CLINICAL STUDY PROTOCOL

NCT Number: NCT02312258

Study Title: A Phase 3, Randomized, Placebo-Controlled, Double-Blind 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

Protocol Version and Date:

Version 9.0: 18-November-2021

CLINICAL STUDY PROTOCOL C16021 AMENDMENT 09

Ixazomib

A Phase 3, Randomized, Placebo-Controlled, Double-Blind 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:	Takeda Development Center Americas, 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, Substantial	23 September 2020
Amendment 08	China Continuation Study	29 September 2020
Amendment 09	Global, Substantial	16 November 2021

Takeda Development Center Americas, Inc
95 Hayden Avenue
Lexington, MA USA 02421
Telephone: +1 (617) 679-7000

Approved by:
Note: If this document was approved electronically, the electronic approval signatures may be found at the end of the document.

[redacted] MD [redacted] Oncology Clinical Research;	Signature	Date DD Month YYYY
[redacted] PhD [redacted] Statistical and Quantitative Sciences (or designee)	Signature	Date DD Month YYYY

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.

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

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 coronavirus disease 2019 (COVID-19) pandemic.
4. Clarify local laboratory assessment recordings.

PROTOCOL SUMMARY

Study Title: A Phase 3, Randomized, Placebo-Controlled, Double-Blind 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 700 patients with newly diagnosed multiple myeloma (NDMM) who had a major response to initial therapy and who have not undergone stem cell transplantation (SCT)

Study Objectives
Note, assessment of several study objectives was completed at the time of the first interim analysis (IA). Upon implementation of Amendment 07, data collected after the first IA will be used to assess overall survival (OS), progression-free survival 2 (PFS2), patient reported outcomes, and safety only. The full list of study objectives is retained here for reference.

Primary

- To determine the effect of ixazomib maintenance therapy on progression-free survival (PFS), defined as the time from randomization to progressive disease (PD) or death from any cause, compared with placebo, in patients 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

Key Secondary

- To determine the effect of ixazomib maintenance therapy on OS compared with placebo

Other Secondary

- To determine the effect of ixazomib maintenance therapy on improving best response for patients who enroll in the study at PR or VGPR and on maintaining best overall response for patients who enroll in the study at CR
- To determine the effect of ixazomib maintenance therapy on time to progression
- To determine the effect of ixazomib maintenance therapy on PFS2, defined as the time from randomization to objective disease progression on next-line treatment or death from any cause
- To determine the effect of ixazomib maintenance therapy on the time to next-line therapy
- To determine the effect of ixazomib maintenance therapy on the time to end of next-line therapy
- To determine the effect of ixazomib maintenance therapy on duration of next-line therapy
- To assess the incidence of new primary malignancy in patients receiving ixazomib maintenance therapy
- To evaluate the frequency of conversion from minimal residual disease (MRD) positive to MRD negative, or the maintenance of MRD negativity, using 8-color flow cytometry

- To assess the correlation between MRD status (detected using 8-color flow cytometry) and PFS and OS, using bone marrow aspirates
- To determine the effect of ixazomib maintenance therapy on PFS and OS in high-risk cytogenetic patient groups characterized by individual or multiple cytogenetic abnormalities including, but not limited to, del17, t(4;14), or t(14;16)
- To determine the long-term safety and tolerability of 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: This is a phase 3, randomized, double-blind, placebo-controlled, multicenter study in patients 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 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. Eligible and consenting patients are to be randomized no later than 60 days after the last dose of initial therapy. Randomization will occur in a 3:2 ratio of ixazomib or matching placebo. Approximately 700 patients are planned to be enrolled in this study at approximately 200 sites worldwide.

There are 4 stratification factors: initial therapy (proteasome-inhibitor–containing or not); International Staging System stage before initial therapy (stage I or II vs stage III); age at time of randomization (<75 vs ≥75 years); and response to initial therapy, as measured during screening (CR or VGPR vs PR).

Patients will receive blinded ixazomib or matching placebo capsules (both 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, disease response, and MRD assessments will be made, as will HRQL assessments with an emphasis on tolerability and symptom burden. After documented PD, subsequent therapy will be determined by the investigator/treating physician.

