration of strong CYP1A2 inhibitors did not affect ixazomib clearance. Therefore, no dose adjustment is required for patients receiving strong inhibitors of CYP1A2. Ixazomib may be a weak affinity substrate of Pgp but not of breast cancer resistance protein (BCRP) or multidrug resistance associated protein (MRP2) efflux pump transporters. Ixazomib is not an inhibitor of Pgp, BCRP, or MRP2. The potential for DDIs with substrates or inhibitors of Pgp, BCRP, and MRP2 is, therefore, inferred to be low.

In a recently completed DDI study, co-administration of ixazomib with rifampin decreased ixazomib C_{max} by 54% and area under the curve (AUC) by 74% (Study C16009, Arm 4).[18] Accordingly, concomitant administration of ixazomib with strong CYP3A inducers should be avoided.

Additional details on the PK and drug metabolism of ixazomib are provided in the IB.

1.4 Study Rationale

1.4.1 Rationale for Investigating Maintenance Therapy in Multiple Myeloma

Multiple myeloma is generally considered an incurable disease. Nonetheless, high-dose chemotherapy incorporating autologous SCT has been found to prolong PFS and OS in patients who are sufficiently fit to undergo the procedure. Although the introduction of modern agents, including immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) such as thalidomide, VELCADE, lenalidomide, carfilzomib, and pomalidomide, has improved the survival of both patients who do and those who do not undergo SCT, OS among patients not receiving SCT remains inferior to OS among patients receiving SCT. For the former population, additional treatment strategies beyond initial therapy will be needed to improve survival.

Maintenance therapy is a long-duration, low-intensity therapy intended to prolong the duration of a patient's response to primary antineoplastic treatment. Requirements for a successful maintenance therapy include good long-term tolerability and adherence (low discontinuation rates due to toxicity and convenience of administration), demonstration of

clinical benefit either in prolonging PFS or OS or improving quality of life without shortening survival, and a favorable benefit:risk ratio.

1.4.1.1 History of Maintenance Therapy in Multiple Myeloma

The role of maintenance therapy in both the post-SCT and non-SCT settings has been extensively explored, but a positive benefit:risk profile has yet to be confirmed for maintenance therapy.

Older Agents

A detailed review of the history of the clinical trials of maintenance therapy was published in 2012 by the International Myeloma Working Group (IMWG) [19]. Initially, trials of maintenance therapy consisted of continuation of chemotherapy with MP following successful remission induction (1975-1988). Although remission periods were prolonged, there was no survival benefit observed in these studies, and maintenance with MP was not pursued further. Maintenance using interferon (1980-2000) demonstrated an improved duration of remission and OS by approximately 6 months each; however, the highly toxic therapy was not pursued after the development of modern therapies because of the unfavorable safety profile. The IMiD thalidomide has been extensively studied as a single agent or in combination maintenance therapy in both patients undergoing and those not undergoing SCT. A progression-free survival benefit was generally observed across studies. Overall survival benefits were observed in some studies [20], whereas a decrement in OS was observed in others [21]. High rates of discontinuation due to toxicity were observed in all studies. In addition, patients with high-risk cytogenetics had no incremental benefit with thalidomide maintenance therapy [22,23], and in 1 study, patients experienced a decrement in benefit [23].

Newer Agents

Newer agents have demonstrated a more favorable safety profile while achieving depth of response in the maintenance setting (eg, the number of patients who improved their response from what was achieved during induction). Several studies with VELCADE have been conducted, both as part of a combination maintenance regimen and in direct comparison with thalidomide [24-26]. In the GIMEMA (Italian Group for Hematologic Diseases in Adults) trial, maintenance with bortezomib and thalidomide (after bortezomib/melphalan/prednisone/thalidomide induction) showed both PFS and OS benefit over bortezomib/melphalan/prednisone induction with no maintenance therapy [24].

The phase 3 HOVON/GMMG study investigated induction therapy leading to autologous SCT and subsequent maintenance therapy in patients with MM [25]. Induction therapy with the regimen of bortezomib, Adriamycin, and dexamethasone (PAD), followed by bortezomib maintenance was evaluated and compared with induction therapy using vincristine, Adriamycin, and dexamethasone followed by thalidomide maintenance. Improvement was observed in responses in the PAD + bortezomib arm during the maintenance period. In addition, an incremental benefit was observed in high-risk cytogenetic patients with del17p13. However, the induction regimens in the 2 arms were different such that only the bortezomib maintenance arm received bortezomib during induction therapy, so the benefit of bortezomib as maintenance alone could not be independently assessed.

Additionally, lenalidomide has been assessed as maintenance therapy in 3 placebo-controlled trials [27-29]. While all studies demonstrated a significant PFS advantage with lenalidomide maintenance therapy, only the Cancer and Leukemia Group B trial showed a possible OS benefit, and data regarding the impact of lenalidomide maintenance on the duration of response to subsequent therapy were limited [28]. In addition, offsetting the potential clinical benefit of lenalidomide maintenance was the increased incidence of new primary malignancies. Therefore, positive benefit:risk could not be established during the Committee for Medicinal Products for Human Use review to date [30]. To understand whether ixazomib maintenance therapy affects the incidence of new primary malignancies, the proposed trial includes a secondary endpoint assessing the incidence of new primary malignancies.

Recent Findings

In 2013, the results of the phase 3 MM-020 study (Study to Determine Efficacy and Safety of Lenalidomide Plus Low-dose Dexamethasone Versus Melphalan, Prednisone, Thalidomide in Patients With Previously Untreated Multiple Myeloma [FIRST]) were reported at the American Society of Hematology annual meeting. This study supports the concept of maintenance therapy. “Continuous” Revlimid and dexamethasone (Rd) was compared with fixed-duration Rd (for 18 cycles, or ~18 months) and fixed-duration melphalan/prednisone/thalidomide (MPT; for 12 cycles, or ~18 months). Continuous Rd showed improved PFS compared with fixed-duration Rd and MPT. In addition, there was rapid increase in PFS events after Rd maintenance therapy (both continuous and fixed duration) was stopped. Overall survival, however, was not statistically different among the arms; therefore, the clinical benefit of continuous therapy was not established, and the

option of no maintenance followed by salvage therapy at relapse remains an alternative. Because the study did not compare continuous MPT with continuous Rd, it cannot be determined whether the apparent PFS advantage of continuous Rd is a phenomenon unique to lenalidomide-based therapy or whether continuous therapy is beneficial with other treatment choices.

1.4.1.2 Current Use of Maintenance Therapy in Multiple Myeloma

The use of maintenance therapy in clinical practice in the non-ASCT setting remains limited globally, with no universally accepted standard of care regarding maintenance therapy in non-SCT patients with NDMM. CancerMPact® surveys conducted by Kantar Health in 2012 [31,32] found that maintenance therapy was administered to less than half of patients not undergoing SCT in most regions (Western European Union, 39.1%; US, 49.9%, Japan, 45.2%; and China, 74.9%). This is most likely due to the lack of an evidence-based positive benefit:risk profile for drugs in the maintenance setting. Lenalidomide was approved by the United States (US) Food and Drug Administration for post-ASCT maintenance therapy in 2017.

1.4.1.3 Current Guidance for Maintenance Therapy in Multiple Myeloma

To date, no maintenance therapy has received regulatory approval for use in patients with MM in the non-autologous stem cell transplantation (ASCT) setting [19], and a true standard of care has not been adopted. Current US National Comprehensive Cancer Network guidelines (version 2.2014) [33] support the use of VELCADE, lenalidomide, and thalidomide maintenance therapies while also highlighting concerns regarding cumulative toxicity with thalidomide therapy and an increased incidence of new primary malignancies with lenalidomide; VELCADE maintenance was described as being well tolerated. In contrast, current IMWG guidelines for non-SCT patients with NDMM [34] and European Society for Medical Oncology (ESMO) guidelines for the treatment of MM [35] do not recommend the routine use of maintenance therapy. The 2014 IMWG consensus statement for the management, treatment, and supportive care of patients with MM not eligible for standard autologous SCT states, “The routine use of maintenance in transplantation-ineligible patients is not yet validated” [36]. The guidelines also point out that the role of other novel agents in this setting is currently under evaluation. The ESMO 2013 guidelines for the treatment of MM [35] state that for patients not undergoing SCT, “systematic maintenance therapy is [also] not recommended in elderly patients.”

In conclusion, maintenance therapy has not yet been proven to be a superior treatment strategy compared with the current paradigm of salvage therapy at relapse. Together with the lack of a universally accepted maintenance standard of care with a demonstrated survival benefit for maintenance therapy, there is justification to conclude that a phase 3, placebo-controlled trial is an appropriate approach for determining the efficacy of single-agent ixazomib maintenance therapy in the MM population not receiving SCT.

1.4.2 Rationale for Placebo Control as the Original Study Design

At the time the C16021 global study was initiated, maintenance therapy had not yet been proven to be a superior treatment strategy in patients not undergoing SCT compared with the current paradigm of salvage therapy at relapse. The lack of a universal maintenance standard of care and an evidence-based comparator with a demonstrated survival benefit for maintenance therapy in patients not undergoing SCT, together with the inclusion of optimal palliative care for all study participants and the availability of second-line therapy to all study participants after withdrawal from the study for any reason, provided a strong justification to run this placebo-controlled trial to determine the efficacy and safety of single-agent ixazomib maintenance therapy.

1.4.3 Rationale for Removal of Placebo Control

Over the past 6 years, as of the initiation of the C16021 global study, maintenance therapy has become more widely utilized. Additionally, the first interim analysis (IA) of the C16021 global study was conducted (data cut-off date 12 August 2019) and the primary endpoint of PFS was found to be both statistically significant and clinically meaningful. No new safety concerns were found in patients receiving ixazomib. Given the positive results from the C16021 global study and the fact that the C16021 China Continuation is still open to enrollment, the sponsor does not believe it is appropriate to continue enrolling patients into a randomized, placebo-controlled maintenance study. The Center for Drug Evaluation (CDE) National Medical Products Administration (NMPA) acknowledged that it will be difficult to continue enrolling patients into the placebo arm of the C16021 China Continuation. The CDE suggested that the sponsor amend the study into a single arm study, so as to collect more efficacy and safety data from Chinese patients receiving ixazomib.

This amendment describes modifications to the China Continuation study procedures specifically for patients who are still on treatment, who are in one of the follow-up periods, or who will be enrolled after this amendment takes effect.

1.4.4 Rationale for Ixazomib Schedule and Dose

Ixazomib will be administered at a once-weekly dose of 3 mg and, if tolerated well after 4 cycles (see Section 6.5), the dose will be increased to 4 mg to provide the maximum clinical benefit possible. The duration of maintenance therapy will be 24 months or until PD or unacceptable toxicity (whichever occurs first). Please see Section 1.4.4.1 and Section 1.4.4.2 below for the rationale for the schedule and dose, respectively.

1.4.4.1 Schedule Rationale

The balance of benefit and risk is paramount in this maintenance study. The study will administer ixazomib on a weekly dosing schedule, consistent with the other ixazomib pivotal trials.

A 24-month duration of therapy was chosen for the proposed study. Although the optimal duration of maintenance therapy in MM is not yet established, clinical experience with the PI VELCADE has found that a 2-year, fixed-duration maintenance regimen yielded good clinical benefit in both the HOVON-65/GMMG-HD4 trial in the post-SCT setting [25] and the GIMEMA trial in the non-SCT setting [24]. In the former study, 1 of the 2 arms included a 2-year maintenance therapy period with VELCADE after VELCADE-containing initial therapy and autologous SCT. Significant PFS and OS advantages were seen in this arm compared with the alternative arm, which included 2 years of thalidomide maintenance following a non-PI-containing initial therapy and autologous SCT. In the GIMEMA study, maintenance with VELCADE and thalidomide for 24 months showed a PFS and OS benefit over no maintenance therapy. Because ixazomib is a boron-based proteasome inhibitor similar to VELCADE (having a similar site of action on the proteasome), these studies suggest that 24 months of maintenance therapy is an acceptable duration for an ixazomib trial, particularly one with a focus on balancing long-term tolerability of maintenance therapy, good clinical response, and risk of toxicity.

There are several potential reasons why a finite therapy duration is preferred over a treat-to-progression approach for maintenance therapy in patients with NDMM who do not receive SCT. The potential of maintenance therapy with a PI to prolong or deepen a patient's response is anticipated to occur within the first 2 years of maintenance therapy, based on results of the GIMEMA trial [24]. With the goal of providing clinical benefit to the patient at a favorable benefit:risk ratio, a finite duration of therapy limits the period of time that a patient will be exposed to the toxicities of the drug. In addition, there is currently no evidence that continued treatment to progression derives any further clinical benefit.

Moreover, patients have the chance of experiencing a treatment-free interval if their disease has not progressed after the 24 months of maintenance therapy. The potential for patients to develop treatment-resistant disease on prolonged therapy additionally supports a finite treatment duration of 24 months—an important consideration for this newly diagnosed population who will inevitably experience relapse as part of the natural course of their disease [37].

1.4.4.2 Dose Rationale

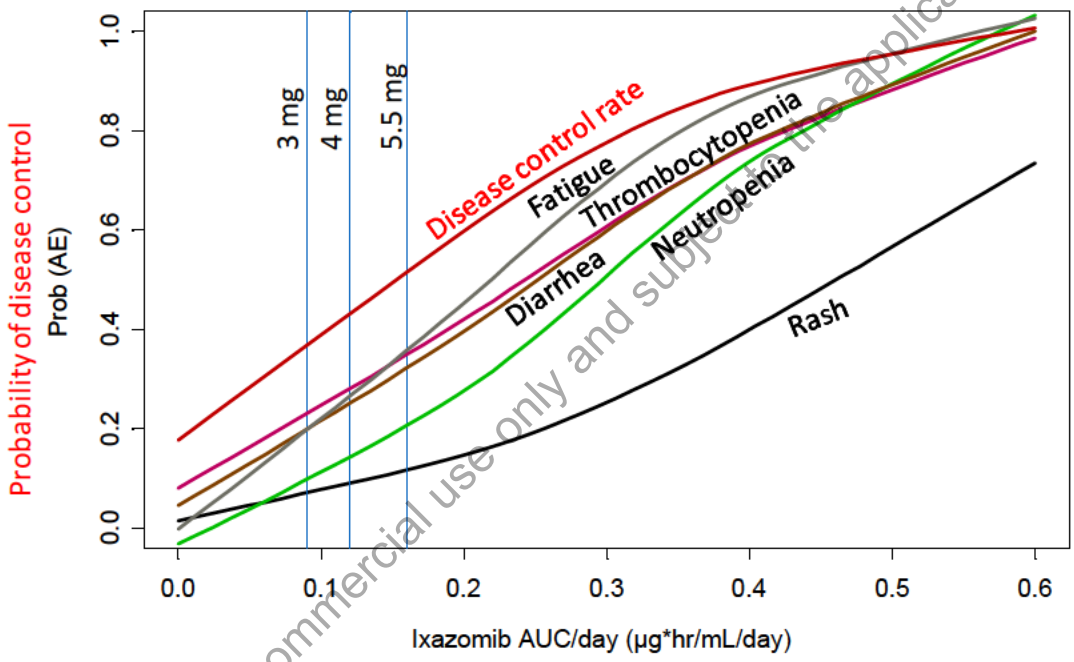
Considering that clinical experience with ixazomib has predominantly been in the RRMM setting, dose selection for this C16021 maintenance treatment trial was guided by exposure-response analyses of safety and efficacy data from the relapsed patient population. These analyses were designed to yield initial estimates of a biologically active exposure/dose range of ixazomib associated with disease control and acceptable tolerability. The overall objective was to use these results to select a dosing scheme that would ensure adequate tolerability for long-term treatment while maintaining drug exposures in the biologically active range (ie, those associated with disease control in the relapsed setting where growth arrest/stable disease [SD] is a relevant indicator of biological activity).

To determine an appropriate maintenance dose for this trial, safety and efficacy data from Study C16004, a phase 1/2 study of single-agent ixazomib dosed weekly (similar to this C16021 phase 3 study) in RRMM patients, were used in a preliminary exposure-response (safety/efficacy) analysis. All available data from patients with both PK and safety/efficacy information (N=44) were included in the analysis. Data were available over a wide dose range (0.5-3.95 mg/m^2), corresponding to a fixed-dose range of approximately 1 to 8.9 mg. The metric of exposure was the area under the plasma concentration versus time curve per day (derived from individual clearance values on the basis of population PK) for both the exposure/safety analysis and the exposure/efficacy analysis.

For the safety analysis, 7 commonly occurring toxicities were evaluated, both hematologic (anemia, thrombocytopenia, and neutropenia) and nonhematologic (fatigue, rash, peripheral neuropathy [PN], and diarrhea). The highest grade of toxicity over the treatment duration was used for each patient in the logistic regression analysis. The nonhematologic AE data were categorized into ≥ Grade 2 versus ≤ Grade 1; the hematologic AE data were categorized into ≥ Grade 3 versus ≤ Grade 2. The data were categorized in this way because maintenance treatment is expected to have a tolerable AE profile and contribute to acceptable quality of life. The different cutoffs were used for hematologic and

nonhematologic AEs because a Grade 2 hematologic AE (eg, Grade 2 platelet count) may have less impact on quality of life and be more manageable than a Grade 2 nonhematologic AE (eg, Grade 2 diarrhea). Results of the logistic regression analysis indicated that of the 7 evaluated AEs, statistically significant relationships to exposure ($p<0.05$) were observed for 5 AEs (fatigue, rash, diarrhea, thrombocytopenia, and neutropenia) (Figure 1.a).

Figure 1.a **Relationship Between Clinical Benefit (≥Stable Disease) from Single-Agent Ixazomib and Adverse Events (≥Grade 2 for Nonhematologic and ≥Grade 3 for Hematologic) and AUC (N=44) in Patients With Relapsed/Refractory Multiple Myeloma**



Abbreviations: AE=adverse event; AUC=area under the plasma concentration versus time curve; SD=stable disease; W=weekly.

Primary logistic regression analysis was also performed for efficacy. For this analysis, efficacy data were separated into 2 groups: SD or higher versus PD. The data were categorized in this way because in the heavily treated RRMM population, clinical benefit rate including SD was considered to represent a meaningful indicator of treatment-related disease control. Results from the analysis showed a significant ($p<0.05$) relationship between the probability of having disease control (eg, SD or higher) and area under the plasma concentration versus time curve. The dose-response curves indicate that a favorable benefit:risk may be achieved at doses of 3 mg and 4 mg, below the MTD of 5.5 mg.

Currently, there are 2 ongoing, phase 3 trials of ixazomib coadministered with lenalidomide and dexamethasone in patients with MM (Study C16010 in patients with RRMM and Study C16014 in patients with NDMM). Millennium's phase 3 dose in these 2 pivotal trials is 4 mg weekly, which is 1 dose level below the ixazomib MTD of 5.5 mg and was chosen to optimize benefit:risk on the basis of results from Study C16004.

As noted previously, the balance of benefit:risk is paramount in the C16021 maintenance study. Patients entering Study C16021 will likely be symptom free, and when they start maintenance therapy, they will not have been previously exposed to ixazomib. Therefore, the approach in this study is to initiate ixazomib maintenance therapy at a once-weekly dose of 3 mg and, if tolerated well after 4 cycles (see Section 6.5), increase the dose to 4 mg to provide the maximum possible clinical benefit.[38].

As shown in Figure 1.a, at the starting dose of 3 mg ixazomib weekly, which is 54% of the 5.5 mg MTD, as a weekly single agent, the logistic regression analysis predicts that the probabilities of Grade 2 or higher nonhematologic AEs and of Grade 3 or higher hematologic AEs are reduced by approximately 10% to 20% compared with a dose of 4 mg. Further, the 3 mg dose is within the therapeutic range for ixazomib (Figure 1.a) and represents the Level-1 dose administered in the ongoing phase 3 trials in the RRMM and NDMM settings.

Nonetheless, to provide patients the opportunity to derive maximum clinical benefit (without prohibitive toxicity), the starting dose of 3 mg will be increased to 4 mg at Cycle 5 Day 1, provided that during the most recent 2 cycles (Cycle 3 and 4), there have been no nonhematologic AEs of Grade 2 or above related to study drug, no dose interruptions related to study drug toxicities, and no delays of greater than 1 week in starting a cycle due to study drug toxicities. Patients who have had any dose reduction in Cycles 1 through 4 will not dose escalate (see Section 6.5). The selection of the time point for dose escalation in patients tolerating ixazomib was based on the observation that patients' tolerance of study drug could be determined early. A review of aggregate data from 275 patients participating in 5 phase 1/2 ixazomib MM studies (data cutoff of 15 February 2013) found 31 patients who had discontinued participation due to AEs (11.6%). Of those who discontinued for AEs, 27 (87%) patients had done so by the end of Cycle 4.

1.4.5 Rationale for Blood-Based Biomarkers [redacted]

1.4.5.1 Single-Nucleotide Polymorphism Analyses

This section is not applicable in this protocol amendment.