The primary endpoint of PFS will be supported by prespecified evidence of clinical benefit as

measured by the key and other secondary endpoints. There will be 2 IAs and 1 final analysis (FA) in the study. The first IA will be the FA (and only analysis) for PFS for statistical testing purposes. If the test for PFS is significant at the first IA, then OS will be tested at this first IA and at the subsequent IA, and at the FA if needed. An independent data monitoring committee will review safety and efficacy data at the IAs and safety data at regularly scheduled meetings. An independent review committee (IRC) will assess disease response and PD.

The first IA has been conducted (data cutoff date 12 August 2019) and the primary endpoint of PFS based on IRC assessment was statistically significant. As such, upon implementation of Amendment 07, all central laboratory efficacy measures of response/progression are discontinued. Bone marrow aspirates for confirmation of CR or MRD status are no longer required. No further IRC response or progression evaluations will be performed; investigators should continue to assess disease response/progression according to International Myeloma Working Group criteria (including use of local efficacy laboratory measures) for documentation of initial disease progression 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 EOT 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 therapies (see the Schedule of Events). Patients will be contacted every 12 weeks until death or termination of the study by the sponsor.

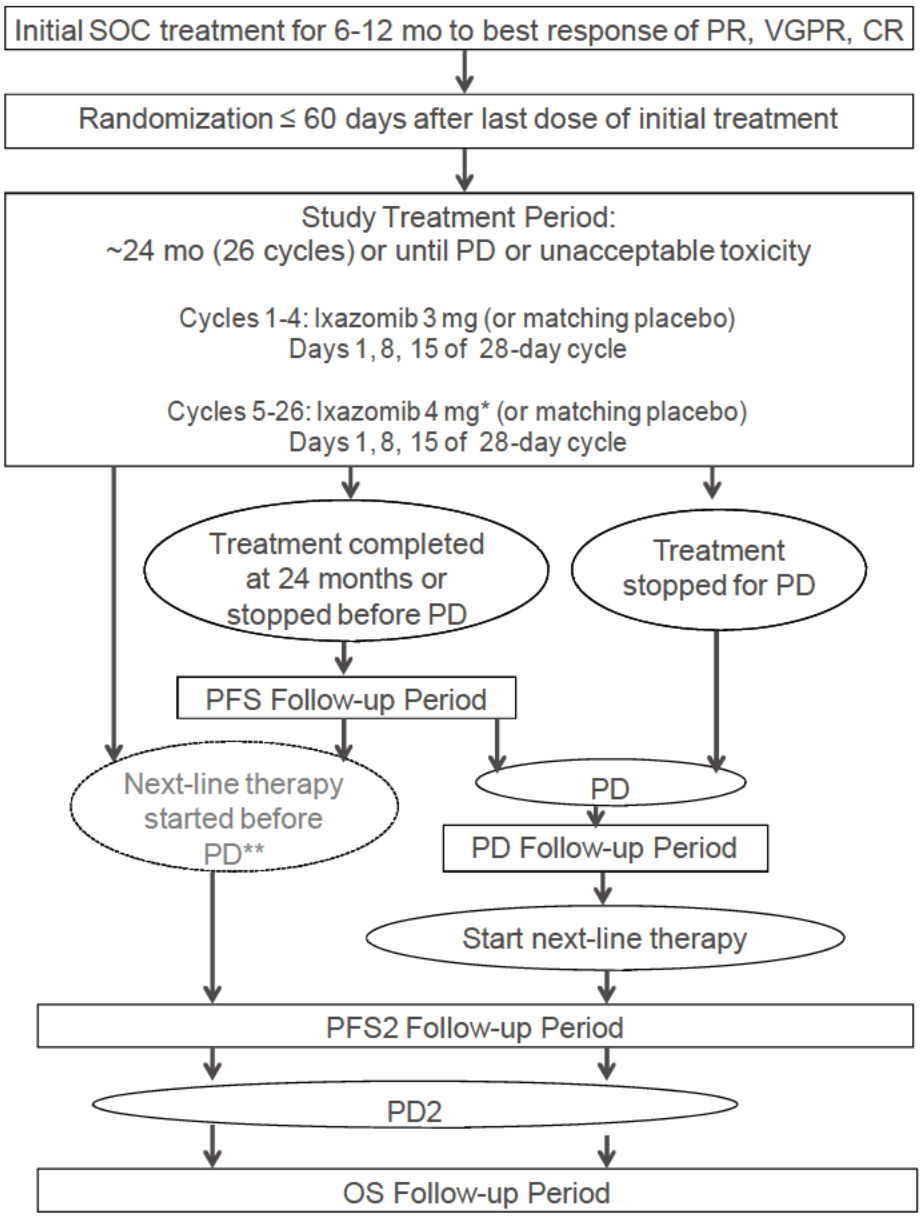
Study Population: Adult patients with NDMM who have had 6 to 12 months of initial therapy that is standard of care, during which the patient was treated to "best response" (in the investigator's judgment), with documented major response (PR, VGPR, or CR, according to International Myeloma Working Group 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.

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, PFS2, and OS Follow-up periods for clinical status, disease status, subsequent therapies, HRQL, new primary malignancy, and survival.

It is anticipated that this study will last for approximately 78 to 106 months, including a 42-month Enrollment period, a 24-month Treatment period, and an additional 12- to 40-month Follow-up period from the time at which the last patient has the opportunity to complete study therapy, depending on the death events for the final OS analysis.

STUDY OVERVIEW DIAGRAM

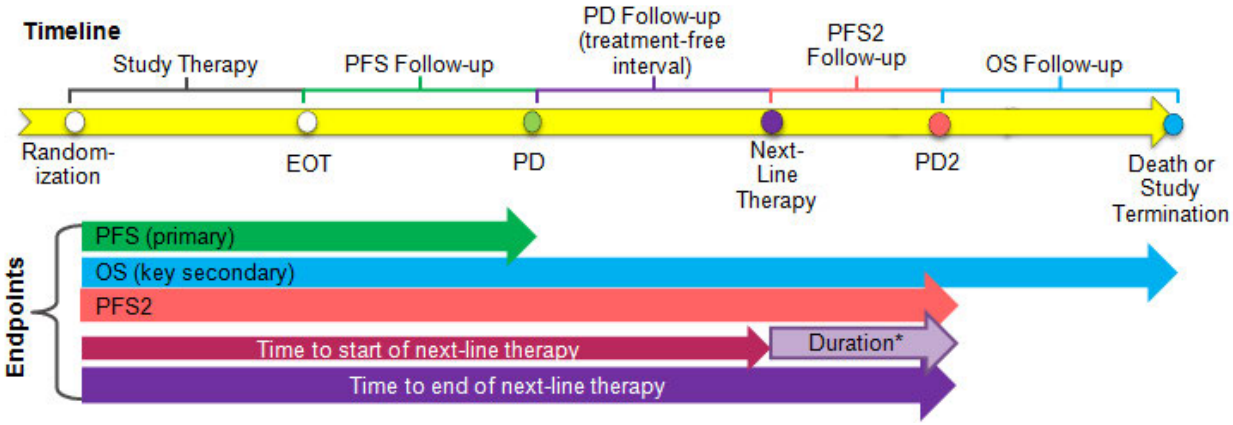


Abbreviations: CR=complete response; mo=months; OS=overall survival; PD=progressive disease (disease progression); PD2=second PD (on next-line therapy); PFS=progression-free survival, defined as time from randomization to PD or death from any cause; PFS2=time from randomization to objective disease progression on next-line treatment or death from any cause; 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 (or matching placebo) 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 PFS2 Follow-up period.

STUDY ENDPOINT AND FOLLOW-UP PERIOD DIAGRAM



Abbreviations: EOT=End of Treatment (visit); OS=overall survival; PD=progressive disease (disease progression); PD2=second PD (on next-line therapy); PFS=progression-free survival, defined as time from randomization to PD or death from any cause; PFS2=time from the date of randomization to objective disease progression on next-line treatment or death from any cause, whichever occurs first.