1.4.5.2 [redacted]

[redacted]

1.5 Potential Risks and Benefits

As of 27 March 2014, 1287 patients comprised the oral ixazomib Safety population. Clinical safety data included experience from patients who received multiple cycles followed by treatment-free periods and from patients who reduced or discontinued treatment. The emerging safety profile (as noted in the IB) indicated that the AEs reported with ixazomib were generally consistent with the class-based effects of proteasome inhibition and were similar to what had been previously reported with bortezomib, though the frequencies may have slightly differed. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention (see Section 6.9).

It is possible that ixazomib used as maintenance therapy will have toxicities that were not previously observed in or predicted from its evaluation in nonclinical studies or from ongoing and completed clinical studies. To mitigate the inherent risks in clinical studies of ixazomib, patients are monitored closely for anticipated toxicities. Guidance for the management of AEs is given in Section 6.9. Procedures for modifying doses are discussed in Section 6.4; drug dosage can be modified by either reducing the dose administered or interrupting the scheduled treatment. The weekly oral schedule that will be evaluated in this trial has been evaluated and determined to be tolerable in other trials of ixazomib in MM.

Ixazomib has shown signs of antitumor activity, as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others, across all ongoing trials. To date, antitumor activity has been seen with ixazomib administered as a single agent, when combined with established therapies, and across all malignancies studied, including advanced solid tumors, non-Hodgkin lymphoma, RRMM, relapsed or refractory

AL amyloidosis, and NDMM. Weekly dosing appears to enable delivery of higher ixazomib doses for a longer period than twice-weekly dosing.

Emerging data from ixazomib clinical studies and discussions with the CDE NMPA have led the sponsor to modify the study design of the China Continuation part of Study C16021. The first IA of the C16021 global study was conducted (data cut-off date 12 August 2019) and the primary endpoint of PFS was found to be both statistically significant and clinically meaningful. Additionally, no new safety concerns were found in patients receiving ixazomib. Given the positive results from the C16021 global study and the fact that the C16021 China Continuation is still open to enrollment, the sponsor does not believe it is appropriate to continue enrolling patients into a randomized, placebo-controlled maintenance study. The CDE NMPA acknowledged that it will be difficult to continue enrolling patients into the placebo arm of the C16021 China Continuation. CDE suggested that the sponsor amend the study into a single arm study, so as to collect more efficacy and safety data from Chinese patients receiving ixazomib.

The China Continuation is now converted to an open-label, single-arm study of ixazomib maintenance. Patients who were randomized to the placebo arm are permitted to cross over to the ixazomib arm; patients receiving placebo who do not cross over will discontinue the study. The study objectives are now focused on long-term tolerability and efficacy of ixazomib in patients in China, so as to evaluate the consistency of the safety and efficacy of ixazomib maintenance between the China population and the C16021 global study population.

This trial will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, Good Clinical Practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- To determine the long-term safety and tolerability of ixazomib maintenance therapy

2.2 Secondary Objectives

- To determine PFS, defined as the time from date of first dose to PD or death from any cause, in patients in China with NDMM who have had a major response—defined as CR, VGPR, or PR—to initial therapy and who have not undergone SCT.
- To determine OS.
- To determine whether response at study entry is improved or maintained.
- To determine the TTP.
- To determine the time to next-line therapy (TTNT).
- To assess the incidence of new primary malignancy in patients receiving ixazomib maintenance therapy.
- To assess health-related quality of life (HRQL) as measured by the global health domain of the EORTC QLQ-C30 in patients who receive ixazomib maintenance therapy.
- To assess the correlation between frailty status and PFS and OS in patients receiving ixazomib maintenance therapy.
- To collect PK data to contribute to population PK and exposure-response (safety/efficacy) analysis.
- To evaluate the resolution and improvement of PN, if it occurs, in patients receiving ixazomib maintenance therapy.

2.3 Exploratory Objectives

[redacted]

- [redacted]
- [redacted]

[redacted]

3. STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint is:

- Long-term safety and tolerability, measured by Eastern Cooperative Oncology Group (ECOG) Performance Status, AEs, serious adverse events (SAEs), and assessments of clinical laboratory values.

3.2 Secondary Endpoints

The secondary endpoints are:

- PFS, defined as the time from date of first dose (patient entered into IXRS and received first dose of ixazomib) to the first occurrence of PD, as evaluated by the investigator, or death from any cause, whichever occurs first.
- Overall survival, measured as the time of date of first dose to the date of death.
- Best response achieved or maintained (including PR, VGPR, and CR) before PD or to subsequent therapy, and duration of CR.
- Time to progression, measured as the time from date of first dose to the date of first documented PD.
- TTNT, defined as the time from date of first dose to the date of first dose of the next line of antineoplastic therapy.
- Incidence of new primary malignancies.

- Health-related quality of life, as measured by the global health domain of the EORTC QLQ-C30 questionnaire.
- Correlation between frailty status and PFS and OS.
- Ixazomib plasma concentration-time data.
- Time to resolution and time to improvement of PN events graded at each subsequent monthly visit until resolution of PN, the start of an alternative antineoplastic treatment, or 6 months after PD, whichever occurs first.

3.3 Exploratory Endpoints

[redacted]

4. STUDY DESIGN

4.1 Overview of Study Design

The China Continuation part of Study C16021 was originally designed as a randomized, double-blind, placebo-controlled, multicenter study in patients in China with NDMM who have not undergone SCT. Upon implementation of Amendment 08, the China Continuation will now be a single-arm, open-label study of ixazomib maintenance for patients in China with NDMM who have not undergone SCT. Patients who have not undergone SCT may not have done so because of frailty due to advanced age (eg, ≥65 years) or comorbidity or because they decline SCT for other reasons. Patients enrolled under Amendment 08 will be enrolled based on the same eligibility criteria.

The Study Overview Diagram depicts the study design.

Screening

The purpose of the study is to evaluate the role of maintenance therapy with ixazomib in patients who, in their initial therapy before study enrollment, have been treated to achieve a major response category (PR or better) that is judged to be their best response by the investigator/treating physician. Patients must have received initial therapy for 6 to 12 months, according to standard of care, and have met all additional inclusion/exclusion criteria before study enrollment. The initial therapy permitted is any standard of care MM therapy. Upon implementation of Amendment 08, new eligible and consenting patients are to be enrolled no later than 60 days after the last dose of initial therapy. For patients who were previously randomized to the placebo arm who reconsent and cross over to ixazomib, reconsenting more than 60 days after the last dose of initial therapy is permitted. A Millennium project clinician or designee will confirm patient eligibility before study treatment is initiated; the investigator will ensure that documentation adequately captures the reasons for not proceeding to SCT. Upon implementation of Amendment 08, all patients will receive open-label ixazomib.

Study Treatment

Prior to implementation of Amendment 08, 10 patients have been randomized and treated in the China Continuation part of Study C16021. Patients who were randomized to study drug (ixazomib or placebo) prior to implementation of Amendment 08 and who are still on study treatment will complete their current cycle of treatment and be unblinded.

- Patients who are in the placebo arm and who have not yet experienced disease progression will have the opportunity to cross over to ixazomib maintenance, based on the investigator's judgement and the patient's informed consent. Patients who cross over will follow the "Schedule of Events for Crossover Patients" starting at Crossover Cycle 1 Day 1. Patients in the placebo arm who do not cross over should complete an EOT visit and discontinue the study.

- Patients who are in the ixazomib arm will continue to receive ixazomib maintenance. Patients who reconsent will follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients" according to their current cycle of treatment.

Approximately 20 additional patients with NDMM will be enrolled in the China Continuation, for a total of approximately 30 patients overall. All newly enrolled patients

will receive ixazomib maintenance and will follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients."

Patients will receive ixazomib (hereafter referred to as "study drug") orally on Days 1, 8, and 15 of every 28-day cycle. A starting dose of 3 mg of study drug will be used for all patients through Cycle 4. Upon evaluation of toxicities at the completion of Cycle 4, and on the basis of the dose escalation criteria detailed in Section 6.5, the study drug dose will be escalated to 4 mg beginning with Cycle 5 Day 1 and administered on the same schedule for the duration of the study to provide maximum possible clinical benefit for patients who tolerated the first 4 cycles of treatment.

The Treatment period of the study is defined as the interval during which any enrolled patient is receiving study drug; 28-day treatment cycles will be used throughout this period. Patients will have study assessments performed at regular treatment-cycle intervals while they are participating in the study: 3 times during the first cycle (weekly; Days 1, 8, and 15), twice during the second cycle (Days 1 and 8), and then once per treatment cycle for the remainder of their participation in the Treatment period, for approximately 24 months (equivalent to 26 cycles [if no cycle delays], to the nearest complete cycle) or until they experience PD or unacceptable toxicity, whichever occurs first. The exception to this is patients who have their dose increased at Cycle 5; these patients will have study assessments performed twice during Cycle 5 (on Days 1 and 8).

Patients will be assessed for disease response and PD every cycle during the Treatment period by the treating physician/investigator, according to the IMWG uniform response criteria, version 2011. Dose-modification guidelines are given in Section 6.3. Unscheduled visits may occur between treatment cycles as required (see Section 7.5). For example, symptomatic pain progression should result in an interim unscheduled visit, as would ongoing Grade 3 or worse AEs.

Patients will receive ixazomib treatment for a maximum duration of approximately 24 months (equivalent to 26 cycles [if no cycle delays], to the nearest complete cycle) or until documented PD (on the basis of the IMWG uniform response criteria, version 2011) or intolerable toxicity, whichever occurs first. Note, patients previously randomized to the placebo arm who reconsent and cross over to ixazomib may receive up to 24 months (26 cycles) of ixazomib treatment. Patients who do not discontinue because of PD or toxicities will complete the treatment cycle that is ongoing at 24 months (regardless of the cycle number) before discontinuing treatment.

Patients will attend an EOT visit 30 days (+1 week) after receiving their last dose of study drug, unless next-line therapy is started before 30 days after the last dose of study drug, in which case the EOT visit should occur before the start of the next-line therapy.

Study Follow-up

At the EOT visit, patients will enter the follow-up phase (see the Study Overview Diagram). There are 3 Follow-up periods: PFS, PD, and OS.

Patients will be assessed for disease response and PD during the PFS Follow-up period by the treating physician/investigator, according to the IMWG uniform response criteria, version 2011.

Progression-Free Survival Follow-up and Progressive Disease Follow-up

If a patient completes 24 months of ixazomib treatment or discontinues the study drug before PD, the patient will enter the PFS Follow-up period of the study and undergo follow-up every 4 weeks until PD occurs. All patients enrolled prior to implementation of Amendment 08 will be unblinded. Patients who were previously randomized to the placebo arm who have discontinued study treatment but who have not yet experienced disease progression or started alternative therapy have the opportunity to cross over to ixazomib maintenance. The decision to cross over is based on the investigator's judgement and the patient's informed consent. Patients who cross over will follow the "Schedule of Events for Crossover Patients" starting at Crossover Cycle 1 Day 1. Patients in the placebo arm who do not cross over will discontinue the study. Patients in the ixazomib arm who reconsent should continue on study and follow the new Schedule of Events.

After PD occurs during the PFS Follow-up period, the patient enters the PD Follow-up period and continues to be followed every 4 weeks until initiation of next line therapy by the investigator/treating physician.

If a patient has PD while on study drug during the Treatment period, the patient will enter directly into the PD Follow-up period and will be followed every 4 weeks until initiation of next-line therapy by the investigator/treating physician. No crossover is permitted after a patient experiences PD.

Overall Survival Follow-up

Patients who start next line therapy (regardless of when) will enter the OS Follow-up period. During the OS Follow-up period, follow-up will occur every 12 weeks until death or termination of the study by the sponsor, whichever occurs first.

Study Endpoints and Other Details

Upon implementation of Amendment 08, the study objectives are now focused on long-term tolerability and efficacy of ixazomib in patients in China, so as to evaluate the consistency of the safety and efficacy of ixazomib maintenance between the China population and the C16021 global study population. There will be 1 IA for the safety and efficacy endpoints. This IA will be the primary analysis for the China Continuation and will be performed approximately 12 months after the additional ~20 patients have been enrolled under this amendment. The safety and efficacy endpoints will be assessed in the overall Chinese patient population (patients from China who were enrolled in the ixazomib arm of the C16021 global study, patients in the ixazomib arm of the China Continuation before implementation of Amendment 08, all patients enrolled in the China Continuation under Amendment 08, and patients who were randomized to the placebo arm before implementation of Amendment 08 and who crossed over to the ixazomib arm). The final analysis will be performed when all patients in the China Continuation are off study treatment and have completed the EOT visit, or upon termination of the study by the sponsor, whichever occurs earlier.

The Schedules of Events and the Study Endpoint and Follow-up Period Diagram describe the study assessments and timing in detail. These include clinical, laboratory, and other response measures; HRQL evaluations through patient self-reported instruments.

For HRQL, the focus is on tolerability [redacted]

Eastern Cooperative Oncology Group Performance Status and AEs will be assessed, and laboratory values, vital signs, and electrocardiograms will be obtained to evaluate the safety and tolerability of ixazomib. Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, effective date 14 June 2010 [52].

4.2 Number of Patients

Approximately 30 total patients from China with NDMM who had a major response to initial therapy and who have not undergone SCT will be enrolled in the China Continuation part of Study C16021. Prior to implementation of Amendment 08, 10 patients have been randomized and treated in the China Continuation. An additional ~20 patients are to be enrolled upon implementation of Amendment 08.

Enrollment is defined as a patient being entered into the IXRS system and receiving the first dose of study drug.

4.3 Duration of Study

Patients will be treated for a maximum duration of approximately 24 months (equivalent to 26 cycles [if no cycle delays], to the nearest complete cycle) or until documented PD or intolerable toxicity, whichever occurs first. Note, patients previously randomized to the placebo arm who reconsent and cross over to ixazomib may receive up to 24 months (26 cycles) of ixazomib treatment. Subsequent to the 24-month Treatment period or removal from study therapy due to PD or toxicity, patients will be followed for clinical status, disease status, HRQL, new primary malignancy, and survival.

The study will last until all patients in the China Continuation are off study treatment and have completed the EOT visit, or upon termination of the study by the sponsor, whichever occurs earlier.

5. STUDY POPULATION

Adult patients aged 18 years or older with a confirmed diagnosis of symptomatic NDMM who have been treated to best response with initial MM therapy for 6 to 12 months and who have achieved a major response (CR, VGPR, or PR) while receiving that regimen will be eligible for this study. These patients will not have undergone SCT, and the reasons will be thoroughly documented. The initial therapy permitted is any standard of care MM therapy.

5.1 Inclusion Criteria

Each patient must meet all the following inclusion criteria to be randomized to treatment:

1. Adult male or female patients aged 18 years or older with a confirmed diagnosis of symptomatic NDMM according to standard criteria (see Section 15.1).

2. Completed 6 to 12 months (± 2 weeks) of initial therapy, during which the patient was treated to best response, defined as the best response maintained for 2 cycles after the M-protein nadir is reached.

3. Documented major response (PR, VGPR, CR) according to the IMWG uniform response criteria, version 2011, after this initial therapy.

4. 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 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 90 days after the last dose of study drug, or
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

   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 drug, or
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

5. 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.

6. Availability of complete documentation for

   - Details of initial disease state, initial therapy, and response

- Cytogenetic assessment at diagnosis (cytogenetic assessment performed after diagnosis must be approved by a Millennium project clinician or designee)
- ISS staging at diagnosis (requiring β_2-microglobulin and serum albumin results).

7. Eastern Cooperative Oncology Group Performance Status of 0 to 2 (see Section 15.2).
8. Suitable venous access for the study-required blood sampling and consent for the specific amounts that will be taken.
9. Patient is willing and able to adhere to the study visit schedule and other protocol requirements including blood sampling and bone marrow aspiration.
10. Patients must meet the following clinical laboratory criteria at study entry:
    - Absolute neutrophil count (ANC) ≥1,000/mm^3 without growth factor support and platelet count ≥75,000/mm^3. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before enrollment.
    - Total bilirubin ≤1.5 × the upper limit of the normal range (ULN).
    - Alanine aminotransferase and aspartate aminotransferase ≤3 × ULN.
    - Calculated creatinine clearance ≥30 mL/min (using the Cockroft-Gault equation [Section 15.3]).

5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be randomized to treatment:

1. Multiple myeloma that has relapsed after, or was not responsive to, initial therapy.
2. Prior SCT.
3. Radiotherapy within 14 days before enrollment.
4. Diagnosed or treated for another malignancy within 5 years before enrollment or previously diagnosed with another malignancy with evidence of residual disease.

Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

5. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the Screening period.

6. Major surgery within 14 days before enrollment.

7. Central nervous system involvement.

8. Infection requiring IV antibiotic therapy or other serious infection within 14 days before enrollment.

9. Diagnosis of Waldenstrom's macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, plasma cell leukemia, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome.

10. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, uncontrolled congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.

11. Systemic treatment with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital) or use of St. John's wort within 14 days before enrollment.

12. Ongoing or active infection, known human immunodeficiency virus positive, active hepatitis B or C infection.

13. Comorbid systemic illnesses or other severe concurrent disease that, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens (eg, PN that is Grade 1 with pain or Grade 2 or higher of any cause).

14. Psychiatric illness/social situation that would limit compliance with study requirements.

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

16. Inability to swallow oral medication, inability or unwillingness to comply with the drug administration requirements, or GI procedure that could interfere with the oral absorption or tolerance of treatment.

17. Treatment with any investigational products within 30 days before enrollment.

6. STUDY DRUG

6.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients should be monitored for toxicity as necessary, and doses of the study drug should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of dose.

Prior to implementation of Amendment 08, 10 patients have been randomized and treated in the China Continuation part of Study C16021. Patients who are still on study treatment will complete their current cycle of treatment and be unblinded.

- Patients who are in the placebo arm and who have not yet experienced disease progression will have the opportunity to cross over to ixazomib maintenance, based on the investigator's judgement and the patient's informed consent. Patients who cross over will follow the "Schedule of Events for Crossover Patients" starting at Crossover Cycle 1 Day 1. Patients in the placebo arm who do not cross over should complete an EOT visit and discontinue the study.
- Patients who are in the ixazomib arm will continue to receive ixazomib maintenance. Patients who reconsent will follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients" according to their current cycle of treatment.

Patients who are in the placebo arm who have discontinued study treatment but who have not yet experienced PD or started alternative therapy (ie, in the PFS Follow-up Period) will also have the opportunity to cross over to ixazomib maintenance, based on the investigator's judgement and the patient's informed consent. Patients who cross over will follow the "Schedule of Events for Crossover Patients" starting at Crossover Cycle 1 Day 1.

Approximately 20 additional patients with NDMM will be enrolled in the China Continuation and will follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients," for a total of approximately 30 patients overall.

Patients will receive oral ixazomib weekly (Days 1, 8, and 15) in each 28-day cycle. The dose will be 3 mg during Cycles 1 through 4 and may be escalated to 4 mg thereafter if the patient has tolerated the initial dose (see Section 6.5). All doses must be taken as outlined in the Schedules of Events. During the first cycle of treatment, all patients will receive doses of ixazomib capsules in the clinic. During the second cycle of treatment, all patients will receive the Day 1 and Day 8 doses in the clinic; patients will take the Day 15 dose at home as directed. For subsequent cycles in which a predose PK is to be drawn on Day 1 (Cycles 3-10), the Day 1 dose should be taken in the clinic (see the Ixazomib Pharmacokinetic Sampling Schedule). All other doses may be taken at home. Of particular note, the Cycle 5 Day 1 dose will be taken in the clinic after determination of whether the study drug dose should be escalated from 3 mg to 4 mg, and patients whose dose is escalated will have the Cycle 5 Day 8 dose given in the clinic also.

Refer to the Study Manual for additional instructions regarding study drug administration.

6.2 Study Drug (Ixazomib Capsules)

Ixazomib capsules will be supplied as single capsules containing 0.5, 2.3, 3.0, or 4.0 mg of ixazomib. Ixazomib capsules will be provided by the sponsor.

Ixazomib capsules will be hereafter referred to as "study drug."

Study drug will be initially given as a single, oral dose of 3 mg weekly (Days 1, 8, and 15) for 3 weeks, followed by 1 week without study drug, in each 28-day cycle. Following the first 4 cycles of therapy, the dose will be increased to 4 mg on Cycle 5 Day 1 for patients tolerating the drug, according to the dose escalation criteria in Section 6.5.

Patients should be instructed to swallow the study drug capsules whole with water and not to break, chew, or open the capsules. Study drug should be taken on an empty stomach, at least 1 hour before and no sooner than 2 hours after a meal. A total of approximately 240 mL (8 oz) 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 never 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. Section 6.14 gives information about returning unused medication.

6.3 Dose-Modification Guidelines

The patient will be evaluated for possible toxicities that may have occurred after the previous dose(s) according to the Schedules of Events. Toxicity will be evaluated according to the NCI CTCAE, Version 4.03, effective 14 June 2010 [52]. These criteria are provided in the Study Manual.

Further clarification can be obtained in consultation with the Millennium project clinician or designee. If multiple toxicities are noted, the dose adjustments and/or delays should be made according to the most severe toxicity guidelines.

6.4 Criteria for Dose Modification (Delays, Reductions, and Discontinuations)

6.4.1 Dose Adjustment

Patients experiencing AEs attributed to study drug may continue in the study but may have doses of study drug held or reduced by at least 1 dose level as shown in Table 6.a. When a dose reduction of study drug is required due to toxicity, no dose re-escalation will be permitted.