PFS is the primary endpoint; OS, the key secondary endpoint; and PFS2, time to start and end of next-line therapy, and duration of next-line therapy are other secondary and exploratory endpoints.

* Duration=duration of next-line therapy, defined as the date of onset of next-line therapy through the date of the last dose of next-line therapy.

SCHEDULE OF EVENTS

As of Amendment 07, the first interim analysis has been conducted and the primary endpoint of progression-free survival based on independent review committee (IRC) assessment was statistically significant. As such, the majority of study objectives and endpoints have been assessed and study procedures are streamlined for patients still on study. Upon implementation of Amendment 07, all central laboratory efficacy measures of response/progression are discontinued. Bone marrow aspirates for confirmation of complete response or minimal residual disease status are no longer needed. No further IRC response or progression evaluations will be performed; investigators should continue to assess disease response/progression according to International Myeloma Working Group criteria (using local efficacy laboratory measures) for documentation of initial disease progression and progression-free survival 2. All central laboratory assessments of safety are also discontinued; patients should be assessed and treated according to standard of care using local laboratory evaluations.

For ease of study conduct, the Schedule of Events now presented has been modified according to protocol requirements to apply to the remainder of the study. Beyond the assessments noted here, patients still on study should be treated by the investigator according to the local- or country-specific standard of care.

The full Schedule of Events before Amendment 07 has been moved to Section 15.13. The pharmacokinetic (PK) sampling schedule has also been moved to Section 15.13, as PK sample collection is no longer applicable because patients have completed at least 10 cycles of treatment.

Study Procedures[a]	**Treatment Period 28-Day Cycles**	**End of Treatment[b]**	**Follow-up**			
			PFS	**PD**	**PFS2**	**OS**
Cycle	**Cycle X[a] and Beyond**		**Every 12 Wk Until PD**	**Every 12 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**
Day	**1**					
Window	**±1 Wk**	**+1 Wk**	**±1 Wk**	**±1 Wk**	**±1 Wk**	**±1 Wk**
Informed Consent (Reconsent)	X[c]					
Complete Physical Examination, including for PN[d]		X				
Symptom-Directed Physical Examination, including for PN[d]	X		X	X		
Vital Signs[d]	X	X	X	X		

Study Procedures[a]	**Treatment Period 28-Day Cycles**	**End of Treatment[b]**	**Follow-up**			
			PFS	**PD**	**PFS2**	**OS**
Cycle	**Cycle X[a] and Beyond**		**Every 12 Wk Until PD**	**Every 12 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**
Day	**1**					
Window	**±1 Wk**	**+1 Wk**	**±1 Wk**	**±1 Wk**	**±1 Wk**	**±1 Wk**
Weight[d]	X	X				
ECOG Performance Status[d]	X	X	X	X		
EORTC QLQ-C30[e]	X	X	X	X	X (twice only)	
EORTC QLQ-MY20[e]	X (C7, 10, 13, 16, 19, 22, 25)	X	X	X	X (twice only)	
EQ-5D-5L[e]	X (C7, 10, 13, 16, 19, 22, 25)	X	X	X	X	X
HU assessment[e]	X	X	X	X	X (twice only)	
Investigator assessment of disease response/status (using local laboratory data)[d]	X	X	X		X[f]	
Ixazomib or placebo	Single dose on Days 1, 8, and 15 of each cycle					
Adverse event/serious adverse event reporting[g]	Recorded from the first dose of study drug through 30 days after last dose of study drugs					
Concomitant medications/procedures	Recorded from the first dose of study drug through 30 days after last dose of study drug					

Study Procedures[a]	**Treatment Period 28-Day Cycles**	**End of Treatment[b]**	**Follow-up**			
			PFS	**PD**	**PFS2**	**OS**
Cycle	**Cycle X[a] and Beyond**		**Every 12 Wk Until PD**	**Every 12 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**
Day	**1**					
Window	**±1 Wk**	**+1 Wk**	**±1 Wk**	**±1 Wk**	**±1 Wk**	**±1 Wk**
New primary malignancy	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)		X[h]				
Hematology laboratory[i]	X	X	X	X		
Chemistry laboratory[i]	X	X	X	X		
Serology and lymphocyte phenotyping[j]	X (C7, 13, 19)	X	X (every 6 mo)			
M-protein (SPEP)[d, i]	X	X	X	X		
M-protein (UPEP [24-hr urine])[d, i]	X	X	X	X		
SFLC assay[d, i]	X	X	X	X		
Immunofixation: serum and urine[d, k]	X	X	X	X		

Abbreviations: C=study cycle; COVID-19=coronavirus disease 2019; CR=complete response; ECOG=Eastern Cooperative Oncology Group; EORTC=European Organization for Research and Treatment of Cancer; EQ-5D-5L=5-level classification system of the EuroQol 5 Dimensional Health Questionnaire; GCP=Good Clinical Practice; HU=health utilization; IEC=independent ethics committee; IRB=institutional review board; OS=overall survival; PD=progressive disease (disease progression); PD2=second PD (on next-line therapy); 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); QLQ-MY20=Quality of Life Questionnaire Multiple Myeloma Module (20 questions); SFLC=serum free light chain; SPEP=serum protein electrophoresis; UPEP=urine protein electrophoresis; wk=week(s).

Tests and procedures should be performed on schedule, but unless otherwise specified, occasional changes are allowable within a 7-day window for holidays, vacations, and other administrative reasons or a longer window after discussion with the Takeda Development Center Americas, Inc (Takeda) project clinician or designee. If the study schedule is shifted, assessments must be shifted to ensure that collection of assessments is completed before dosing.

a Follow this Schedule of Events at the start of the next full treatment cycle upon implementation of Amendment 07.

b When a study patient has documented disease progression, the investigator should unblind the patient to determine the study treatment assignment and take this information into account in planning the patient's second-line therapy. See Section 6.10 for more information.

c Before dosing on Day 1 of the next full treatment cycle upon implementation of Amendment 07, patients must be reconsented. Patients 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/IEC, and GCP standards and local regulations.

d Alternative methods for administering study procedures/assessments may be considered when it is not possible for the patient to come to the study site due to the COVID-19 pandemic. Alternative methods should be considered for performing the assessments by other means than the patient presenting to the clinic (eg, remote assessment, having laboratory assessment performed at a facility closer to the patient's home). If any of the following study procedures/assessments is missed because a site visit is done remotely, the study procedure/assessment is waived: complete physical examination, symptom-directed physical examination, weight, ECOG performance status, HU. Patients should otherwise be assessed by the investigator, with data recorded, according to standard of care.

e Patient-reported outcomes and HU assessment (eg, number of medical encounters) should be completed before any other study procedures are performed or study drug is administered. During the PFS2 Follow-up period only, the EORTC QLQ-C30, EORTC QLQ-MY20, and HU assessments should be done twice—ideally once approximately 12 weeks after the start of next-line therapy and again 12 weeks later. Patient-reported outcome questionnaires are preferred to be completed by patients in the clinic, but if needed due to COVID-19 pandemic, the EORTC QLQ-C30 and EORTC QLQ-MY20 questionnaires may be completed at the patient's home using mailed paper versions of the questionnaires. At time points when a clinic visit is not required, or if needed due to the COVID-19 pandemic, the EQ-5D-5L questionnaire may be administered over the telephone. HU data may be obtained over the telephone and/or via patient medical records, as needed.

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

g 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.

h A serum pregnancy test will be performed for women of childbearing potential at the End of Treatment visit, or more frequently as required per local regulations.

i As of Amendment 07, all central laboratory efficacy measures of response/progression are discontinued. Investigators should continue to assess disease response/ progression according to International Myeloma Working Group criteria, using local efficacy laboratory measures, for documentation of initial disease progression, and PFS2 (see Section 7.4.13 and the Laboratory Manual). All central laboratory assessments of safety are also discontinued; patients should be assessed and treated according to standard of care using local laboratory evaluations. Local laboratory assessments are not recorded in the electronic data capture (EDC).

j Blood samples (using local laboratory assessment) for serology will be used to measure antibody levels against measles, varicella-zoster virus, and tetanus and to quantify B cells, T cells, and natural killer cells.