Table 6.a Study Drug Dose Adjustments

Dose Level	Dose Reduction	
Starting Dose	3 mg[a]	4 mg[b]
-1	2.3 mg	3 mg
-2	1.5 mg[c]	2.3 mg
-3	Discontinue	1.5 mg[c]
-4	Discontinue	Discontinue

a Cycles 1-4, or for patients unable to dose escalate at Cycle 5.
b Patients who dose escalated at Cycle 5.
c This dose consists of three 0.5 mg capsules taken together.

6.4.2 Criteria for Toxicity Recovery Before Beginning the Next Treatment Cycle

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

- Absolute neutrophil count ≥1,000/mm^3.
- Platelet count ≥75,000/mm^3.
- All nonhematologic toxicity considered to be related to treatment with study drug 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 fails to meet the above-cited criteria for retreatment, initiation of the next cycle of treatment should be delayed for 1 week. After 1 week, the patient should be re-evaluated to determine whether the criteria for re-treatment have been met. If the patient continues to fail to meet the previously cited criteria, delay therapy 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 dose will be reduced by 1 dose level when therapy resumes. Should treatment need to be delayed for 4 weeks because of incomplete recovery from treatment-related toxicity, therapy with study drug 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.

6.4.3 Study Drug Dose Modification for Hematologic Toxicities

Please refer to Table 6.b for dose delay and reduction recommendations for hematologic toxicities attributed to study drug. Dose level reductions should be made in accordance with those outlined in Table 6.a.

Table 6.b Study Drug Dose Modification for Hematologic Toxicities

Criteria	Action
Within-Cycle Dose Modifications	
If platelet count ≤50×10^9/L or absolute neutrophil count (ANC) ≤0.75×10^9/L on an ixazomib dosing day (other than Day 1)	Study drug 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 ≥ 1.0 × 10^9/L; platelet count ≥ 75 × 10^9/L). Upon recovery, study drug may be reinitiated and reduced by 1 dose level in accordance with reductions outlined in Table 6.a.
Dose Modifications for Subsequent Treatment Cycles	
Delay of ≥2 weeks at the start of a subsequent cycle due to lack of toxicity recovery as defined in Section 6.4.2: • ANC<1.0×10^9/L; platelet count<75×10^9/L (Or other nonhematologic toxicities>Grade 1 or not to the patient's baseline condition)	Hold study drug until resolution per criteria. Reduce study drug by 1 dose level as outlined in Table 6.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 due to timing—ie, a toxicity after Day 15 dosing such that a dose reduction was not required at that point in the cycle—then reduce study drug 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.

When a dose reduction of study drug is required, no re-escalation of dose will be permitted. Please refer to Table 6.d for criteria for re-treatment and cycle delays.

6.4.4 Study Drug Dose Modification for Nonhematologic Toxicities

Please refer to Table 6.c for dose delay and reduction recommendations for nonhematologic toxicities considered related to study drug. Dose level reductions should be made in accordance with those outlined in Table 6.a.

Table 6.c Study Drug 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 study drug 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 study drug until resolution to ≤ Grade 1 or baseline. Reduce study drug to next lower dose upon recovery as outlined in Table 6.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 study drug.	
Grade 2 Rash	Symptomatic recommendations per Section 6.9. The investigator and project clinician or designee may discuss considerations for dose modifications and symptom management.	
All Other ≥ Grade 2 Nonhematologic Toxicities	Hold study drug until resolution to ≤ Grade 1 or baseline. Reduce study drug by 1 dose level as outlined in Table 6.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 study drug, 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 study drug is continued, the dose should be reduced by at least 1 level.	

Grade 4 nonhematologic toxicities will, in general, require that treatment with study drug 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 drug, then the dose of study drug 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.

When a dose reduction of study drug is required, no re-escalation of dose will be permitted.

Please refer to Table 6.d for criteria for retreatment and cycle delays. Dose level reductions should be made in accordance with those outlined in Table 6.a.

Table 6.d Criteria for Study Drug Retreatment and Cycle Delays Subsequent to Hematologic and Nonhematologic Toxicities

Criteria	Action
Both hematologic and nonhematologic events	Delay therapy × 1 week. Re-evaluate patient; if still not resolved, delay therapy × 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 6.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).

6.5 Criteria for Dose Escalation at Cycle 5

To provide patients the opportunity to derive maximum clinical benefit from study drug maintenance, the dose of 3 mg will be increased to 4 mg at Cycle 5 provided that, during the most recent 2 cycles (Cycle 3 and 4), there have been no nonhematologic AEs ≥ Grade 2 related to study drug, no dose interruptions related to study drug toxicities, and no delays of greater than 1 week in starting a cycle due to study drug toxicities. Patients who have had *any* dose reductions will not dose escalate. If dose escalation was inadvertently missed at Cycle 5, escalation at a later cycle may be performed with permission from the Millennium project clinician or designee.

6.6 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

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

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

The following medicinal products and procedures are prohibited during the Treatment period of the study:

- St. John's wort

- Any antineoplastic treatment with activity against MM, other than study drugs
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates PD)
- Platelet transfusions to help patients meet eligibility criteria

6.7 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 first dose of the study drug until 30 days after the final dose will be recorded in the electronic case report forms (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 product label, 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.
- Erythropoietin will be allowed in this study.
- Patients should be transfused with red cells and platelets as clinically indicated.
- Patients who are receiving bisphosphonates 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 product label, unless specifically contraindicated. If bisphosphonate therapy was not started before the study start, initiation of treatment should be discussed with the project clinician.
- Supportive measures consistent with optimal patient care may be given throughout the study.

6.8 Precautions and Restrictions

Fluid deficit should be corrected before initiation of treatment and during treatment.

Nonsteroidal anti-inflammatory drugs should be avoided in patients with impaired renal function, given reported renal failure induced by these drugs in patients with decreased renal function.

It is not known what effects ixazomib has 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 and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form through 90 days after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study Treatment period and through 90 days after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

6.9 Management of Clinical Events

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. Antiviral therapy such as acyclovir, valacyclovir, or other antivirals may be initiated as clinically indicated.

Nausea or Vomiting

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

Diarrhea

Prophylactic antidiarrheals will not be used in this protocol; however, 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.

Fluid deficit should be corrected before initiation of treatment and during treatment.

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 predominately on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash is most commonly reported within the first 3 cycles of therapy. The rash is often transient and self-limiting and is typically Grade 1 or 2 in severity. As in any other oncology trial, rash may occur in patients receiving placebo and in patients receiving ixazomib. 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 [see Section 15.4]) is permitted. Management of a Grade 3 rash may require intravenous antihistamines or corticosteroids. Administration of ixazomib (and other causative agent if

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

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

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 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 6.4.3). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. Thrombotic microangiopathy, including thrombotic thrombocytopenia purpura and hemolytic uremic syndrome, 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. Thrombotic microangiopathy should be managed symptomatically according to standard medical practice.

Neutropenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable. Growth factor support is not required but may be considered according to

standard clinical practice. Ixazomib administration should be modified according to dose modification recommendations in the protocol when neutropenia occurs (see Section 6.4.3). Therapy can be reinitiated at a reduced level upon recovery of ANCs.

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 corrected before initiation of study drug and as needed during treatment to avoid dehydration (see Section 6.4.4).

Hypotension

Symptomatic hypotension and orthostatic hypotension with or without syncope have been reported with ixazomib. Blood pressure should be closely monitored while the patient is on study treatment, and fluid deficit should be corrected as needed, especially in the setting of concomitant symptoms such as nausea, vomiting, diarrhea, or 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 initiation of study drug and as needed during treatment to avoid dehydration.

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome, which ultimately resolved, has been reported with ixazomib. This condition 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 it happened while 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.

6.10 Blinding and Unblinding

6.10.1 Blinding and Unblinding Prior to Implementation of Amendment 08

To maintain the blind, all study personnel, including the investigators, site personnel, study clinicians, and the sponsor, will be blinded to the treatment assignments for the duration of the study. When a patient is discontinued from the study, the investigator may request unblinding if it is necessary for determination of the patient's subsequent anticancer treatment.

Treatment assignments will be obtained through the interactive voice/web response system (IXRS) according to the procedures outlined in the Study Manual. Information regarding the treatment assignments will be kept securely at Millennium or designee, per its standard operating procedures. Emergency unblinding, if necessary, will be conducted via the IXRS.

Records of the patient number, the date the study drug was dispensed, and the treatment assignment will be maintained by the study site. If the treatment assignment must be revealed for the safety of the patient, to treat an AE, or to inform decisions for subsequent therapy, the investigator will contact the Millennium project clinician or designee (contact information is in the Study Manual). A decision to break the blind must be reached by the Millennium project clinician or designee and the investigator. The investigator, or designee, may break the blind through the IXRS independent of the Millennium project clinician or designee only if it is considered to be an emergency by the investigator that requires specific knowledge of the blinded study treatment to properly treat the AE/safety issue. If the treatment of the AE/safety issue is the same regardless of the study drug assignment, the blind should not be broken. The event requiring breaking the blind must be documented in the eCRF, including the date the blind was broken. In addition, the patient will be discontinued from further study drug administration in this study.

6.10.2 Blinding and Unblinding Upon Implementation of Amendment 08

Upon implementation of Amendment 08, the China Continuation part of Study C16021 will transition from a double-blind, placebo-controlled design to an open-label, single-arm design (ixazomib only). Individual treatment assignments are now available in the IXRS. Note, the C16021 global study remains blinded.

Prior to implementation of Amendment 08, 10 patients have been randomized and treated in the China Continuation part of Study C16021. Patients who are still on study treatment will complete their current cycle of treatment and be unblinded.

- Patients who are in the placebo arm and who have not yet experienced disease progression will have the opportunity to cross over to ixazomib maintenance, based on the investigator's judgement and the patient's informed consent. Patients who cross over will follow the "Schedule of Events for Crossover Patients" starting at Crossover Cycle 1 Day 1. Patients in the placebo arm who do not cross over should complete an EOT visit and discontinue the study.

- Patients who are in the ixazomib arm will continue to receive ixazomib maintenance. Patients who reconsent will follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients" according to their current cycle of treatment.

Patients who are in the placebo arm who have discontinued study treatment but who have not yet experienced PD or started alternative therapy (ie, in the PFS Follow-up Period) will also have the opportunity to cross over to ixazomib maintenance, based on the investigator's judgement and the patient's informed consent. Patients who cross over will follow the "Schedule of Events for Crossover Patients" starting at Crossover Cycle 1 Day 1.

6.11 Description of Investigational Agents

The ixazomib drug product is provided in strengths of 4.0, 3.0, 2.3, and 0.5 mg capsules as ixazomib (the active boronic acid). The dose strengths are differentiated by both capsule size and color, as described in the Table 6.e.

Table 6.e Ixazomib Capsule Size and Color

Dose Strength	Capsule Size	Capsule Color
4.0 mg	Size 3	Ivory
3.0 mg	Size 4	Light gray
2.3 mg	Size 4	Flesh
0.5 mg	Size 3	Dark green

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

6.12 Preparation, Reconstitution, and Dispensation

The study drug is dispensed in a blister pack in a child-resistant carton.

6.13 Packaging and Labeling

The study drug will be provided by Millennium. The study drug labels will fulfill all requirements specified by governing regulations.

The capsules are individually packaged using cold form foil-foil blisters that are child resistant. There are 3 capsules per package.

6.14 Storage, Handling, and Accountability

On receipt at the investigative site, study drug should remain in the blister pack and carton provided until use or dispensation. The container should be stored according to the storage conditions that are in the pharmacy manual or equivalent storage guidelines. All excursions that occurred at the site storage or during transportation from depot to the site 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.

Study drug dispensed to the patient for take-home dosing should remain in the blister packaging and carton until the point of use. Comprehensive instructions should be provided to the patient to ensure compliance with, and understanding of, dosing procedures. Patients are permitted to transport study drug from the site to home at room temperature. If circumstances due to the coronavirus disease 2019 [COVID-19] pandemic prevent a patient from attending the study site, sites may utilize 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 sponsor's project clinician/designee. This may include planned shipments of the study drug from the central pharmacy (which may be a sub-depot), depot, or a clinical site to the patients, referred to as DTP (Direct-to-Patient). Patients who are receiving take-home medication should ordinarily be given only 1 cycle of medication at a time. More than 1 cycle of medication may be dispensed on a case-by-case basis for holidays, travel, or other circumstances upon discussion with the investigator and sponsor's project clinician/designee. Patients should be instructed to store the medication according to the storage conditions that are in the pharmacy manual or equivalent storage guidelines for the duration of each cycle. Patients should be instructed to return their empty or partially used cartons to the investigative site, rather than discarding them, as permitted by site policy. Reconciliation will occur accordingly when the patient returns for their next cycle of take-home medication. If circumstances due to the COVID-19 pandemic prevent a patient from attending the study site, 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 when handling the study drug. 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 study drug, including that study drug is to be taken as intact capsules.

Please refer to the Pharmacy Manual for additional instructions.

6.15 Other Protocol-Specified Materials

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

7. STUDY CONDUCT

This trial 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.
- ICH E6 GCP: Guideline for Good Clinical Practice.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

7.1 Study Personnel and Organizations

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

7.2 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.

7.3 Treatment Group Assignments

After written informed consent has been obtained, the patient will be assigned an enrollment code (country-, site-, and patient-specific) using the IXRS.

Patient eligibility will be confirmed by a Millennium project clinician or designee before study entry. If a patient discontinues from the study, that enrollment code will not be reused, and the patient will not be allowed to re-enter the study.

Upon implementation of Amendment 08, the China Continuation part of Study C16021 will transition from a double-blind, placebo-controlled design to an open-label, single-arm study of ixazomib maintenance. Patients who are still on study treatment will complete their current cycle of treatment and be unblinded.

- Patients who are in the placebo arm and who have not yet experienced disease progression will have the opportunity to cross over to ixazomib maintenance, based on the investigator's judgement and the patient's informed consent. Patients who cross over will follow the "Schedule of Events for Crossover Patients" starting at Crossover Cycle 1 Day 1. Patients in the placebo arm who do not cross over should complete an EOT visit and discontinue the study.

- Patients who are in the ixazomib arm will continue to receive ixazomib maintenance. Patients who reconsent will follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients" according to their current cycle of treatment.

Patients who are in the placebo arm who have discontinued study treatment but who have not yet experienced PD or started alternative therapy (ie, in the PFS Follow-up Period) will also have the opportunity to cross over to ixazomib maintenance, based on the investigator's judgement and the patient's informed consent. Patients who cross over will follow the "Schedule of Events for Crossover Patients" starting at Crossover Cycle 1 Day 1.

Note, the C16021 global study will remain a double-blind, placebo-controlled design.

7.4 Study Procedures

In acknowledgement of hospital, local, state or national government restrictions, or other site-related factors caused by the COVID-19 pandemic 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. Patients must present to the study site for all visits shown in the Schedules of Events during Cycles 1-5 to ensure proper safety, efficacy, and PK monitoring. Alternative methods for administering study procedures/assessments may be considered for Cycle 6 and beyond when it is not possible for the patient to come to the study site due to the COVID-19 pandemic.

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 that 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. If an in-clinic visit is not possible, the permitted alternatives are as follows. These assessments/procedures may be waived: symptom-directed physical examination, ECOG performance status, vital signs, weight, whole blood, [redacted]. These assessments/procedures may be deferred until the next in-clinic visit: SPEP, UPEP, serum free light-chain assay, immunofixation, quantification of immunoglobulins, BMA, and biopsy. These assessments/procedures may be performed locally if possible and, if not, may be deferred until the next in-clinic visit: hematology and chemistry laboratory tests.

Patients will be evaluated at scheduled visits over 4 study periods: Screening, Treatment, EOT, and Follow-up (PFS, PD, and OS).

Tests and procedures should be performed on schedule but, unless otherwise specified, occasional changes are allowable within a 2-day window during Cycles 1-5 and within a 7-day window during Cycle 6 and beyond for holidays, vacations, and other administrative reasons; a longer window is allowable 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. These windows are also permissible for study days not specified in the Schedules of Events, including Cycle 2 Day 15 and Day 8 and Day 15 of Cycle 3 and beyond.

Refer to the Schedules of Events for timing of assessments. Additional details are provided as necessary in the sections that follow.

7.4.1 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. For patients enrolled prior to implementation of Amendment 08 and still on study treatment, all patients must be reconsented before dosing on Day 1 of the next full treatment cycle. Patients enrolled prior to implementation of Amendment 08 who are in one of the follow-up periods must also be reconsented. Consenting/reconsenting should be done in person. Remote consenting/reconsenting is permitted as long as the process adheres to site, IRB/EC, and GCP standards and local regulations.

7.4.2 Patient Demographics

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

7.4.3 Medical History

During the Screening period, a complete medical history will be compiled for each patient, including the following.

- Diagnosis of MM (Section 15.1) and initial ISS staging (based on serum albumin and β_2-microglobulin levels) (Section 15.5), including biochemistry, serum protein electrophoresis, urine protein electrophoresis, serum/urine immunofixation, serum free light chains, bone marrow results, and lactate dehydrogenase (LDH) levels.

- Cytogenetic evaluation should be performed at diagnosis (or after diagnosis, only with approval from the Millennium project clinician or designee) using fluorescence in situ hybridization (FISH) and/or conventional cytogenetics (karyotyping); if only 1 test is available, FISH is preferred. At a minimum, this should include reporting of 2 of the following 3 high-risk abnormalities, listed in order of preference: del17, t(4;14), and t(14;16). All cytogenetic evaluations will be performed locally by the site according to local standards. In selected regions where cytogenetic evaluation at the time of disease diagnosis is not routinely conducted, the sponsor may elect to make prescreening cytogenetic evaluation possible. For those regions, a prescreening informed consent form (ICF) will be developed to permit cytogenetic evaluation on BMA samples.

- Multiple myeloma-directed therapy including initial therapies and dates and clinically significant toxicities

- Disease response evaluations during and at the end of initial therapy. Patients must have been treated to their best response to initial therapy, defined as the best response maintained for 2 cycles after the M-protein nadir is reached. The best response must have been PR or better.

  NOTE: To minimize clinically redundant procedures, the investigator may choose to use the Screening visit to serve as the clinical evaluation of disease status after initial therapy, as long as all requirements for screening are met.

- Review of all current medications, prior radiation (as permitted >14 days before enrollment for symptomatic bone lesion or >5 years before enrollment for another malignancy), and the patient's current smoking status.

Refer to the Schedules of Events for specific time requirements and windows.

7.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the Schedules of Events. Symptom-directed examinations should include examination of organ systems related to patient symptoms to document potential AEs, AE severity, or AE resolutions. Assessment for PN will be conducted as part of all physical examinations.

7.4.5 Vital Signs, Body Weight, and Height

Measurement of vital signs, including temperature, blood pressure, heart rate, respiratory rate (as clinically indicated), and body weight will be done at the time points specified in the Schedules of Events. Height will be measured only at the Screening visit.

7.4.6 Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed using the ECOG Performance Scale (see Section 15.2) at the time points specified in the Schedules of Events.

7.4.7 Frailty Status

Patients' frailty status will be assessed at the Screening visit on the basis of 4 components: age, the Charlson Comorbidity Scoring System without age weighting (see Section 15.6), the Katz Index of Independence in Activities of Daily Living (see Section 15.7), and the Lawton Instrumental Activities of Daily Living Scale (see Section 15.8).

Specifically, ages of<75, 75-80, and>80 years correspond to frailty scores of 0, 1, and 2, respectively. Charlson Comorbidity Scoring System scores of ≤ 1 and ≥ 2 correspond to frailty scores of 0 and 1, respectively. Katz Index of Independence in Activities of Daily Living scores of>4 and ≤ 4 correspond to frailty scores of 0 and 1, respectively. Instrumental Activities of Daily Living Scale scores of>5 and ≤ 5 correspond to frailty scores of 0 and 1, respectively. The sum of the 4 frailty scores equals the total frailty score. A total frailty score of 0 corresponds to a frailty status of fit; a total score of 1, to unfit; and a total score of 2 or more, to frail [1,2].

7.4.8 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at screening, predose on Cycle 1 Day 1, and at EOT, or more frequently as required per local regulations. The results from these tests must be available and negative before the first dose of the study drug is administered.

The Cycle 1 Day 1 pregnancy test may be collected up to 3 days before dosing. The results must be available and negative before the first dose. If the Cycle 1 Day 1 serum pregnancy results are not available before dosing, a urine pregnancy test may be performed.

Pregnancy tests may also be repeated during the study upon request by IEC/IRBs or if required by local regulations.

7.4.9 Concomitant Medications and Procedures

Concomitant medications and therapy will be recorded from the first dose of the study drug through 30 days after the last dose of study drug (see the Schedules of Events). See Section 6.6 for a list of prohibited concomitant medications and therapies and Section 6.7 for a list of allowed concomitant medications and therapies.

7.4.10 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedules of Events. Refer to Section 10 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

7.4.11 Enrollment

Prior to implementation of Amendment 08, a patient was considered to be enrolled in the study when the patient had been randomized to study treatment. Upon implementation of

Amendment 08, a patient will be considered to be enrolled when they meet all eligibility criteria, are entered into IXRS, and receive their first dose of ixazomib. For newly enrolled patients under Amendment 08, ixazomib must be initiated within 5 days of the patient being entered into the IXRS system.

Procedures for completing the enrollment information are described in the Study Manual.

7.4.12 Electrocardiogram

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

7.4.13 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed by a central laboratory. For dosing decisions, local hematology and chemistry laboratory results may be used; however, samples must also be sent to the central laboratory. Hematology and chemistry panels may be collected up to 3 days before Day 1 dosing and 24 hours before Day 8 and Day 15 dosing (when required). Local laboratory evaluations may be performed more frequently at the investigator's discretion (eg, for acute management of TEAEs). Local laboratory evaluations should be entered into the eCRF only if required to document an AE, dose modification, or other event, and the information entered should be limited to that required to understand the event (eg, for a dose hold for thrombocytopenia, enter the platelet count only). Handling and shipment of central clinical laboratory samples are outlined in the Study Manual.

As the laboratory results may not be available at the initiation of the next cycle, it is not required that these measurements be reviewed before initiating the next treatment cycle unless either of the following applies:

1. The patient has an ongoing toxicity. If the patient has had a toxicity resulting in a dose hold, it is mandatory that safety labs (local or central) are collected AND reviewed before starting the next cycle of treatment.

2. It is required per your local practice to have safety labs reviewed before starting the next cycle of treatment.

Patient eligibility should be decided using central laboratory results. If central lab results are not available at the time of enrollment, local laboratory results may be used as long as

samples are also sent to the central laboratory before the patient is enrolled. The central laboratory results will be used as reference for all response assessments. For situations where the local sample results are borderline in terms of meeting eligibility, the site is discouraged from relying on the local laboratory results for eligibility determination and encouraged to confirm eligibility using the central lab results. Such situations should be discussed with the Millennium project clinician or designee. The Millennium project clinician or designee will review the local and central laboratory eligibility results to ensure that the two are consistent.

Progressive disease should be documented and confirmed (by medical review of data; confirmatory testing should be done for biochemical changes but for bone sites, for example, this may not be appropriate). Before an investigator discontinues a patient from treatment for PD, the pertinent data must be confirmed by a Millennium project clinician or designee. If another therapy must be started immediately (within the next 10 business days), the investigator should provide the rationale to the Millennium project clinician or designee. In situations where the local results are borderline in terms of meeting criteria for PD, the site is discouraged from using only the local laboratory results.

Clinical Chemistry, Hematology, Urinalysis, [redacted]

Blood samples for analysis of the following clinical chemistry, hematologic, and serologic parameters and urine samples for urinalysis will be obtained as specified in the Schedules of Events.

Hematology

- Hemoglobin
- Hematocrit
- Platelet (count)
- Leukocytes with differential
- Neutrophils (absolute neutrophil count [ANC])

Serum Chemistry

- Blood urea nitrogen (BUN)
- Creatinine
- Bilirubin (total)
- Urate
- Lactate dehydrogenase (LDH)
- Gamma glutamyl transferase (GGT)
- Phosphate
- Albumin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Glucose
- Sodium
- Potassium
- Calcium
- Chloride
- Carbon dioxide (CO_2)
- Magnesium

Urinalysis

- Turbidity and color
- pH
- Specific gravity
- Protein
- Ketones
- Bilirubin
- Occult blood
- Nitrite
- Urobilinogen
- Glucose
- Leukocytes

[redacted]

7.4.14 [redacted]

[redacted]

7.4.15 Quality of Life Assessments

The HRQL assessments (EORTC QLQ-C30 [redacted]; see Sections 15.9 and 15.10) will be completed by the patient as specified in the Schedules of Events. The

EORTC QLQ-C30 incorporates 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

[redacted]

The time recall period for this instrument is 1 week (the week immediately preceding the assessment). These are reliable and valid measures of HRQL in patients with cancer and take about 15 minutes to administer. The instruments consist of a total of [redacted] and have been validated and used in many countries.

These assessments should be completed during the study visit, before other assessments are performed or study drug is taken.

These patient-reported outcome questionnaires are preferred to be completed by patients in the clinic but, if needed due the COVID-19 pandemic, the questionnaires may be completed at the patient's home using mailed paper versions of the questionnaires. In the case of paper-based questionnaires, only copies of questionnaires supplied by Millennium or ordered from the publisher may be used.

[redacted]

Note that signs and symptoms assessed with the patient-reported outcome questionnaires will not be considered AEs unless entered as such into the eCRF.

7.4.16 Bone Marrow Aspiration

7.4.16.1 Local Laboratory Evaluations

Disease Assessment

A BMA will be obtained at screening for disease assessment. In addition, a BMA will be obtained at any time during the study to assess CR or to investigate suspected PD. All of these evaluations will be performed locally.

Determination of the κ/λ immunoglobulin light-chain ratio by immunohistochemistry or immunofluorescence should be performed to assess for stringent CR when a CR has been documented. A bone marrow biopsy can additionally be performed per local standards for disease assessments.

An additional, optional BMA may be collected from patients at any time that PD is suspected or before the patient starts a new therapy. This BMA specimen will be evaluated locally.

7.4.17 Imaging Assessments

Skeletal survey of disease will be performed at screening (within 8 weeks before enrollment is acceptable). At least the following areas should be assessed: head, neck, chest, abdomen, pelvis, arms, and legs. For patients with documented extramedullary disease at the time of diagnosis, other assessments and scans, such as a CT, positron emission tomography (PET)–CT, or MRI, may be required to better delineate the sites and measurements of extramedullary disease at the time of screening. This imaging will also be used to delineate the extent of bone disease, sites and measurements of extramedullary disease, and PET positivity consistent with active MM. Additional assessments can be performed at the discretion of the investigator (ie, for suspected new lesions or PD or CR). The modality to be used is at the discretion of the investigator, and all follow-up scans should use the same imaging modality as was used at screening. Imaging assessments will be analyzed locally and reports maintained with the patient record for review during monitoring visits.

7.4.18 Quantification of M-Protein

A blood sample and urine sample will be obtained at screening and at the time points specified in the Schedules of Events.

7.4.19 Quantification of Immunoglobulins

A blood sample for quantification of immunoglobulins (IgM, IgG, IgA, IgD, and IgE) will be obtained at screening and at times specified in the Schedules of Events. Quantitative IgD and IgE will be performed at screening (and baseline, if needed) only. For the rare patient with IgD or IgE MM, the quantitative test for that antibody will be followed at the same time points as quantitative Igs (in addition to IgM, IgG, and IgA).

7.4.20 Serum Free Light Chain Assay

A blood sample for serum free light chain assay will be obtained at screening and at the times outlined in the Schedules of Events.

7.4.21 Immunofixation of Serum and Urine

Serum and urine samples will be obtained for serum and urine immunofixation tests at screening and at the times outlined in the Schedules of Events. 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.

7.4.22 Disease Response Assessment

Patients will be assessed for disease response according to the IMWG uniform response criteria, version 2011 (see Section 15.12) [53].

Response assessments are made on the basis of central laboratory data and should occur at Day 1 of every cycle during the Treatment period beginning with Cycle 2 Day 1, at EOT, and every 4 weeks during the PFS Follow-up period until PD (see the Schedules of Events). 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 be assessed for disease response by the investigator.

Response categories are as follows in Table 7.a:

Table 7.a Response Assessment

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

Complete response 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 15.12. One bone marrow assessment must occur to document CR; no second bone marrow confirmation of CR is needed.

Please note that 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.

At any point during treatment, patients suspected of having PD will have response assessments repeated to confirm PD (ie, 2 sets of response assessments at least 1 week apart).

7.4.23 Pharmacokinetic Measurements

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 10. Samples are to be collected at the time points specified in the Ixazomib Pharmacokinetic Sampling Schedule.

7.4.24 Follow-up Assessment for Progression-Free Survival, Progressive Disease, and Overall Survival

At EOT, patients will enter a Follow-up period for PFS, PD, and/or OS. See the Schedules of Events for assessments during each period. See the Study Overview Diagram for information about the sequence of follow-up. Information about any new primary malignancies will be collected during the study, including during all 3 Follow-up periods.

7.4.24.1 Progression-Free Survival Follow-up and Progressive Disease Follow-up

Patients who complete 24 months of treatment or who have stopped treatment for any reason other than PD will first enter the PFS Follow-up period. During this period, follow-up will occur every 4 weeks until the occurrence of PD. After PD occurs during the PFS Follow-up period, patients enter the PD Follow-up period. During this period, follow-up will occur every 4 weeks until next-line antineoplastic therapy is initiated by the investigator/treating physician.

If a patient has PD while on study drug during the Treatment period, the patient will enter directly into the PD Follow-up period and will be followed every 4 weeks until initiation of next-line therapy by the investigator/treating physician.

In both the PFS and PD Follow-up periods, the EORTC QLQ-C30 [redacted] questionnaires [redacted] will be administered every 4 weeks. [redacted]

7.4.24.2 Overall Survival Follow-up

After patients have PD, they enter into the OS Follow-up period (Note: Upon implementation of Amendment 08, the PFS2 Follow-up period is removed from the study.) During the OS Follow-up period, follow-up will occur every 12 weeks until death or termination of the study by the sponsor, whichever occurs first.

During the OS Follow-up period, assessments can be made over the telephone and do not require a clinic visit. Data may be collected by methods that include, but are not limited to, telephone, e-mail, mail, and by accessing publicly-available information. Both the patient and the current treating physician will be contacted during the OS Follow-up period to provide information about all MM treatments (drug regimen, interval, dose, start/stop date).

[redacted]

Related SAEs must be reported to the Millennium Department of Pharmacovigilance or designee. This includes deaths that the investigator considers related to study drug that occur during posttreatment follow-up. In addition, new primary malignancies that occur during Follow-up periods, irrespective of causality to study drug, must be reported to the Millennium Department of Pharmacovigilance or designee.

Refer to Section 10 for details regarding definitions, documentation, and reporting of SAEs.

7.5 Unscheduled Visits

Unscheduled visits may occur between treatment cycles as required. Assessments may be performed as clinically indicated at the discretion of the investigator.

7.6 Study Compliance

Study drug 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 drug receipt and dispensing.

7.7 Completion of Treatment

Patients will be considered to have completed study treatment if they meet any of the following criteria:

- Have received the maximum treatment duration of approximately 24 months
- Progressive disease or death at any time after the completion of Cycle 1

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 the study drug and will continue to be followed for other follow-up assessments specified in the Schedules of Events. Also refer to the Schedules of Events for EOT visit assessments.

7.8 Completion of Study

Patients will be considered to have completed the study if they are followed until death or until the sponsor terminates the study. The study will be considered complete when all patients in the China Continuation are off study treatment and have completed the EOT visit, or upon termination of the study by the sponsor, whichever occurs earlier.

7.9 Discontinuation of Treatment With Study Drug

For patients who did not complete study treatment as defined in Section 7.7, treatment with study drug must be discontinued for pregnancy. Treatment with study drug may also be discontinued permanently for any of the following reasons:

- Adverse event (including SAE)
- Protocol violation
- Study terminated by sponsor
- Withdrawal by subject or investigator
- Lost to follow-up
- Pregnancy (patient must be discontinued)
- Other

Once study drug has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the Schedules of Events. The primary reason for study drug discontinuation will be recorded on the eCRF.

In addition, upon implementation of Amendment 08, patients previously randomized to the placebo arm who do not cross over to ixazomib will complete an EOT visit and discontinue the study.

7.10 Withdrawal of Patients from Study

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

- Lost to follow-up
- Study terminated by sponsor
- Withdrawal by patient
- Other

In addition, upon implementation of Amendment 08, patients previously randomized to the placebo arm who do not cross over to ixazomib will complete an EOT visit and discontinue the study. 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.

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Statistical Methods

In general, summary tabulations will be presented 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 (K-M) survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided 95% CIs for time-to-event data.

Details for the statistical analysis will be provided in the statistical analysis plan (SAP).

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

8.1.1 Determination of Sample Size

The primary objective of the China Continuation is to allow the continued evaluation of any emerging safety signals and efficacy trends in patients in China. Prior to implementation of Amendment 08, 10 patients have been randomized and treated in the China Continuation. An additional ~20 patients are to be enrolled upon implementation of Amendment 08 for a total of approximately 30 patients overall.

With 30 patients, if the true rate for an AE is 10%, the probability of observing at least one patient with that AE is more than 95%. Similarly, if the true rate for an AE is 5%, the probability of observing at least one patient with that AE is more than 79%. Thus, the sample size is enough to give a large probability of observing AEs that are expected to commonly occur (ie, 5% or more) in this population.

8.1.2 Stratification

Upon implementation of Amendment 08, there will be no randomization or stratification of patients. All patients will receive open-label ixazomib.

8.1.3 Populations for Analysis

All analyses will be performed on the Overall Chinese Patient Population, defined as follows:

Overall Chinese Patient Population:

- Patients from China who were enrolled in the ixazomib arm of the C16021 global study, PLUS
- Patients in the ixazomib arm of the China Continuation before implementation of Amendment 08, PLUS
- All patients enrolled in the China Continuation under Amendment 08
- Patients who were randomized to the placebo arm before implementation of Amendment 08 and who crossed over to the ixazomib arm.

All Chinese patients listed in the above bullets constitute the population of interest for this study. Subsets from this population of interest will be derived and used for analysis, as follows:

Ixazomib Safety population: The Ixazomib Safety population is defined as all patients who receive at least 1 dose of ixazomib. Patients will be analyzed according to the treatment they actually received; patients who were randomized to the placebo arm prior to implementation of Amendment 08 and who cross over to the ixazomib arm will contribute safety data from the time they initiate ixazomib onward. The primary analysis of safety will focus on the Ixazomib Safety population.

Placebo Safety population: The Placebo Safety population is defined as all patients who receive at least 1 dose of placebo. Patients will be analyzed according to the treatment they actually received; patients who were randomized to the placebo arm prior to implementation of Amendment 08 and who cross over to the ixazomib arm will contribute safety data to this population only during the time they receive placebo. Adverse event data from this patient population will be listed.

Efficacy population: The Efficacy population is defined as all patients who receive ixazomib treatment for the duration of their study participation. Patients who were randomized to the placebo arm and crossed over to the ixazomib arm upon implementation of Amendment 08 will not be included in the Efficacy population.

Per-Protocol population: The Per-Protocol population is a subset of the Efficacy population and consists of all patients who do not have major protocol violations. The

definition of major protocol violations will follow the definitions used in the C16021 global study.

8.1.4 Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and 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.

In general, missing data will be treated as missing, and no data imputation will be applied, unless otherwise specified. For patient-reported outcomes data, missing data will be imputed; imputation will be based primarily on published instrument-specific methods. Other missing data imputation methods such as last observation carried forward and multiple imputation may be explored as sensitivity analyses for patient-reported outcomes data.

8.1.5 Demographic and Baseline Characteristics

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

8.1.6 Safety Analysis

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 Ixazomib Safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

Treatment-emergent AEs that occur after administration of the first dose of study drug and through 30 days after the last dose of study drug will be tabulated.

Adverse events will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) and will include the following categories:

- Treatment-emergent AEs
- Drug-related TEAEs
- Grade 3 or higher TEAEs

- Grade 3 or higher drug-related TEAEs
- The most commonly reported TEAEs (ie, those reported by both 5% and 10% of all patients)
- Serious adverse events

A listing of TEAEs resulting in study drug discontinuation will be provided.

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. Eastern Cooperative Oncology Group 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 drug 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.

8.1.6.1 New Primary Malignancy

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

1. Incidence proportions, defined as the percentage of the subjects reporting any new primary malignancy in the Ixazomib Safety population with available information

2. Incidence rates, defined as the number of the subjects reporting any new primary malignancy divided by the total duration of follow-up in the Ixazomib Safety population with available information up to the onset of new primary malignancies

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.

8.1.6.2 Time to Resolution and Improvement of Peripheral Neuropathy Events

Peripheral neuropathy is defined as the TEAE in the High Level Term of Peripheral neuropathies NEC (not elsewhere classified) according to MedDRA.

A PN event is considered to be resolved if its final outcome is resolved with no subsequent PN event of the same Preferred Term occurring on the resolution date or on the day before and the day after. A PN event is considered to be improved if the event improves from the maximum grade; that is, all the grades recorded after the maximum grade are less than the maximum grade.

Time to resolution and time to improvement are to be defined for each PN event. Time to resolution is defined as the time from the initial onset date (inclusive) to the resolution date for resolved events. Time to improvement is defined as the time from the initial onset date (inclusive) of the maximum grade to the first onset date that the toxicity grade is below the maximum grade with no higher grade thereafter, or the resolution date, whichever occurs first.

Time to improvement and time to resolution of PN events will be summarized by outcome (improvement or resolution) using the K-M method. The K-M survival curve and K-M medians (if estimable), along with their 2-sided 95% CIs, will be presented. This analysis is based on events; thus, 1 subject could contribute multiple observations if the subject has more than 1 PN event.

The analysis may be conducted for patients with any PN events or those with ≥ 2 PN events or those ≥ 3 PN events, respectively, if data permit.

8.1.7 Efficacy Analysis

8.1.7.1 Analyses for PFS

The analysis of PFS will be based on the Efficacy population using investigator-assessed progression data.

Progression-free survival is defined as the time from date of first dose to date of first documentation of 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 descriptively using Kaplan-Meier K-M) method. The K-M survival curves and medians (if estimable), along with their 2-sided 95% CIs, will be provided. The K-M estimates along with 95% CI will be provided by 6-month intervals at 6 months, 12 months, 18 months, and so on.

The analysis of PFS will be conducted at the time of the IA, approximately 12 months after the additional ~20 patients have been enrolled under this amendment. The analysis will be performed on the overall Chinese patient population (patients from China who were enrolled in the ixazomib arm of the C16021 global study, patients in the ixazomib arm of the China Continuation before implementation of Amendment 08, all patients enrolled in the China Continuation under Amendment 08, and patients who were randomized to the placebo arm before implementation of Amendment 08 and who crossed over to the ixazomib arm). The final analysis (FA) will be performed when all patients in the China Continuation are off treatment and have completed the EOT visit, or upon termination of the study by the sponsor, which occurs earlier. Descriptive statistics will be used to summarize patient data collected after the IA. A sensitivity analysis of PFS, as assessed by the investigator, in the Per-Protocol population may also be conducted.

Progression-free survival assessed by the investigator using different censoring mechanisms (eg, not censoring for patients who discontinue treatment and go on alternative antineoplastic therapy) will be analyzed in the Efficacy population. Details of different censoring approaches will be included in the SAP.

Subgroup analyses may be performed for PFS, as appropriate.

8.1.7.2 Analyses of OS

OS will be analyzed on the basis of the Efficacy population and is defined as the time from the date of the first dose of study drug to the date of death. Patients without documentation

of death at the time of analysis will be censored at the date last known to be alive. OS will be analyzed descriptively using K-M method. The K-M survival curves and medians (if estimable), along with their 2-sided 95% CIs, will be provided. The K-M estimates along with 95% CI will be provided by 6-month interval at 6 months, 12 months, 18 months, and so on.

Subgroup analyses for OS may be performed as appropriate.

8.1.7.3 Analyses of Other Secondary Efficacy Endpoints

Disease response–related endpoints will be analyzed using investigator-assessed response rate.

Best Response During the Treatment Period

The percentage of each response category (CR, VGPR, and PR) and of the combination CR + VGPR will be determined.

Duration of Complete Response

Duration of CR is defined as the time from the date of the first dose (for those who had a CR at study entry) or the date of CR (for those in whom CR was achieved during the treatment period) to the date of first documentation of PD. Responders without documentation of PD will be censored at the date of the last assessed CR. Duration of CR will be summarized descriptively using the K-M method.

Time to Progression

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

Time to Next-Line Therapy

TTNT is defined as the time from date of first dose to date of first dose of next-line antineoplastic therapy. TTNT will be analyzed on the basis of the Efficacy population. Patients who have not started next-line therapy will be censored at the last known contact date.

Correlation Between Frailty Status and Progression-Free Survival and Overall Survival

The K-M survival curves and K-M median PFS or OS (if estimable), along with their 2-sided 95% CIs, will be provided for each frailty status.

8.1.8 Analyses of Patient-Reported Outcomes [redacted]

Analyses of patient-reported outcomes [redacted] will be performed using the Efficacy population.

8.1.8.1 Patient-Reported Outcomes Analysis

The actual value and change from baseline of the subscale scores for the EORTC QLQ-C30 [redacted] will be summarized using descriptive statistics and plotted over time.

The number and percentage of patients with a meaningful change from baseline in subscale scores will be summarized over time. The published minimally important difference will be used to define such meaningful change from baseline. Specific interest will be on global health status, but data on all other subscales will also be analyzed.

The change from baseline in subscale scores will be presented using cumulative distribution function figures.

8.1.8.2 [redacted]

8.1.9 Pharmacokinetics/Pharmacodynamics/Biomarkers

8.1.9.1 Pharmacokinetic Analysis

Pharmacokinetic data collected in this study will 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.