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

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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
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
CI	confidence interval
COVID-19	coronavirus disease 2019
CR	complete response
CT	computed tomography
CYP	cytochrome P450
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EORTC QLQ-MY20	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOT	End of Treatment (visit)
EQ-5D-5L	5-Level classification system of the EuroQol 5-Dimensional Health Questionnaire
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
GIMEMA	Italian Group for Hematologic Diseases in Adults
HRQL	health-related quality of life

Abbreviation	Term
HU	health utilization
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
NFκB	nuclear factor kappa-light chain enhancer of activated B-cells
NK	natural killer (cells)
OS	overall survival
PAD	bortezomib, Adriamycin, and dexamethasone
PD	progressive disease (disease progression)
PD2	second progressive disease (on next-line therapy)
PET	positron emission tomography

Abbreviation	Term
PFS	progression-free survival, defined as the time from randomization to progressive disease or death from any cause
PFS2	progression-free survival 2, defined as the time from randomization 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
SNP	single-nucleotide polymorphism
Takeda	Takeda Development Center Americas, Inc
TEAE	treatment-emergent adverse event
TMA	thrombotic microangiopathy
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
VZV	varicella-zoster virus

1.0 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.[10] In the Americas and Western European countries, approximately 5 to 7 new cases of MM are diagnosed per 100,000 people each year.[10-12] 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.[13,14]

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).[15-19]

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 with 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, Takeda Development Center Americas, Inc (Takeda) has developed ixazomib, a small molecule 20S proteasome inhibitor.

1.1.2 Ixazomib: Takeda'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 Takeda. Building on the

efficacy seen with bortezomib in MM and other hematologic malignancies, Takeda 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 MM [RRMM] and Study C16014 in newly diagnosed MM [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 1-1.

Table 1-1 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.[20] 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.[21] 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 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 (C_{max} and $AUC_{0\text{-last}}$) was similar with and without co-administration of clarithromycin, a strong CYP3A inhibitor (Study C16009, Arm 5) [22]; 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 P-gp but not of breast cancer resistance protein (BCRP) or multidrug resistance associated protein (MRP2) efflux pump transporters. Ixazomib is not an inhibitor of P-gp, BCRP, or MRP2. The potential for DDIs with substrates or inhibitors of P-gp, 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 AUC by 74% (Study C16009, Arm 4).[22] 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).[23] 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,[24] whereas a decrement in OS was observed in others.[25] 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,[26,27] and in 1 study, patients experienced a decrement in benefit.[27]

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.[28-30] 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.[28]

The phase 3 HOVON/GMMG study investigated induction therapy leading to autologous SCT and subsequent maintenance therapy in patients with MM.[29] 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.[5,31,32] 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.[32] 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.[33] 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

Most recently, 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 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[34,35] 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. Although lenalidomide is approved by the US Food and Drug Administration for treatment of patients with RRMM, the drug is currently prescribed off-label as maintenance therapy for about 50% of patients after SCT.

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,[23] and a true standard of care has not been adopted. Current US National Comprehensive Cancer Network guidelines (version 2.2014)[36] 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[37] and European Society for Medical Oncology (ESMO) guidelines for the treatment of MM[38] 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."[39] 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[38] 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

Maintenance therapy has 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, provides 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 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 disease progression (PD) or unacceptable toxicity (whichever occurs first). Please see Section 1.4.3.1 and Section 1.4.3.2 below for the rationale for the schedule and dose, respectively.