8.1.10 Interim and Final Analyses

The primary analysis for safety and efficacy will be performed at the time of the first IA, approximately 12 months after the additional ~20 patients have been enrolled under this amendment. The safety and efficacy endpoints will be assessed in the overall Chinese patient population (patients in China enrolled to the ixazomib arm of the C16021 global study, patients from the ixazomib arm of the China Continuation before implementation of Amendment 08, and all patients enrolled under Amendment 08). The final analysis will be performed when all patients in the China Continuation part of Study C16021 are off treatment and have completed an EOT visit, or upon termination of the study by the sponsor, which occurs earlier.

9. STUDY COMMITTEES

9.1 Steering Committee

A steering committee that includes a subset of investigators in this study and representatives from Millennium will be formed to provide advice on the conduct of the study and publications.

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event is 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 require a causal relationship with study participation.

10.1.2 Adverse Event Definition

Adverse event (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 drug.

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 Serious Adverse Event Definition

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

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

Overdose in and of itself is not an SAE. If an overdose results in an SAE, an SAE form should be completed and sent to Cognizant (refer to Section 10.2).

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [52]. 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 Adverse Events and Serious Adverse Events

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 Department of Pharmacovigilance or designee (contact information provided below). This should be done by emailing or 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 must confirm successful transmission of all pages and include an e-mail address on the fax cover sheet so that an acknowledgment of receipt can be returned via e-mail within 1 business day. E-mail 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 e-mail, site personnel must confirm successful transmission by awaiting an acknowledgment of the receipt via e-mail within 1

business day. If SAEs are reported via fax or by e-mail, the EDC application must be updated as soon as possible with the appropriate information.

SAE Reporting Contact Information

Cognizant
US and Canada
Toll-Free Fax #: 1-800-963-6290
E-mail: takedaoncocases@cognizant.com

All Other Countries (Rest of World)
Fax #: 1-202-315-3560
E-mail: takedaoncocases@cognizant.com

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

For both serious and nonserious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [52]. The criteria are provided in the Study Manual.

Relationship to study drug administration will be determined by the investigator responding yes or no to this question: Is there a reasonable possibility that the AE is associated with the study drug?

10.3 Monitoring of Adverse Events and Period of Observation

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

- AEs will be reported from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRFs. AEs should

be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

- Serious pretreatment events will be reported to the Millennium Department of Pharmacovigilance or designee from the time of the signing of the ICF up to first dose of study drug but will not be recorded in the eCRF.

- Related and unrelated SAEs will be reported to the Millennium Department of Pharmacovigilance or designee from the first dose of study drug through 30 days after administration of the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first, and recorded in the eCRF. After this period, only related SAEs must be reported to the Millennium Department of Pharmacovigilance or designee. Serious adverse events should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). In addition, new primary malignancies that occur must be reported, irrespective of causality to the study drug, from the first dose of study drug through death or termination of the study by the sponsor.

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female patient occurring while the patient is on study drug, or within 90 days of the patient's last dose of study drug, are considered immediately reportable events. Study drug is to be discontinued immediately. The sponsor must also be contacted immediately by emailing or faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance 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 or within 90 days of the patient's last dose of study drug, the sponsor must also be contacted immediately by emailing or faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11. ADMINISTRATIVE REQUIREMENTS

11.1 Good Clinical Practice

The study will be conducted in accordance with the ICH-GCP and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and the IB.

11.2 Data Quality Assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Study data will be entered into an eCRF by site personnel using a secure, validated, web-based electronic data capture (EDC) application. Millennium will have access to all data upon entry in the EDC application.

Study monitors will discuss instances of missing or uninterpretable data with the investigator for resolution. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

11.3 Electronic Case Report Form Completion

Millennium or designee will provide the study sites with secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for whom they are responsible.

Electronic case report forms will be completed for each study patient. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF.

The investigator, or designated representative, should complete the eCRF as soon as possible after information is collected.

The investigator must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for which he or she is responsible. The audit trail entry will show the user's identification information and the date and time of the correction.

Millennium, or a designee, will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk or other electronic media will be placed in the investigator's study file.

11.4 Study Monitoring

Monitoring and auditing procedures developed or approved by Millennium will be followed to comply with GCP guidelines.

All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner that ensures that patient confidentiality is maintained.

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 (SDV) 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 the local Health Authority and permitted by the IRB/IEC.

11.5 Ethical Considerations

The study will be conducted with the highest respect for the individual participants (ie, patients) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or the sponsor, as allowed by local regulations.

11.6 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. For patients enrolled prior to implementation of Amendment 08 and still on study treatment, all

patients must be reconsented before dosing on Day 1 of the next full treatment cycle. Patients enrolled prior to implementation of Amendment 08 who are in one of the follow-up periods must also be reconsented.

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.

11.7 Patient Confidentiality

To maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by initials where permitted and/or by the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

11.8 Investigator Compliance

The investigator will conduct the trial in compliance with the protocol provided by Millennium and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol are not to be made without agreement of both the investigator and Millennium. Changes to the protocol will require written IRB/IEC approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard or hazards to patients. Millennium, or a designee, will submit all protocol modifications to the appropriate regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard or hazards to patients, the investigator will contact Millennium, or a designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

11.9 On-site Audits

Regulatory authorities, the IEC/IRB, and/or Millennium may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

11.10 Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at the trial site is the responsibility of the investigator. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to Millennium, or a designee (or disposal of the drug, if approved by Millennium) will be maintained by the clinical site. Millennium or its designee will review drug accountability at the site on an ongoing basis.

All material containing study drug will be treated and disposed of in accordance with governing regulations.

11.11 Product Complaints and Medication Errors (Including Overdoses)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report the event to ctmcomplaint@takeda.com.

Product complaints in and of themselves are not AEs. If a product complaint is associated with an SAE, a Millennium SAE Form should be completed and sent to Cognizant (refer to Section 10.2).

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. Whereas overdoses constitute medication errors, doses missed inadvertently by a patient do not. Investigators must record all medication errors (including overdose) on the appropriate eCRF. Individuals who identify a potential medication error situation should immediately to ctmcomplaint@takeda.com.

11.12 Closure of the Study

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 trial 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 IA
- 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 EDC application, will not have a right to use the EDC application, and will cease using the password or access materials once their 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.

11.13 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and Millennium notified.

12. USE OF INFORMATION

All information regarding ixazomib supplied by Millennium to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Millennium. It is understood that there is an obligation to provide Millennium with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of ixazomib and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

Upon completion of the clinical study and evaluation of results by Millennium, the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

A Steering Committee that includes a subset of investigators in this study and representatives from Millennium will be formed to advise on the conduct of the study and development of publications and presentations. This policy may be changed with the agreement of both the investigators and Millennium.

13. INVESTIGATOR AGREEMENT

I have read Protocol C16021 Amendment 10: China Continuation: A Single-Arm, Open-Label Study of Oral Ixazomib Maintenance Therapy After Initial Therapy in Patients With Newly Diagnosed Multiple Myeloma Not Treated With Stem Cell Transplantation

I agree to conduct the study as detailed herein and in compliance with International Conference on Harmonisation Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____
Principal investigator printed name

_____ _____
Principal investigator signature Date

_____

_____

_____
Investigational site or name of institution and location (printed)

14. REFERENCES

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15. APPENDICES

15.1 Multiple Myeloma Diagnostic Criteria

International Myeloma Working Group Criteria for the Diagnosis of Myeloma

Diagnosis	Diagnostic Criteria: All Three Required
Symptomatic multiple myeloma[a]	• Monoclonal plasma cells in the bone marrow ≥10% and/or presence of a biopsy-proven plasmacytoma • Monoclonal protein present in the serum and/or urine[b] • Myeloma-related organ dysfunction (≥1)[c] [C] Calcium elevation in the blood (serum calcium>10.5 mg/dL or upper limit of normal) [R] Renal insufficiency (serum creatinine>2 mg per 100 ml) [A] Anemia (hemoglobin<10 g per 100 ml or 2 g<normal) [B] Lytic bone lesions or osteoporosis[d]

Source: International Myeloma Foundation, myeloma.org. Accessed 16 January 2012.

a These criteria identify Stage IB and Stages II and III A/B myeloma by Durie-Salmon stage. Stage IA becomes smoldering or indolent myeloma.

b If no monoclonal protein is detected (nonsecretory disease), then ≥30% monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma required.

c A variety of other types of end-organ dysfunctions can occasionally occur and lead to a need for therapy. Such dysfunction is sufficient to support classification as myeloma if proven to be myeloma related.

d If a solitary (biopsy-proven) plasmacytoma or osteoporosis alone (without fractures) is the sole defining criteria, then ≥30% plasma cells are required in the bone marrow.

15.2 Eastern Cooperative Oncology Group 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 MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55 [54].

15.3 Cockcroft-Gault Equation

For males:

$$\text{Creatinine Clearance} = \frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine[mg/dL]})} \text{ OR } \frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine[µmol/L]})}$$

For females:

$$\text{Creatinine Clearance} = \frac{0.85\ (140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine[mg/dL]})} \text{ OR } \frac{0.85\ (140 - \text{age[years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine[µmol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41 [55].

15.4 Steroid Equivalent Doses

Approximate equivalent doses:

Steroid	Glucocorticoid Anti-inflammatory (mg)	Mineralocorticoid (mg)	Half-life (hours)
Cortisone	100	100	8–12
Hydrocortisone	80	80	8–12
Prednisone	20	100	12–36
Prednisolone	20	100	12–36
Methylprednisolone	16	no effect	12–36
Dexamethasone	2	no effect	36–72

Source: Knoben JE, Anderson PO. Handbook of Clinical Drug Data, 6th ed. Drug Intelligence Pub, Inc. 1988 [56].

15.5 ISS Staging Criteria

International Staging System

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: Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer 1975;36(3):842-54 [57].

Abbreviations: ISS=International Staging System.

a There are two 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.

15.6 Charlson Comorbidity Scoring System Without Age Weighting

Table 1. Charlson Comorbidity Index Scoring System

Score	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral vascular disease (includes aortic aneurysm ≥6 cm)
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumor without metastases (exclude if >5 y from diagnosis)
	Leukemia (acute or chronic)
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS (not just HIV positive)

NOTE. For each decade > 40 years of age, a score of 1 is added to the above score.
Abbreviations: ECG, electrocardiogram; CVA, cerebrovascular accident; TIA, transient ischemic attack; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

Source: Charlson et al., 1987.[3]

15.7 Activities of Daily Living Index

Katz Index of Independence in Activities of Daily Living

Slightly adapted from Katz, S., Down, T.D., Cash, H.R., & Grotz, R.C. (1970) Progress in the development of the index of ADL. *The Gerontologist, 10*(1), 20-30.

Source: Hartford Institute of Geriatric Nursing, ConsultGeriRN.org, General Assessment Try This, accessed 24 May 2014: Issue 2, Revised 2012 (consultgerirn.org/uploads/File/trythis/try_this_2.pdf): Katz Index of Independence in Activities of Daily Living.

15.8 Instrumental Activities of Daily Living Index

The Lawton Instrumental Activities of Daily Living Scale

A. Ability to Use Telephone

1. Operates telephone on own initiative; looks up and dials numbers 1
2. Dials a few well-known numbers 1
3. Answers telephone, but does not dial 1
4. Does not use telephone at all 0

B. Shopping

1. Takes care of all shopping needs independently 1
2. Shops independently for small purchases 0
3. Needs to be accompanied on any shopping trip 0
4. Completely unable to shop 0

C. Food Preparation

1. Plans, prepares, and serves adequate meals independently 1
2. Prepares adequate meals if supplied with ingredients 0
3. Heats and serves prepared meals or prepares meals but does not maintain adequate diet 0
4. Needs to have meals prepared and served 0

D. Housekeeping

1. Maintains house alone with occasion assistance (heavy work) 1
2. Performs light daily tasks such as dishwashing, bed making 1
3. Performs light daily tasks, but cannot maintain acceptable level of cleanliness 1
4. Needs help with all home maintenance tasks 1
5. Does not participate in any housekeeping tasks 0

E. Laundry

1. Does personal laundry completely 1
2. Launders small items, rinses socks, stockings, etc. 1
3. All laundry must be done by others 0

F. Mode of Transportation

1. Travels independently on public transportation or drives own car 1
2. Arranges own travel via taxi, but does not otherwise use public transportation 1
3. Travels on public transportation when assisted or accompanied by another 1
4. Travel limited to taxi or automobile with assistance of another 0
5. Does not travel at all 0

G. Responsibility for Own Medications

1. Is responsible for taking medication in correct dosages at correct time 1
2. Takes responsibility if medication is prepared in advance in separate dosages 0
3. Is not capable of dispensing own medication 0

H. Ability to Handle Finances

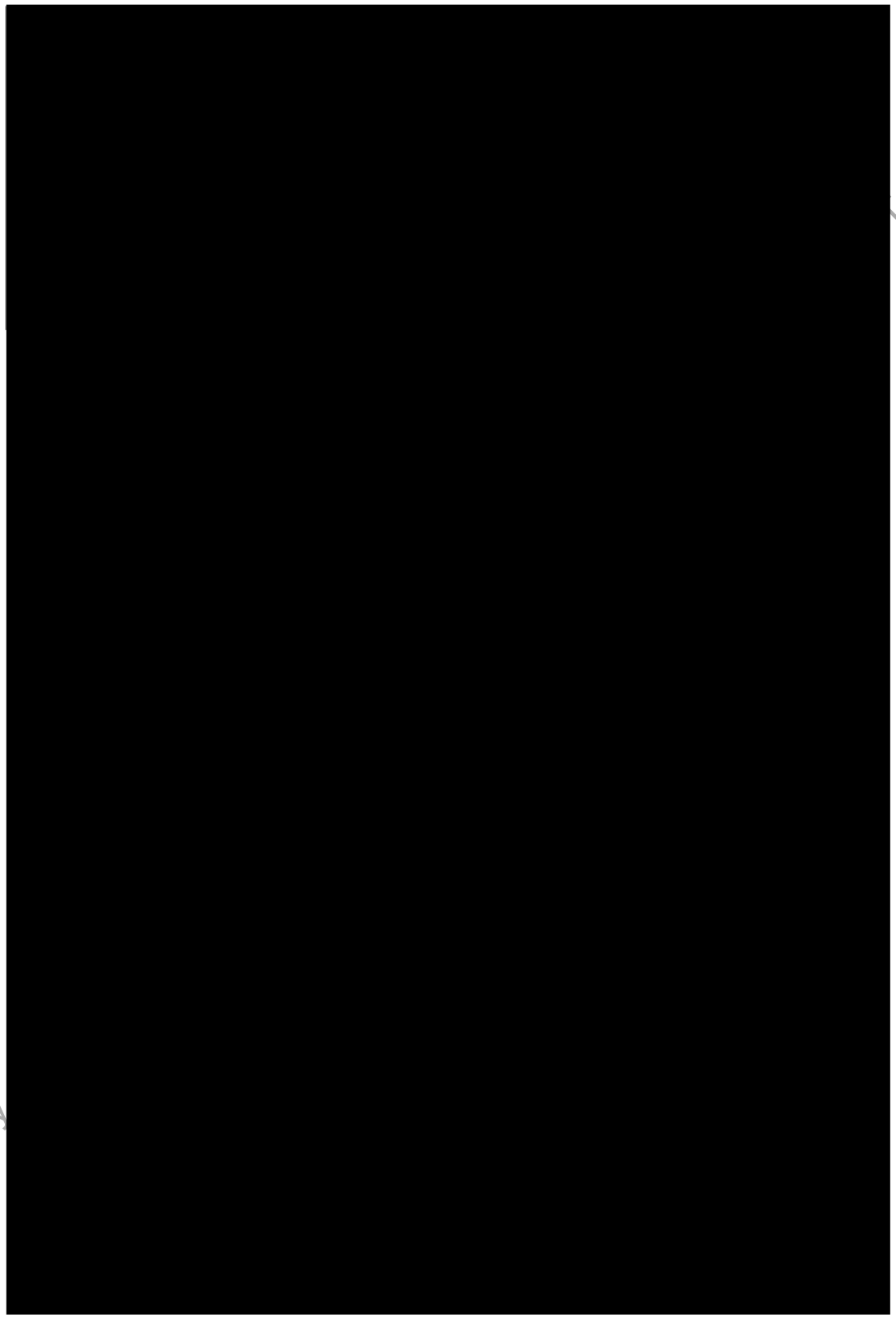
1. Manages financial matters independently (budgets, writes checks, pays rent and bills, goes to bank); collects and keeps track of income 1
2. Manages day-to-day purchases, but needs help with banking, major purchases, etc 1
3. Incapable of handling money 0

Scoring: For each category, circle the item description that most closely resembles the client's highest functional level (either 0 or 1).

Lawton, M.P., & Brody, E.M. (1969). Assessment of older people: Self-maintaining and instrumental activities of daily living. *The Gerontologist, 9*(3), 179-186.

Source: Hartford Institute of Geriatric Nursing, ConsultGeriRN.org, General Assessment Try This, accessed 24 May 2014: Issue 23, Revised 2013 (consultgerirn.org/uploads/File/trythis/try_this_23.pdf): The Lawton Instrumental Activities of Daily Living Scale.

15.9 European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3)



[redacted]

15.10 [redacted]

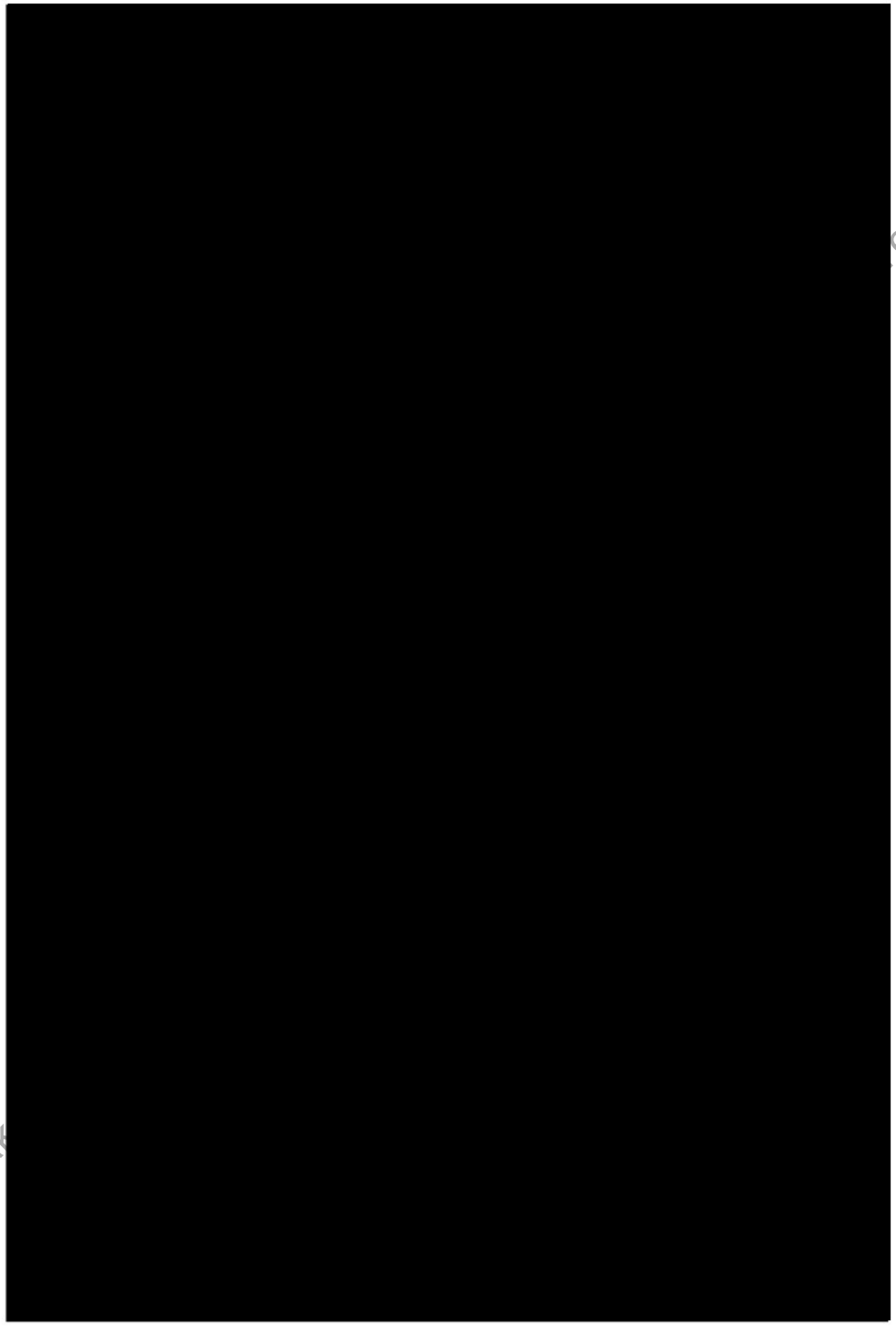
[redacted]

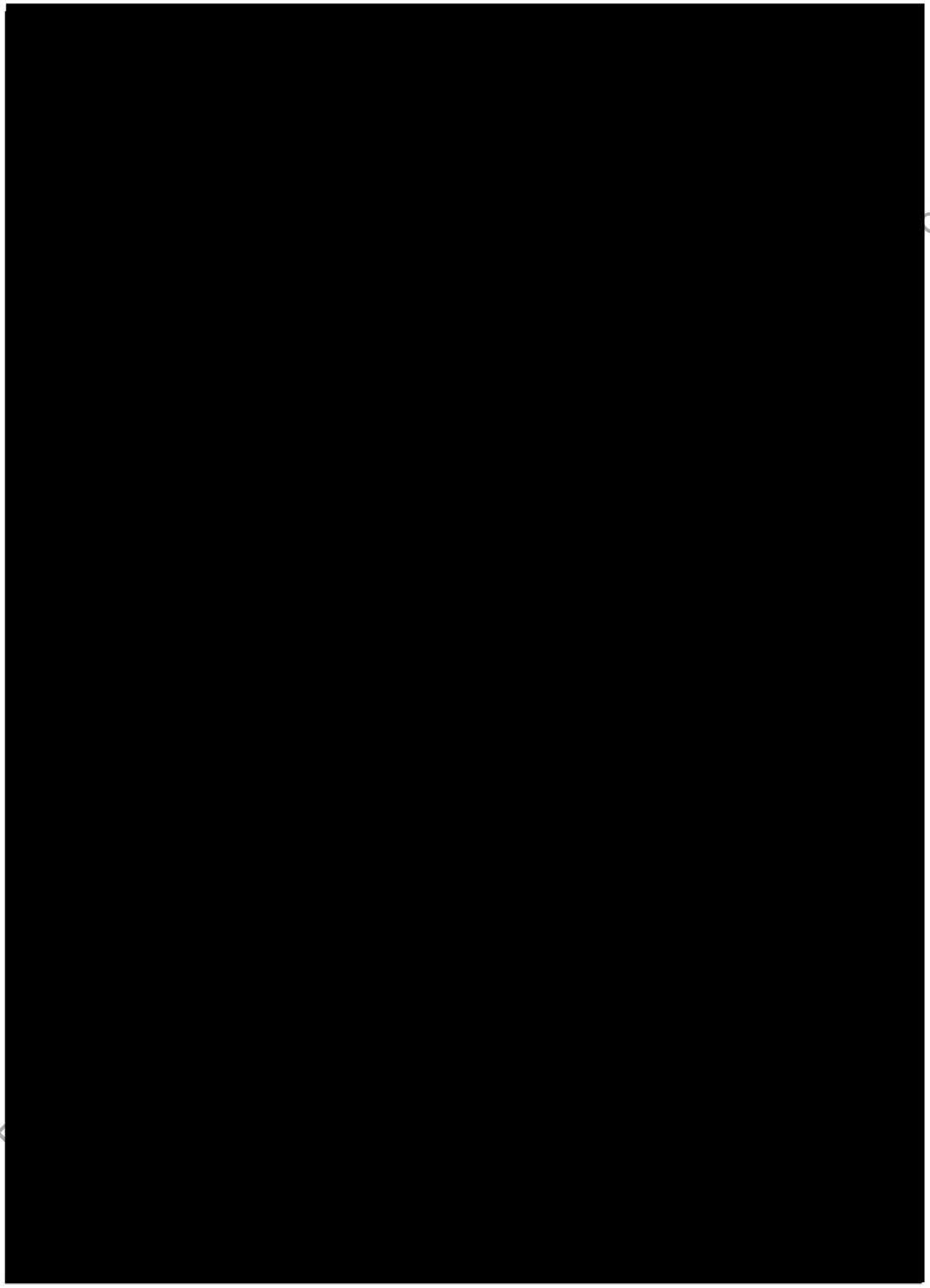
[redacted]

[redacted]

15.11 [redacted]

[redacted]





15.12 Response Criteria

Table 1. IMWG uniform response criteria by response subcategory for multiple myeloma[7]

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 required		Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 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 SV, et al. 2011 [58]. (adapted from Durie et al. [53] and Kyle et al. [59] with permission).

15.13 Schedule of Events Prior to Implementation of Amendment 08

Study Procedures	**Screening**	**Treatment Period**									**EOT[a]**	**Follow-up[b]**			
		28-Day Cycles[b]										**PFS**	**PD**	**PFS2**	**OS**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3**	**Cycles 4–5**	**Cycle 5[c]**	**Cycles 6-26**		**Every 4 Wk Until PD**	**Every 4 Wk After PD Until Next-Line Therapy**	**Every 12 Wk Until PD2 on Next-Line Therapy**	**Every 12 Wk After PD on Next-Line Therapy**
Days	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**1**	**1**	**8**	**1**					
Window		**±2 Days**									**+1 Wk**	**±1 Wk**	**±1 Wk**	**±1 Wk**	**±1 Wk**
Informed consent	X														
Inclusion/ exclusion criteria[d]	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		X	X		
ECOG Performance Status	X				X		X	X		X	X	X	X		
Frailty status[e]	X														
Vital signs	X	X			X		X	X		X	X	X	X		
Height (cm)	X														
Weight (kg)	X	X			X		X	X		X	X				
12-lead ECG	X														

Study Procedures	Screening	Treatment Period									EOT[a]	Follow-up[b]			
		28-Day Cycles[b]										PFS	PD	PFS2	OS
Cycle		Cycle 1			Cycle 2		Cycle 3	Cycles 4–5	Cycle 5[c]	Cycles 6-26		Every 4 Wk Until PD	Every 4 Wk After PD Until Next-Line Therapy	Every 12 Wk Until PD2 on Next-Line Therapy	Every 12 Wk After PD on Next-Line Therapy
Days	-28 to -1	1	8	15	1	8	1	1	8	1					
Window		±2 Days									+1 Wk	±1 Wk	±1 Wk	±1 Wk	±1 Wk
EORTC QLQ-C30[f]	X	X			X		X	X		X	X	X	X	X (twice only)	
[redacted]															
Imaging disease assessment[g]	X														
Investigator assessment of disease response/status	X				X		X	X		X	X	X		X[h]	
Ixazomib or placebo[i]		Single dose on Days 1, 8, and 15 of each cycle													
Determination of dose escalation[i]								X (Cycle 5)							
Adverse event reporting[j]		Recorded from the first dose of study drug through 30 days after last dose of study drug[s]													

Study Procedures	**Screening**	**Treatment Period**									**EOT[a]**	**Follow-up[b]**			
		28-Day Cycles[b]										**PFS**	**PD**	**PFS2**	**OS**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3**	**Cycles 4–5**	**Cycle 5[c]**	**Cycles 6-26**		**Every 4 Wk Until PD**	**Every 4 Wk After PD Until Next-Line Therapy**	**Every 12 Wk Until PD2 on Next-Line Therapy**	**Every 12 Wk After PD on Next-Line Therapy**
Days	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**1**	**1**	**8**	**1**					
Window		**±2 Days**									**+1 Wk**	**±1 Wk**	**±1 Wk**	**±1 Wk**	**±1 Wk**
	Serious adverse events and serious pretreatment events will be collected from signing of the informed consent form through 30 days after the last dose of study drug														
Concomitant medications/ procedures		Recorded from the first dose of study drug through 30 days after last dose of study drug													
New primary malignancy assessment		Continuous from start of study drug administration until death or termination of the study by sponsor													
Survival															X
Subsequent therapy														X	X
Samples/Laboratory Assessments															
Pregnancy test (serum)[k]	X	X									X				
Hematology laboratory[l]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry laboratory[l]	X	X			X		X	X		X	X	X	X		
Urinalysis	X														
[redacted]															
M-protein (SPEP)	X	X[n]			X		X	X		X	X	X	X		

Study Procedures	**Screening**	**Treatment Period**									**EOT[a]**	**Follow-up[b]**			
		28-Day Cycles[b]										**PFS**	**PD**	**PFS2**	**OS**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3**	**Cycles 4–5**	**Cycle 5[c]**	**Cycles 6-26**		**Every 4 Wk Until PD**	**Every 4 Wk After PD Until Next-Line Therapy**	**Every 12 Wk Until PD2 on Next-Line Therapy**	**Every 12 Wk After PD on Next-Line Therapy**
Days	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**1**	**1**	**8**	**1**					
Window		**±2 Days**									**+1 Wk**	**±1 Wk**	**±1 Wk**	**±1 Wk**	**±1 Wk**
M-protein (UPEP [24-hr urine])	X	X[n]			X		X	X		X	X	X	X		
SFLC assay	X	X[n]			X		X	X		X	X	X	X		
Immunofixation: serum and urine[o]	X	X[n]			X		X	X		X	X	X	X		
Quantification of Ig[p]	X	X[n]			X		X	X		X	X	X	X		
Bone marrow aspiration (BMA)															
Disease assessment BMA (local lab)[q]	X														
MRD BMA in patients with confirmed or suspected CR (central lab)[r]	X	Additional MRD BMA specimen is requested at the time of first CR (may be collected during the BMA procedure for CR confirmation)								X (Cycle 13)	X				
Archival BMA sample[s]	X (if N/A at this time, can be submitted later)														

Study Procedures	**Screening**	**Treatment Period**								**EOT[a]**	**Follow-up[b]**			
		28-Day Cycles[b]									**PFS**	**PD**	**PFS2**	**OS**
Cycle		**Cycle 1**			**Cycle 2**		**Cycle 3**	**Cycles 4–5**	**Cycle 5[c]**	**Cycles 6-26**		**Every 4 Wk After PD Until Next-Line Therapy**	**Every 12 Wk Until PD2 on Next-Line Therapy**	**Every 12 Wk After PD on Next-Line Therapy**
Days	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**1**	**1**	**8**	**1**	**Every 4 Wk Until PD**			
Window		**±2 Days**								**+1 Wk**	**±1 Wk**	**±1 Wk**	**±1 Wk**	**±1 Wk**
Progressive disease BMA (local lab)[t]		Progressive disease BMA specimen is requested at any time of progressive disease confirmation												

Abbreviations: BMA=bone marrow aspirate; CT=computed tomography; ECG=electrocardiography; ECOG=Eastern Cooperative Oncology Group; EORTC=European Organization for Research and Treatment of Cancer; EOT=End of Treatment; [redacted]; Ig=immunoglobulins; MRD=minimal residual disease; MRI=magnetic resonance imaging; N/A=not available; OS=overall survival; PD=progressive disease (disease progression); PD2=second PD (on next-line therapy); PET=positron emission tomography; PFS=progression-free survival, defined as time from randomization to PD or death from any cause; PFS2=time from randomization to objective disease progression on next-line treatment or death from any cause; PN=peripheral neuropathy; QLQ-C30=Quality of Life Questionnaire Core 30 (questions); [redacted] SFLC=serum free light chain; SPEP=serum protein electrophoresis; UPEP=urine protein electrophoresis.

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 Pharmaceuticals, Inc. (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. This 2-day window also is permissible for study days not specified in this Schedule of Events, including Cycle 2 Day 15 and Day 8 and Day 15 of Cycle 3 and beyond.

a Before an investigator discontinues a patient from treatment for PD, the pertinent data must be confirmed by a Millennium project clinician or designee.

b For Cycle 4 and 5 and Cycle 6 through 26 procedures, all cycles are meant unless numbers are given in parentheses, indicating the specific cycles meant. For PFS and PD follow-up, exceptions to the follow-up interval of every 4 weeks are given in parentheses.

c Cycle 5 Day 8 assessments should be done only for patients who have the dose escalated after Cycle 4.

d Confirmation of patient eligibility by the Millennium project clinician or designee is required before randomization.

e Patients' frailty status is classified as fit, unfit, or frail on the basis of 4 components: age, the Katz Index of Independence in Activities of Daily Living, the Lawton Instrumental Activities of Daily Living Scale, and the Charlson Comorbidity Scoring System [1-3].

f Patient-reported outcomes [redacted] should be completed before any other study procedures are performed or study drug is administered. During the PFS2 Follow-up period only, assessments should be done twice—ideally once approximately 8-12 weeks after the start of next-line therapy and again 8-12 weeks later—and are preferred to be administered in the clinic, but if needed, the QLQ-C30 [redacted] questionnaires may be completed at home. At time points when a clinic visit is not required, [redacted].

g A skeletal survey to assess status of bone disease and extramedullary disease will be done at screening (within 8 weeks before randomization) for all patients. Additional assessments can be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD). At the discretion of the investigator, a

Study Procedures	Screening	Treatment Period								EOT[a]	Follow-up[b]			
		28-Day Cycles[b]									PFS	PD	PFS2	OS
Cycle		Cycle 1			Cycle 2		Cycle 3	Cycles 4–5	Cycle 5[c]	Cycles 6-26				
Days	-28 to -1	1	8	15	1	8	1	1	8	1	Every 4 Wk Until PD	Every 4 Wk After PD Until Next-Line Therapy	Every 12 Wk Until PD2 on Next-Line Therapy	Every 12 Wk After PD on Next-Line Therapy
Window		±2 Days								+1 Wk	±1 Wk	±1 Wk	±1 Wk	±1 Wk

CT scan, a PET-CT scan, or whole body MRI may be done at screening in place of a skeletal survey, provided that the same modality for assessment is used throughout the study.

h Information about disease response/status should be collected during the PFS2 Follow-up period, until PD2 has occurred during next-line therapy.

i Study drug must be initiated within 5 days after randomization. Patients will receive blinded study drug (ixazomib or matching placebo) orally on Days 1, 8, and 15 of every 28-day cycle. A starting dose of 3 mg of ixazomib (or matching placebo) will be given to all patients through Cycle 4. Upon evaluation of toxicities at Cycle 4, and on the basis of the dose escalation criteria detailed in Section 6.5, the dose will be escalated to 4 mg (or matching placebo) on Cycle 5 Day 1 and administered on the same schedule for the duration of the study to provide maximum possible clinical benefit for patients who tolerated the first 4 cycles of treatment (see Section 6.5). If dose escalation was inadvertently missed at Cycle 5, escalation at a later cycle may be performed with permission from the Millennium project clinician or designee.

j When PN occurs, each subsequent monthly evaluation will record the grade of PN at that visit. (This is in contrast to other adverse events 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 the PN, 2) the start of a second-line alternative antineoplastic treatment, or 3) 6 months after PD has occurred—whichever occurs first.

k A serum pregnancy test will be performed for women of childbearing potential during screening, predose on Cycle 1 Day 1, and at the EOT visit, or more frequently as required per local regulations. The Cycle 1 Day 1 pregnancy test may be collected up to 3 days before dosing. The results must be available and negative before the study drug is administered.

l Clinical laboratory evaluations will be performed by a central laboratory (see Section 7.4.13 and the Laboratory Manual). For dosing decisions, local hematology and chemistry laboratory results may be used; however, samples must still be sent to the central laboratory also. Hematology and chemistry panels may be collected up to 3 days before Day 1 dosing and 24 hours before Day 8 and Day 15 dosing, where required. Local laboratory evaluations may be done more frequently at the investigator's discretion (ie, for acute management of treatment-emergent adverse events).

[redacted]

n If the screening test was performed more than 14 days before the first dose, the test will be repeated at baseline.

o Immunofixation is also to be done to confirm CR (if the M-protein level is undetectable by protein electrophoresis in both serum and urine, the central laboratory will perform immunofixation testing in both serum and urine).

p Blood samples for IgM, IgG, and IgA will be obtained throughout the study at the time points specified. Quantitative IgD and IgE measurement will be done at screening (and baseline if needed) only, except for the rare patient who has IgD or IgE multiple myeloma, for whom quantitative measurement for that antibody will

Study Procedures	Screening	Treatment Period									EOT[a]	Follow-up[b]			
		28-Day Cycles[b]										PFS	PD	PFS2	OS
Cycle		Cycle 1			Cycle 2		Cycle 3	Cycles 4–5	Cycle 5[c]	Cycles 6-26		Every 4 Wk Until PD	Every 4 Wk After PD Until Next-Line Therapy	Every 12 Wk Until PD2 on Next-Line Therapy	Every 12 Wk After PD on Next-Line Therapy
Days	-28 to -1	1	8	15	1	8	1	1	8	1					
Window		±2 Days									+1 Wk	±1 Wk	±1 Wk	±1 Wk	±1 Wk

be done at the same time points as, and in addition to, IgM, IgG, and IgA measurements.

q BMA for disease assessment is to be evaluated at a local laboratory at screening. BMA with local assessment should be repeated if the patient has reduction of serum and urine M-protein consistent with possible CR or when indicated to investigate suspected PD.

r In patients with confirmed or suspected CR at study entry, during the screening BMA procedure, and additional BMA sample for central evaluation of MRD will be collected. In addition, all patients in CR at Cycle 13 and at EOT (approximately 24 months [equivalent to 26 cycles, if no cycle delays]) will have BMA samples collected for MRD at those 2 time points (unless already done within the most recent 2 cycles). BMA samples for MRD will also be obtained in patients in CR who stop therapy before Cycle 26. For all other patients, when a BMA is performed to confirm suspected CR, an additional BMA sample for MRD will be collected. All BMA samples for MRD are required to be sent to the central laboratory for processing immediately after collection.

s Archival tumor material from the time of diagnosis and any available other prestudy time points (when the patient has a high disease burden) is to be used for the identification of the MM tumor clone, which will then be followed in the serial MRD BMA samples obtained during the study. The material should consist of BMA as unstained slides (preferred) or stained slides. Bone marrow biopsy samples will not be accepted. If not available at screening, the archival BMA sample may be submitted at any time during the study.

t An additional BMA for patients who have PD is optional but highly recommended and should be collected at any time PD is suspected or before starting a new therapy. This marrow will be evaluated locally.

15.14 Amendment 01 (China) Rationale and Purposes

Rationale for Amendment 01

The primary rationale for this amendment is to modify the global study procedures for patients who enroll in the global study in China: [redacted]

Purposes for Amendment 01

The purposes of this amendment are to:

- [redacted]
- Add information about multiple myeloma (MM) incidence and prevalence in China.
- [redacted]
- Correct typographical errors, punctuation, grammar, and formatting.

15.15 Amendment 02 (Global) Rationale and Purposes

Rationale for Amendment 02

The primary rationale for this amendment is to extend the follow-up period in which health-related quality of life (HRQL) measurements are obtained, update the description of the HRQL analyses, and update the HRQL statistical analysis methods; remove the exclusion of cytochrome P450 (CYP) inhibitors; and change the Charlson Comorbidity Scoring System in use, which is weighted for age, to the original scoring system, which is not weighted for age. Other purposes for the amendment are the addition of a secondary endpoint and numerous administrative changes.

Purposes for Amendment 02

The purposes of this amendment are to:

- Extend the duration of HRQL data collection into the period of next-line therapy and update the description of HRQL analyses.
- Update HRQL statistical analysis methods.
- Update the pharmacokinetics (PK) and concomitant medication information to reflect recent population PK analyses and drug-drug interaction study results from Study C16009 demonstrating that CYP inhibitors do not affect ixazomib PK.
- Remove *Ginkgo biloba* use as an exclusion criterion.
- Change the Charlson Comorbidity Scoring System in use, which is weighted for age, to the original scoring system, which is not weighted for age.
- Clarify details around the window for study procedures.
- Update the Schedule of Events to include inadvertently missing information.
- Add a new secondary objective pertaining to the effect of ixazomib maintenance therapy on the time to next-line therapy (TTNT).
- Add a new secondary endpoint to measure the TTNT.
- Add methods of statistical analysis for the new secondary endpoint.
- Clarify the wording of certain secondary endpoints.
- [redacted]
- Clarify the wording of certain exploratory objectives and endpoints.
- Reclassify certain exploratory endpoints as secondary, and reword them.
- Clarify inclusion criterion 6.
- Clarify exclusion criterion 4.
- Reflect the completion of Study C16009.
- Clarify the criteria for beginning a treatment cycle.
- Remove waveforms as a type of electrocardiogram data that may be obtained.

- Clarify details about disease response assessment.
- Clarify the purposes of the interim and final analyses.
- Clarify the definition of the safety population.
- Clarify the definition and analysis of time to end of next-line therapy.
- Clarify the definition and analysis of duration of next-line therapy.
- Specify details about medical history compilation.
- Clarify details about bone marrow aspiration.
- Clarify details about MRD assessments in the Schedule of Events.
- Clarify details of the MRD analyses.
- Correct the reference citations in Section 1.4.1.1, History of Maintenance Therapy in Multiple Myeloma, and Section 1.4.4.2, Rationale for Mutational Analyses.
- Add the citation of newly published reference supporting dose selection.
- Clarify physical examination procedures.
- Clarify imaging procedures.
- Clarify that respiratory rate should be measured as clinically indicated.
- Clarify when central laboratory results must be reviewed before initiating the next treatment cycle.
- Clarify the local laboratory data that must be entered into the electronic case report form.
- Allow for more frequent pregnancy testing in compliance with local regulations.
- Correct a dose reduction detail.
- Clarify the circumstances under which dose escalation can occur.
- Clarify that the end-of-treatment (EOT) window is +1 week, rather than ±1 week.
- Clarify an exception to the EOT visit 30 days (+1 week) after last dose of study drug.
- Clarify details about storage and transport of study drug.
- Update Section 6.9, Management of Clinical Events, to align with ixazomib clinical development program language.
- Clarify details around monitoring of adverse events.
- Update the product complaint and medication error reporting contact information.
- Clarify that study drug treatment may be discontinued permanently if the patient is withdrawn by the investigator.
- Correct the unit of serum calcium used to determine calcium elevation for the diagnosis of myeloma.
- Remove mention of the Safety Management Attachment, which is no longer relevant.
- Use the term “next-line therapy” consistently.
- Correct typographical errors, punctuation, grammar, and formatting.

15.16 Amendment 03 (China) Rationale and Purposes

Rationale for Amendment 03

The primary rationale for the changes in the global Amendment 2, which are incorporated in this China-specific Amendment 3, is to extend the follow-up period in which health-related quality of life (HRQL) measurements are obtained, update the description of the HRQL analyses, and update the HRQL statistical analysis methods; remove the exclusion of cytochrome P450 (CYP) inhibitors; and change the Charlson Comorbidity Scoring System from one that is weighted for age to the original scoring system, which is not weighted for age. Other purposes for the amendment are the addition of a secondary endpoint and numerous administrative changes. Additional changes in Amendment 3 include the assessment of minimum residual disease (MRD) by next generation sequencing (NGS), not flow cytometry, and clarification that the ixazomib storage conditions are provided in the pharmacy manual or equivalent.

Purposes for Amendment 03

The purposes of this amendment are to:

- Update the cover page with current signatories.
- Extend the duration of HRQL data collection into the period of next-line therapy and update the description of HRQL analyses.
- Update HRQL statistical analysis methods.
- Update the pharmacokinetics (PK) and concomitant medication information to reflect recent population PK analyses and drug-drug interaction study results from Study C16009 demonstrating that CYP inhibitors do not affect ixazomib PK.
- Remove Ginkgo biloba use as an exclusion criterion.
- Change the Charlson Comorbidity Scoring System in use, which is weighted for age, to the original scoring system, which is not weighted for age.
- Clarify details around the window for study procedures.
- Update the Schedule of Events to include inadvertently missing information.
- Add a new secondary objective pertaining to the effect of ixazomib maintenance therapy on the time to next-line therapy (TTNT).
- Add a new secondary endpoint to measure the TTNT.
- Add methods of statistical analysis for the new secondary endpoint.
- Clarify the wording of certain secondary endpoints.
- Reclassify certain exploratory endpoints as secondary, and reword them.
- Clarify inclusion criterion 6.
- Clarify exclusion criterion 4.
- Reflect the completion of Study C16009.
- Clarify the criteria for beginning a treatment cycle.
- Remove waveforms as a type of electrocardiogram data that may be obtained.

- Clarify details about disease response assessment.
- Clarify the purposes of the interim and final analyses.
- Clarify the definition of the safety population.
- Clarify the definition and analysis of time to end of next-line therapy.
- Clarify the definition and analysis of duration of next-line therapy.
- Specify details about medical history compilation.
- Clarify details about bone marrow aspiration.
- Clarify details about MRD assessments in the Schedule of Events.
- Clarify details of the MRD analyses.
- Correct the reference citations in Section 1.4.1.1, History of Maintenance Therapy in Multiple Myeloma.
- Add the citation of newly published reference supporting dose selection.
- Clarify physical examination procedures.
- Clarify imaging procedures.
- Clarify that respiratory rate should be measured as clinically indicated.
- Clarify when central laboratory results must be reviewed before initiating the next treatment cycle.
- Clarify the local laboratory data that must be entered into the electronic case report form.
- Allow for more frequent pregnancy testing in compliance with local regulations.
- Correct a dose reduction detail.
- Clarify the circumstances under which dose escalation can occur.
- Clarify that the end-of-treatment (EOT) window is +1 week, rather than ±1 week.
- Clarify an exception to the EOT visit 30 days (+1 week) after last dose of study drug.
- Clarify details about storage and transport of study drug.
- Update Section 6.9, Management of Clinical Events, to align with ixazomib clinical development program language.
- Clarify details around monitoring of adverse events.
- Update the product complaint and medication error reporting contact information.
- Clarify that study drug treatment may be discontinued permanently if the patient is withdrawn by the investigator.
- Correct the unit of serum calcium used to determine calcium elevation for the diagnosis of myeloma.
- Remove mention of the Safety Management Attachment, which is no longer relevant.
- Use the term “next-line therapy” consistently.
- Clarify that MRD assessment will be by NGS.
- Correct typographical errors, punctuation, grammar, and formatting.

15.17 Amendment 04 (China Continuation Study) Rationale and Purposes

Rationale for Amendment 04

The primary rationale for this amendment is to establish a China continuation of the global Study C16021. This amendment describes modifications to the global study procedures specifically for those patients who enroll in the China continuation. Approximately 105 patients with newly diagnosed multiple myeloma will be enrolled in China.

The China continuation is an extension of the global study that will continue to assess the primary objective of progression-free survival (PFS) and the key secondary objective of overall survival (OS). PFS will be assessed when a total of approximately 58 PFS events have been reported in China (pooled from patients enrolled in the global study from the most recent interim analysis and the China continuation). The final analysis for OS will be performed when a total of approximately 60 death events have been reported for patients in China (pooled between the events among the China patients in the global study from the most recent interim analysis or final analysis and events among patients in the China continuation), or when the final analysis of OS in the global study has been conducted, whichever occurs later, or termination of the study by the sponsor.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

Purposes for Amendment 04

The purposes of this amendment are to:

1. Update the number of patients to reflect that approximately 105 patients from China will be enrolled.
2. Emphasize that the primary objective is for patients in China.
3. Update the Endpoint and Follow-up Period Diagram to include the time to start of next-line therapy endpoint.
4. Provide the number of events required for the primary analysis of PFS for the China continuation, and define the primary and final analyses for patients in China.
5. Provide the number of death events required for the final analysis for OS and clarify the duration of the study.
6. Provide the approaches for the statistical analysis of endpoints (PFS and OS) in the China continuation.
7. Clarify the statistical methods and subgroup analyses for key secondary efficacy analyses.
8. Clarify the analysis of average scores from the EORTC QLQ-C30 global quality of life domain.

[redacted]

10. Clarify the planned safety and efficacy review by the IDMC.

15.18 Amendment 05 (Global, Substantial) Rationale and Purposes

Rationale for Amendment 05

This document describes the changes to the protocol incorporating Amendment 05. The primary rationale for this amendment is fourfold: to reduce the sample size, to include subgroup analyses of progression-free survival (PFS), to update the PFS assumptions and type I error allocation, and to adopt an adaptive design for the final analysis for overall survival (OS). Details are provided below.

- **Reduce the sample size.** The enrollment for this study is slower than originally expected, resulting in the timing of the first interim analysis (IA) (which is the final analysis [FA] for the primary endpoint, PFS) being very close to the timing of the completion of enrollment. As such, later-enrolled patients will not have a follow-up period that is long enough to ascertain their PFS at the time of the first IA, resulting in potential bias of the analysis results. To allow for reasonable follow-up for all enrolled patients, the sample size will be reduced from the original plan for 761 patients to 700 patients, and the timing of the first IA will be changed to approximately 10 months after the last patient has been enrolled or approximately 392 PFS events have been observed, whichever occurs later.
- **Include a subgroup analysis approach focusing on patients who may derive particular benefit from ixazomib.** A subgroup analysis is prospectively planned for the first IA, in parallel with the PFS analysis, in the intent-to-treat (ITT) population. The addition of this subgroup analysis will serve to determine whether the ixazomib group shows superiority over the placebo group with regard to PFS in 3 prespecified subgroups using the Hochberg procedure for multiplicity correction: patients ≥75 years of age, patients who have International Staging System (ISS) stage III disease before initial therapy, and patients with a best response of complete response (CR) or very good partial response (VGPR) to initial therapy, as assessed during screening.
  - With this subgroup analysis approach, the type I error is divided and reallocated for 2 statistical tests: an alpha level of 0.04 is used for the primary PFS analysis in the ITT population, and an alpha level of 0.01 is used for the subgroup analysis.
  - Three subgroups were selected for the subgroup analysis: 1) patients with ISS stage III disease at diagnosis, 2) patients aged ≥75 years; and 3) patients with a response of CR or VGPR at study entry. These subgroups were selected on the basis of recent data suggesting the potential for preferential benefit of maintenance therapy in these patients, as follows.
    - Patients with MM who have ISS stage III have historically worse outcomes following initial therapy [1]; thus, maintenance therapy may preferentially improve outcomes in this subgroup, particularly because the lenalidomide maintenance benefit is less than in other patients [2].
    - Older patients generally receive less intense induction therapy and have poorer outcomes [3,4], such that maintenance therapy may provide a preferential benefit in this subgroup as well—particularly because lenalidomide maintenance therapy did not provide a meaningful clinical benefit in patients >75 years of age [5].

  - Finally, patients with CR or VGPR at study entry may benefit preferentially from maintenance therapy, as they have less residual disease at the start of maintenance therapy than other patients and may experience further reduction of the tumor cell mass during the study [6].

- **Update the PFS assumptions and the type I error allocation.** The sponsor believes an assumption of median PFS of 11 months for the control (placebo) arm is more reasonable than the original assumption of 15 months, on the basis of data from other relevant clinical trials, including the MM-15 and MM-20 studies of lenalidomide and the VISTA study of bortezomib. The target number of PFS events assessed by the independent review committee (IRC) will not change from 392, and statistical power will remain at 90% with a 2-sided alpha = 0.04 and a hazard ratio (HR) of 0.71 (median PFS, 15.5 months with ixazomib vs 11 months with placebo).
- **Implement an adaptive design to test OS, the key secondary endpoint, at the second IA.** The sponsor has observed that blinded OS events are accumulating at a rate slower than estimated initially. To allow for greater maturity of data and reasonable timing of analyses, the second IA for OS will be updated to occur when 206 deaths have occurred (approximately 70% of 295 death events, the minimal number of events for the OS final analysis). At this time, an adaptive approach will also be implemented to determine the number of OS events needed for the final analysis—which could range from 295 events to approximately 393 events, according to the unblinded event re-estimation adaptation rule. In addition, the O'Brien-Fleming alpha spending function (the Lan-DeMets method) will be used to calculate the significant boundary for OS analyses instead of the gamma method with gamma = -1.

Changes in Amendment 05

The purposes of this amendment are to:

1. Reduce the number of patients to be enrolled from 761 to 700.
2. Modify the statistical design to change the timing of the first IA, allocate statistical power to a subgroup analysis, and update the PFS assumptions and type I error allocation.
3. Modify the statistical design to adopt an adaptive design to test OS at the second IA.
4. Clarify the timing of discontinuation of sample collection and stopping of the study relative to the timing of PFS analyses.
5. Move the details of analysis of the secondary endpoint, duration of the next line of therapy, to the correct section.
6. Clarify a detail about sensitivity analyses for PFS.
7. Describe how adjustment for potential effects of subsequent therapy used after study discontinuation may be analyzed.
8. Change the duration of the study to accommodate other changes to the statistical design.

[redacted]

10. List 2 secondary objectives in the Protocol Summary that were accidentally not yet listed there: "To determine the effect of ixazomib maintenance therapy on duration of next-line therapy"; and "To assess the correlation between MRD status (detected using 8-color flow cytometry) and PFS and OS, using bone marrow aspirates."
11. Update details about storage of study drug.

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

15.19 Amendment 06 (China) Rationale and Purposes

Rationale for Amendment 06

This document describes the changes to the protocol incorporating Amendment 05. The primary rationale for this amendment is fourfold: to reduce the sample size, to include subgroup analyses of progression-free survival (PFS), to update the PFS assumptions and type I error allocation, and to adopt an adaptive design for the final analysis for overall survival (OS). Details are provided below.

- **Reduce the sample size.** The enrollment for this study is slower than originally expected, resulting in the timing of the first interim analysis (IA) (which is the final analysis [FA] for the primary endpoint, PFS) being very close to the timing of the completion of enrollment. As such, later-enrolled patients will not have a follow-up period that is long enough to ascertain their PFS at the time of the first IA, resulting in potential bias of the analysis results. To allow for reasonable follow-up for all enrolled patients, the sample size will be reduced from the original plan for 761 patients to 700 patients, and the timing of the first IA will be changed to approximately 10 months after the last patient has been enrolled or approximately 392 PFS events have been observed, whichever occurs later.
- **Include a subgroup analysis approach focusing on patients who may derive particular benefit from ixazomib.** A subgroup analysis is prospectively planned for the first IA, in parallel with the PFS analysis, in the intent-to-treat (ITT) population. The addition of this subgroup analysis will serve to determine whether the ixazomib group shows superiority over the placebo group with regard to PFS in 3 prespecified subgroups using the Hochberg procedure for multiplicity correction: patients ≥75 years of age, patients who have International Staging System (ISS) stage III disease before initial therapy, and patients with a best response of complete response (CR) or very good partial response (VGPR) to initial therapy, as assessed during screening.
    - With this subgroup analysis approach, the type I error is divided and reallocated for 2 statistical tests: an alpha level of 0.04 is used for the primary PFS analysis in the ITT population, and an alpha level of 0.01 is used for the subgroup analysis.

- Three subgroups were selected for the subgroup analysis: 1) patients with ISS stage III disease at diagnosis, 2) patients aged ≥75 years; and 3) patients with a response of CR or VGPR at study entry. These subgroups were selected on the basis of recent data suggesting the potential for preferential benefit of maintenance therapy in these patients, as follows.
  - Patients with MM who have ISS stage III have historically worse outcomes following initial therapy [1]; thus, maintenance therapy may preferentially improve outcomes in this subgroup, particularly because the lenalidomide maintenance benefit is less than in other patients [2].
  - Older patients generally receive less intense induction therapy and have poorer outcomes [3,4], such that maintenance therapy may provide a preferential benefit in this subgroup as well—particularly because lenalidomide maintenance therapy did not provide a meaningful clinical benefit in patients >75 years of age [5].
  - Finally, patients with CR or VGPR at study entry may benefit preferentially from maintenance therapy, as they have less residual disease at the start of maintenance therapy than other patients and may experience further reduction of the tumor cell mass during the study [6].

- **Update the PFS assumptions and the type I error allocation.** The sponsor believes an assumption of median PFS of 11 months for the control (placebo) arm is more reasonable than the original assumption of 15 months, on the basis of data from other relevant clinical trials, including the MM-15 and MM-20 studies of lenalidomide and the VISTA study of bortezomib. The target number of PFS events assessed by the independent review committee (IRC) will not change from 392, and statistical power will remain at 90% with a 2-sided alpha = 0.04 and a hazard ratio (HR) of 0.71 (median PFS, 15.5 months with ixazomib vs 11 months with placebo).
- **Implement an adaptive design to test OS, the key secondary endpoint, at the second IA.** The sponsor has observed that blinded OS events are accumulating at a rate slower than estimated initially. To allow for greater maturity of data and reasonable timing of analyses, the second IA for OS will be updated to occur when 206 deaths have occurred (approximately 70% of 295 death events, the minimal number of events for the OS final analysis). At this time, an adaptive approach will also be implemented to determine the number of OS events needed for the final analysis—which could range from 295 events to approximately 393 events, according to the unblinded event re-estimation adaptation rule. In addition, the O'Brien-Fleming alpha spending function (the Lan-DeMets method) will be used to calculate the significant boundary for OS analyses instead of the gamma method with gamma = -1.

Changes in Amendment 06

1. Reduce the number of patients to be enrolled from 761 to 700.
2. Modify the statistical design to change the timing of the first IA, allocate statistical power to a subgroup analysis, and update the PFS assumptions and type I error allocation.
3. Modify the statistical design to adopt an adaptive design to test OS at the second IA.

4. Clarify the timing of discontinuation of sample collection and stopping of the study relative to the timing of PFS analyses.
5. Move the details of analysis of the secondary endpoint, duration of the next line of therapy, to the correct section.
6. Clarify a detail about sensitivity analyses for PFS.
7. Describe how adjustment for potential effects of subsequent therapy used after study discontinuation may be analyzed.
8. Change the duration of the study to accommodate other changes to the statistical design.
9. [redacted]
10. Update details about storage of study drug.
11. Correct the Charlson Comorbidity Index Scoring System table.

15.20 Amendment 07 (Global [for use in all countries except China], Substantial) Rationale and Purposes

Rationale for Amendment 07

This document describes the changes to the protocol incorporating Amendment 07, which reflects updates from analysis of the study's primary endpoint of progression-free survival (PFS). As noted in the previous version of the protocol, after PFS is tested at the first interim analysis (IA), central efficacy and investigator assessments of disease response for protocol purposes will be discontinued (except for investigator assessment of progression-free survival 2 [PFS2]). Also, if the test for PFS is not statistically significant in any population (the intent-to-treat or any of the 3 subgroups), the study will be stopped.

The first IA has now been conducted (data cut-off date 12 August 2019) and the primary endpoint of PFS was found to be statistically significant. Additionally, no new safety concerns were found in patients receiving ixazomib. However, the analysis was very early for overall survival, and no benefit was detected in patients receiving ixazomib at that time. On the basis of these findings, the Independent Data Monitoring Committee recommended that the study continue as planned. As such, upon implementation of Amendment 07, the study will continue and patients will be monitored for survival and long-term safety. However, all central laboratory efficacy measures of response/progression are discontinued. Bone marrow aspirates for confirmation of complete response (CR) or minimal residual disease (MRD) status are no longer required. No further Independent Review Committee (IRC) response or progression evaluations will be performed; investigators should continue

to assess disease response/progression according to International Myeloma Working Group (IMWG) criteria (including use of local efficacy laboratory measures) for documentation of initial disease progression (PD) and PFS2. All central laboratory assessments of safety are also discontinued; patients should be assessed and treated according to standard of care using local laboratory evaluations.

All patients will continue to be followed in the study Follow-up periods. After the End of Treatment visit, all patients will be followed every 3 months (12 weeks) for each of the follow-up periods, depending on their disease status and subsequent anticancer therapies (see the Schedule of Events). Patients will be contacted every 12 weeks until death or termination of the study by the sponsor.

Additionally, this amendment clarifies other elements of the study design and procedures. Descriptions of how to manage study procedures during unavoidable circumstances, such as the coronavirus disease 2019 (COVID-19) pandemic, have additionally been added. Language regarding a new adverse drug reaction of thrombotic microangiopathy has been added to the management of clinical events. Procedures for unblinding patients at the time of PD and subsequent therapy are clarified. Paper-based serious adverse event (SAE) reporting procedures are additionally clarified.

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

For specific examples of changes in text and where the changes are located, see Section 15.14.

Purposes for Amendment 07

The purposes of this amendment are to:

1. Clarify the study objectives as of Amendment 07.
2. Clarify the study endpoints as of Amendment 07.
3. Discontinue a number of efficacy response assessments, including central laboratory assessments of efficacy for protocol purposes and IRC evaluations, and clarify safety laboratory evaluation.
4. Update the estimated study duration.
5. Clarify the frequency of PFS Follow-up and PD Follow-up visits.

6. Update language about the management of clinical events in patients receiving ixazomib.
7. Clarify the unblinding procedures for patients during the Treatment period and in the Follow-up periods.
8. Require all patients to reconsent.
9. Clarify that pharmacokinetic assessments are complete for all patients.
10. Clarify the duration of evaluation for new primary malignancies.
11. Clarify details about ixazomib dispensing.
12. Clarify that additional packaging information can be found in the Pharmacy Manual.
13. Clarify the procedures for storage, handling, and accountability.
14. Clarify ethical principles that are to be considered for patients in the study.
15. Add flexibility in study conduct in unavoidable circumstances (eg, the COVID-19 pandemic).
16. Clarify the schedule, collection procedures, and analyses for [redacted] patient-reported outcomes.
17. Clarify that the first IA has been conducted but all statistical and quantitative analyses details are retained for reference.
18. Update the procedures for SAE reporting.
19. Add information about alternative monitoring approaches, such as remote source data verification, in the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic.

For specific examples of changes in text and where the changes are located, see Section 15.14

15.21 Amendment 08 (China Continuation Study) Rationale and Purposes

Rationale for Amendment 08

This document describes the changes to the protocol incorporating Amendment 08. The primary rationale for this amendment is to convert the China Continuation part of Study C16021 (herein referred to as the C16021 China Continuation) from a double-blind, placebo-controlled design to an open-label, single-arm design (ixazomib only). Two factors led to the change in design:

- The first interim analysis (IA) of the C16021 global study has been conducted (data cut-off date 12 August 2019) and the primary endpoint of progression-free survival (PFS) was found to be statistically significant and clinically meaningful. Additionally, no new safety concerns were found in patients receiving ixazomib.
- Recently available treatment options for patients with multiple myeloma (MM) have contributed to enrollment challenges in the C16021 China Continuation; to date, only 10 patients have been randomized.

Given the positive results from the C16021 global study and the fact that the C16021 China Continuation is still open to enrollment, the sponsor does not believe it is appropriate to continue enrolling patients into a randomized, placebo-controlled maintenance study. The Center for Drug Evaluation (CDE), National Medical Products Administration acknowledged that it will be difficult to continue enrolling patients into the placebo arm of the C16021 China Continuation. The CDE suggested that the sponsor amend the study into a single arm study, so as to collect more efficacy and safety data from Chinese patients receiving ixazomib.

This amendment describes modifications to the C16021 China Continuation procedures for patients who are still on treatment, who are in 1 of the follow-up periods, or who will be enrolled after this amendment takes effect.

- ***Patients enrolled prior to implementation of Amendment 08:*** Prior to implementation of Amendment 08, 10 patients had been randomized and treated in the China Continuation. All patients continuing in the study under Amendment 08 must be reconsented.
    - ***Patients still on treatment:*** Patients who were randomized to study drug (ixazomib or placebo) prior to implementation of Amendment 08 and who are still on study treatment will complete their current cycle of treatment and be unblinded.
        - Patients who are in the placebo arm and who have not yet experienced disease progression will have the opportunity to cross over to ixazomib maintenance, based on the investigator's judgement and the patient's informed consent. Patients who cross over will follow the "Schedule of Events for Crossover Patients" starting at Crossover Cycle 1 Day 1. Patients in the placebo arm who do not cross over should complete an End of Treatment (EOT) visit and discontinue the study.
        - Patients who are in the ixazomib arm will continue to receive ixazomib maintenance. Patients who reconsent will follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients" according to their current cycle of treatment.
    - ***Patients in the PFS Follow-up period:*** All patients will be unblinded.
        - Patients in the placebo arm who have discontinued study treatment but who have not yet experienced disease progression or started alternative therapy have the opportunity to cross over to ixazomib maintenance. The decision to cross over is based on the investigator's

judgement and the patient's informed consent. Patients who cross over will follow the "Schedule of Events for Crossover Patients" starting at Crossover Cycle 1 Day 1. Patients in the placebo arm who do not cross over will discontinue the study.

- Patients in the ixazomib arm who reconsent should continue on study and follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients" according to the PFS Follow-up period schedule.

- ***Patients in the progression-free survival (PFS2) or overall survival (OS) Follow-up periods:*** All patients will be unblinded.
  - Patients in the placebo arm will discontinue the study. No crossover to the ixazomib arm is permitted in these patients who have experienced primary disease progression or who have initiated alternative therapy.
  - Patients in the ixazomib arm who reconsent will continue on study and follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients" according to the OS Follow-up period schedule. Note, the PFS2 Follow-up period has been removed in Protocol Amendment 08; patients previously in PFS2 follow-up will be followed in the OS Follow-up period.

- ***Patients to be enrolled after implementation of Amendment 08:*** Approximately 20 additional patients with newly diagnosed multiple myeloma who responded to initial treatment will be enrolled in the China Continuation, for a total of approximately 30 patients overall. All newly enrolled patients will receive ixazomib maintenance and will follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients."

As the primary endpoint of PFS has been met in the C16021 global study, upon implementation of Amendment 08 for the China Continuation and the change to an open-label, single-arm design of ixazomib maintenance, the primary study objective will be safety. PFS and OS will become secondary objectives. The primary analysis will be performed approximately 12 months after the additional ~20 patients have been enrolled under this amendment. Safety and efficacy endpoints will be assessed in the overall Chinese patient population (patients from China who were enrolled in the ixazomib arm of the C16021 global study, patients in the ixazomib arm of the China Continuation before implementation of Amendment 08, and all patients enrolled in the China Continuation under Amendment 08). The final analysis will be performed when all patients in the China Continuation are off study treatment and have completed the EOT visit, or upon termination of the study by the sponsor, whichever occurs earlier.

Additionally, this amendment clarifies other elements of the study design and procedures. Descriptions of how to manage study procedures during unavoidable circumstances, such as the coronavirus disease 2019 (COVID-19) pandemic, have additionally been added. Language regarding a new adverse drug reaction of thrombotic microangiopathy was added to the management of clinical events. Paper-based serious adverse event (SAE) reporting

procedures were additionally clarified. See the purposes below for a list of all changes included in this amendment.

Purposes for Amendment 08

The purposes of this amendment are to:

1. Update the study design from a double-blind, placebo-controlled study to an open-label single-arm study of ixazomib maintenance in all patients. Patients who were previously randomized to the placebo arm are permitted to cross over to ixazomib.
2. Modify the existing Schedule of Events table to apply only to patients who were previously randomized to the ixazomib arm or to patients who will be enrolled under Amendment 08, and to create a new Schedule of Events table for patients who were previously randomized to the placebo arm and who will cross over to ixazomib.
3. Modify the primary objective to be long-term safety and tolerability of ixazomib maintenance therapy for patients in the C16021 China Continuation.
4. Remove the key secondary objective because there will be no alpha-controlled secondary objective, and to update the list of secondary objectives to align with the new study design.
5. Update the study endpoints for alignment with the new study design and study objectives.
6. Update the number of patients to be enrolled in the C16021 China Continuation.
7. Update the duration of study definition.
8. Indicate that, given the changes in the current amendment, patients enrolled prior to implementation of Amendment 08 remaining on study will need to be reconsented.
9. Add flexibility in study conduct in unavoidable circumstances (eg, the COVID-19 pandemic).
10. Clarify the Pharmacokinetic Sampling schedule for patients enrolled prior to implementation of Amendment 08 and for newly enrolled patients under Amendment 08.
11. Update the definition of study enrollment.
12. Clarify the schedule, collection procedures, and analyses [redacted] patient-reported outcomes.
13. Remove minimal residual disease and biomarker assessments from the study analyses, as they are no longer informative endpoints given the changes in the study design.
14. Remove the PFS2 Follow-up period, as it is no longer an informative follow-up period given the changes in the study design.
15. Update the text on the use of maintenance therapy in MM to reflect the new treatment landscape.
16. Update the Study Rationale section to reflect the new study design.

17. Update the number of events required for the IA of PFS for the C16021 China continuation, and to clarify the interim and final efficacy analyses for patients in China.
18. Clarify that review of disease response data will be done by the investigator and that independent review committee review is optional.
19. Remove the independent data monitoring committee (IDMC) review now that the study is an open-label study of ixazomib maintenance.
20. Update language about management of clinical events in patients receiving ixazomib.
21. Clarify details about ixazomib dispensing.
22. Clarify details about ixazomib packaging, handling, and storage guidelines.
23. Clarify ethical principles that are to be considered for patients in the study.
24. Update the study populations for analysis.
25. Clarify the safety analyses.
26. Add information about submitting SAE reports.
27. Clarify the time period for assessing new primary malignancies.
28. Add information about alternative monitoring approaches, such as remote source data verification, in the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic.

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

15.22 Amendment 09 (Global, Substantial) Rationale and Purposes

Rationale for Amendment 09

This document describes the changes to the protocol incorporating Amendment 09. The primary reason for this amendment is to change the legal entity name of the sponsor. In addition, the China-specific Protocol Amendment 06 of the Global study has been subsumed into this Global protocol amendment so that the China-specific version of the Global protocol amendment will no longer be needed. This change is not reflected in the Purposes for Amendment 09 below because the patients in China currently in the Global study are in progression-free survival 2 (PFS2) follow up; therefore, the changes originally necessitating a China-specific amendment do not affect these patients any longer. Note that this Global Amendment 09 does not apply to the China Continuation Study, the current protocol for which is Protocol Amendment 08.

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

Purposes for Amendment 09

The purposes of this amendment are to:

1. Change the legal entity name of the sponsor.
2. Clarify language regarding procedures for reporting product complaints or medication errors.
3. Clarify language in study conduct regarding the COVID-19 pandemic.
4. Clarify local laboratory assessment recordings.

15.23 Amendment 10 Detailed Summary of Changes

The primary section(s) of the protocol affected by the changes in Amendment No. 10 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Remove the references to randomization throughout the protocol.

The primary change occurs in the 3.2 Secondary Endpoints:

Initial wording:	Overall survival, measured as the time of randomization to the date of death
Amended or new wording:	Overall survival, measured as the time of ~~randomization~~**date of first dose** to the date of death

Rationale for Change: Replaced "randomization" with "date of first dose" or "enrollment," depending on context, to align with changes incorporated in Protocol Amendment 08.

The following sections also contain this change:

- Protocol Summary.
- Study Overview Diagram.
- Study Endpoint and Follow-up Period Diagram.
- Schedules of Events.
- List of Abbreviations.
- Section 2.2 Secondary Objectives.
- Section 3.2 Secondary Endpoints.
- Section 5.1 Inclusion Criteria.
- Section 5.2 Exclusion Criteria.
- Section 7.4.3 Medical History.
- Section 7.4.13 Clinical Laboratory Evaluations.

- Section 7.4.17 Imaging Assessments.
- Section 8.1.7.1 Analyses for PFS.

Change 2: Remove reference to second progressive disease (PD2) throughout the protocol.

The primary change occurs in Study Endpoint and Follow-up Period Diagram.

Description of change: Removed "PD2=second PD (on second line therapy)" from abbreviations.

Rationale for Change: The PD2 endpoint was removed in Protocol Amendment 08.

The following sections also contain this change:

- Schedules of Events.
- List of Abbreviations.

Change 3: Clarify "vital signs" with a footnote in the Schedules of Events.

The primary change occurs in Schedules of Events:

Description of change: Added footnote "f" to vital signs.

Rationale for Change: Added footnote to clarify the proper assessment of vital signs.

Change 4: Clarify unblinding of patients off study.

The primary change occurs in Schedules of Events:

Added text:

- ***Patients enrolled prior to implementation of Amendment 08:*** Prior to implementation of Amendment 08, 10 patients had been randomized and treated in the China Continuation. All patients continuing in the study under Amendment 08 must be reconsented.

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  - ***Patients in the PFS2 or Overall Survival (OS) Follow-up Periods:*** All patients will be unblinded.
    - Patients in the placebo arm will discontinue the study. No crossover to the ixazomib arm is permitted in these patients who have experienced primary disease progression or who have initiated alternative therapy.
    - Patients in the ixazomib arm who reconsent will continue on study and follow the "Schedule of Events for Patients Randomized to Ixazomib + Newly Enrolled Patients" according to the OS Follow-up Period schedule. Note, the PFS2 Follow-up period has been removed in Protocol Amendment 08; patients previously in PFS2 follow-up will be followed in the OS follow-up period.
  - ***Patients Off Study:*** **All these patients will be unblinded.**

Rationale for Change: Clarified that patients off study will be unblinded if they were enrolled before implementation of Amendment 08.

Change 5: Clarify language regarding procedures for reporting product complaints or medication errors.

The primary change occurs in Section 11.11 Product Complaints and Medication Errors (Including Overdoses):

Initial wording:

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

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

For Product Complaints or Medication Errors (Including Overdose) for Ixazomib

Contact Dohmen Life Sciences Services at
1-844-N1-POINT (1-844-617-6468)

E-mail: GlobalOncologyMedinfo@takeda.com
FAX: 1-800-881-6092

Product complaints or medication errors in and of themselves are not AEs and may or may not be associated with an AE. If a product complaint or a medication error results in an AE or SAE, an additional report describing the AE or SAE should also be completed and sent to Cognizant (refer to Section 10.2).

Amended or new wording:

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact ~~Dohmen Life Sciences (see below) and~~ report the event **to ctmcomplaint@takeda.com**. ~~Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Takeda Quality representative.~~

Product complaints in and of themselves are not AEs. If a product complaint is associated with an SAE, a Millennium SAE Form should be completed and sent to Cognizant (refer to Section 10.2).

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. Whereas overdoses constitute medication errors, doses missed inadvertently by a patient do not. Investigators must record all medication errors (including overdose) on the appropriate eCRF. Individuals who identify a potential medication error situation should immediately report this ~~via the phone number or email address provided below~~**to ctmcomplaint@takeda.com.**

~~**For Product Complaints or Medication Errors (Including Overdose) for Ixazomib**~~

~~Contact Dohmen Life Sciences Services at~~
~~1-844-NI-POINT (1-844-617-6468)~~

~~E-mail: GlobalOncologyMedinfo@takeda.com~~
~~FAX: 1-800-881-6092~~

~~Product complaints or medication errors in and of themselves are not AEs and may or may not be associated with an AE. If a product complaint or a medication error results in an AE or SAE, an additional report describing the AE or SAE should also be completed and sent to Cognizant (refer to Section 10.2).~~

Rationale for Change: To clarify proper reporting procedures for product complaints and medication errors.

Change 6: Clarify language in study conduct regarding the coronavirus disease 2019 (COVID-19) pandemic.

The primary change occurs in Section 6.14 Storage, Handling, and Accountability:

Initial wording:	Study drug dispensed to the patient for take-home dosing should remain in the blister packaging and carton until the point of use. Comprehensive instructions should be provided to the patient to ensure compliance with, and understanding of, dosing procedures. Patients are permitted to transport study drug from the site to home at room temperature. In case of extenuating circumstances that prevent a patient from attending the study site (eg, the coronavirus disease 2019 [COVID-19] pandemic), sites may utilize 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 sponsor's project clinician/designee. Patients who are receiving take-home medication should ordinarily be given only 1 cycle of medication at a time. More than 1 cycle of medication may be dispensed on a case-by-case basis for holidays, travel, or other circumstances upon discussion with the investigator and sponsor's project clinician/designee. Patients should be instructed to store the medication according to the storage conditions that are in the pharmacy manual or equivalent storage guidelines for the duration of each cycle. Patients should be instructed to return their empty or partially used cartons to the investigative site, rather than discarding them, as permitted by site policy. Reconciliation will occur accordingly when the patient returns for their next cycle of 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.

Amended or new wording: Study drug dispensed to the patient for take-home dosing should remain in the blister packaging and carton until the point of use. Comprehensive instructions should be provided to the patient to ensure compliance with, and understanding of, dosing procedures. Patients are permitted to transport study drug from the site to home at room temperature. ~~In case of extenuating~~ **If** circumstances **due to the coronavirus disease 2019 [COVID-19] pandemic**~~that~~ prevent a patient from attending the study site ~~(eg, the coronavirus disease 2019 [COVID-19] pandemic)~~, sites may utilize 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 sponsor's project clinician/designee. **This may include planned shipments of the study drug from the central pharmacy (which may be a sub-depot), depot, or a clinical site to the patients, referred to as DTP (Direct-to-Patient).** Patients who are receiving take-home medication should ordinarily be given only 1 cycle of medication at a time. More than 1 cycle of medication may be dispensed on a case-by-case basis for holidays, travel, or other circumstances upon discussion with the investigator and sponsor's project clinician/designee. Patients should be instructed to store the medication according to the storage conditions that are in the pharmacy manual or equivalent storage guidelines for the duration of each cycle. Patients should be instructed to return their empty or partially used cartons to the investigative site, rather than discarding them, as permitted by site policy. Reconciliation will occur accordingly when the patient returns for their next cycle of take-home medication. ~~In case of extenuating~~**If** circumstances due to the **COVID-19 pandemic**~~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.

Rationale for Change: Clarified that alternative strategies can occur only for circumstances related to the COVID-19 pandemic.

The following sections also contain this change:

- Schedules of Events.
- Section 7.4 Study Procedures.
- Section 7.4.14 [redacted]
- Section 7.4.15 Quality of Life Assessments.

Change 7: Clarify definitions of some of the populations for analysis.

The primary change occurs in Section 8.1.3 Populations for Analysis:

Added text:

Overall Chinese Patient Population:

- Patients from China who were enrolled in the ixazomib arm of the C16021 global study, PLUS
- Patients in the ixazomib arm of the China Continuation before implementation of Amendment 08, PLUS
- All patients enrolled in the China Continuation under Amendment 08
- **Patients who were randomized to the placebo arm before implementation of Amendment 08 and who crossed over to the ixazomib arm.**

Initial wording:

Ixazomib Safety population: The Ixazomib Safety population is defined as all patients who receive at least 1 dose of ixazomib. Patients will be analyzed according to the treatment they actually received; patients who were randomized to the placebo arm prior to implementation of Amendment 08 and who cross over to the ixazomib arm will contribute safety data from the time they initiate ixazomib onward. The primary analysis of safety will focus on this patient population.

Placebo Safety population: The Placebo Safety population is defined as all patients who receive at least 1 dose of placebo. Patients will be analyzed according to the treatment they actually received; patients who were randomized to the placebo arm prior to implementation of Amendment 08 and who cross over to the ixazomib arm will contribute safety data to this population only during the time they receive placebo. Data from this patient population will be briefly summarized using descriptive statistics.

Amended or new wording:

Ixazomib Safety population: The Ixazomib Safety population is defined as all patients who receive at least 1 dose of ixazomib. Patients will be analyzed according to the treatment they actually received; patients who were randomized to the placebo arm prior to implementation of Amendment 08 and who cross over to the ixazomib arm will contribute safety data from the time they initiate ixazomib onward. The primary analysis of safety will focus on the~~is~~ **Ixazomib Safety** ~~patient~~ population.

Placebo Safety population: The Placebo Safety population is defined as all patients who receive at least 1 dose of placebo. Patients will be analyzed according to the treatment they actually received; patients who were randomized to the placebo arm prior to implementation of Amendment 08 and who cross over to the ixazomib arm will contribute safety data to this population only during the time they receive placebo. **Adverse event** ~~D~~**d**ata from this patient population will be ~~briefly summarized using descriptive statistics~~**listed**.

Rationale for Change: Clarified that patients in the placebo arm who crossed over to ixazomib contribute to the Overall Chinese Patient Population and other aspects of the study populations.

The following sections also contain this change:

- Protocol Summary.
- Section 4.1 Overview of Study Design.
- Section 8.1.6 Safety Analysis.
- Section 8.1.6.1 New Primary Malignancy.
- Section 8.1.7.1 Analyses for PFS.

Change 8: Remove the Independent Review Committee section.

The primary change occurs in Section 9.2:

Deleted text: ~~**9.2 Independent Review Committee**~~

~~The sponsor may choose to use an IRC review to independently establish PFS. If so, the IRC will review all disease evaluation data from the study and determine disease status (response and progression, including in the PFS follow-up period).~~

Rationale for Change: The Independent Review Committee is no longer needed.

The following sections also contain this change:

- Section 3.2 Secondary Endpoints.
- Section 7.4.22 Disease Response Assessment.
- Section 8.1.7.1 Analyses for PFS.
- Section 8.1.7.3 Analyses of Other Secondary Efficacy Endpoints.

Change 9: Update the management of transverse myelitis for ixazomib to reflect evolving data.

The primary change occurs in Section 6.9 Management of Clinical Events:

Initial wording:

Transverse Myelitis
Transverse myelitis has been reported with ixazomib. It is not known whether ixazomib causes transverse myelitis; however, because it 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:

Transverse Myelitis
Transverse myelitis has been reported with ixazomib. It is not known whether ixazomib causes transverse myelitis; however, because it happened ~~to a patient~~**while** 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: Removed reference to 1 patient for transverse myelitis.

Change 10: Clarify reporting of patient-reported outcome questionnaires.

The primary changes occur in Section 7.4.15 Quality of Life Assessments and 8.1.8.1 Patient-Reported Outcomes Analysis:

Added text: **Section 7.4.15**

Note that signs and symptoms assessed with the patient-reported outcome questionnaires will not be considered AEs unless entered as such into the eCRF.

Deleted text: **Section 8.1.8.1**

The actual value and change from baseline of the subscale scores for the EORTC QLQ-C30 [redacted] will be summarized using descriptive statistics and plotted over time.

The number and percentage of patients with a meaningful change from baseline in subscale scores will be summarized over time. The published minimally important difference will be used to define such meaningful change from baseline. Specific interest will be on global health status, but data on all other subscales will also be analyzed.

The change from baseline in subscale scores will be presented using cumulative distribution function figures. ~~The subscale scores will also be analyzed using mixed models by incorporating the measurements across all available time points.~~

Rationale for Change: Clarified that signs and symptoms will not be considered AEs unless recorded as such and clarified analysis of subscale scores.

Change 11: Clarify the wording of some secondary and exploratory study objectives.

The primary change occurs in Section 2.2 Secondary Objectives and Section 2.3 Exploratory Objectives:

Initial wording:

Section 2.2

- To determine the effect of ixazomib maintenance therapy on PFS, defined as the time from date of first dose to PD or death from any cause, in patients in China with NDMM who have had a major response—defined as CR, VGPR, or PR—to initial therapy and who have not undergone SCT.
- To determine the effect of ixazomib maintenance therapy on OS.
- To determine the effect of ixazomib maintenance therapy on improving or maintaining response at study entry.
- To determine the effect of ixazomib maintenance therapy on TTP.
- To determine the effect of ixazomib maintenance therapy on the time to next-line therapy (TTNT).

…

Section 2.3

…

[redacted]

…

Amended or new wording:

Section 2.2

- To determine ~~the effect of ixazomib maintenance therapy on~~ PFS, defined as the time from date of first dose to PD or death from any cause, in patients in China with NDMM who have had a major response—defined as CR, VGPR, or PR—to initial therapy and who have not undergone SCT.
- To determine ~~the effect of ixazomib maintenance therapy on~~ OS.
- To determine ~~the effect of ixazomib maintenance therapy on improving or maintaining~~**whether** response at study entry **is improved or maintained**.
- To determine ~~the effect of ixazomib maintenance therapy on~~ TTP.
- To determine ~~the effect of ixazomib maintenance therapy on the~~ time to next-line therapy (TTNT).

…

Section 2.3

…

[redacted]

…

Rationale for Change: Reflect that this study is now single arm (ixazomib maintenance therapy), with no comparator regimen.

The following section also contains this change:

- Protocol Summary.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	29-Aug-2022 16:26 UTC
[redacted]	Clinical Science Approval	29-Aug-2022 16:26 UTC
[redacted]	Clinical Approval	30-Aug-2022 01:20 UTC