1.4.3.1 Schedule Rationale

The balance of benefit and risk is paramount in this phase 3 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[29] and the GIMEMA trial in the non-SCT setting.[28] 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.[28] 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.[40]

1.4.3.2 Dose Rationale

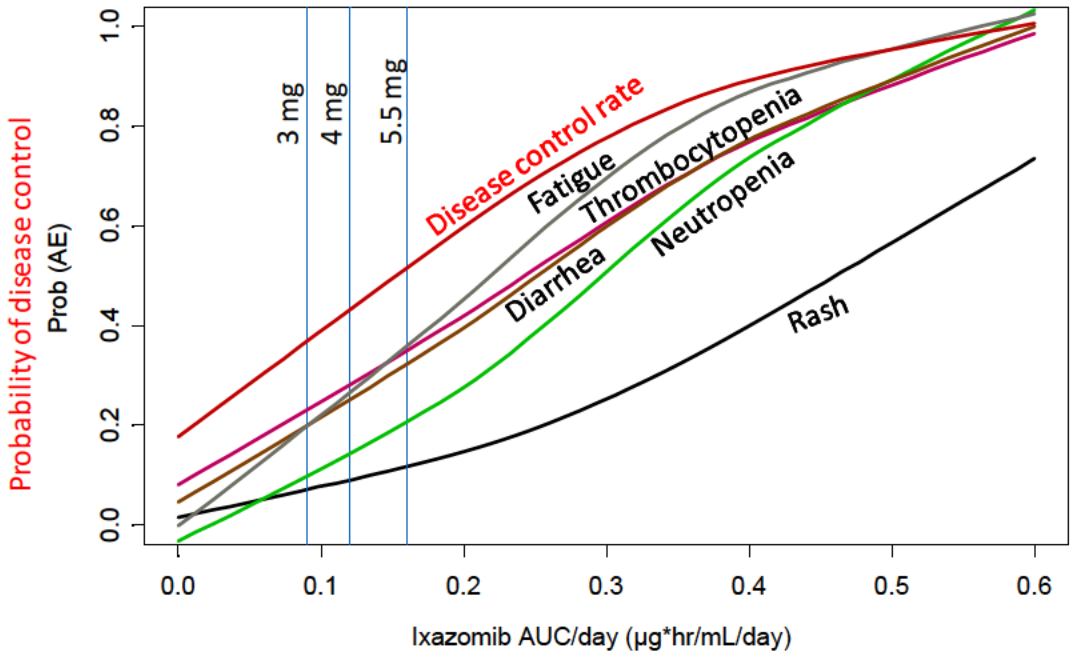
Considering that clinical experience with ixazomib has predominantly been in the RRMM setting, dose selection for this C16021 maintenance treatment trial was guided by exposure-response analyses of safety and efficacy data from the relapsed patient population. These analyses were designed to yield initial 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 1-1).

Figure 1-1 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). Takeda'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.[41]

As shown in Figure 1-1, 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 1-1) 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.

1.4.4 Rationale for Minimal Residual Disease Assessment

The assessment of residual tumor cells persisting after therapy, or MRD, is a central component of accurate disease prognosis and monitoring in many hematologic malignancies. The prognostic value of MRD has been clearly established in the chronic and acute leukemias and lymphomas.[42-49] As a result, molecular MRD analysis is currently used for risk stratification, and assessment of therapy-induced reduction in tumor burden and regrowth after chemotherapy in these indications.[50]

Recent studies have suggested that MRD assessment may also play a role in the MM treatment paradigm. Specifically, numerous reports have shown that molecular MRD status (ie, absence of MRD) is predictive of PFS and OS in MM patients.[51-54]

In this study, a serial assessment of MRD in CR patients will be performed to characterize the benefit of ixazomib maintenance therapy versus placebo in terms of improving or maintaining the depth of response.

1.4.4.1 Assessment of Minimal Residual Disease

In patients with confirmed or suspected CR at study entry, during the screening bone marrow aspirate (BMA) procedure, an additional BMA sample for MRD will be collected. In addition, all patients in CR at Cycle 13 and at the End of Treatment visit (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.

Minimal residual disease will be evaluated using multiparametric flow cytometry, and remaining cells, if available, will be used for the assessment of MRD using a sequencing methodology.

The quality of CRs, as defined by achievement of "depth of response (MRD negative)," and the maintenance of MRD-negative CRs will be evaluated in this study, along with the correlation between MRD status and long-term clinical benefits such as PFS and OS. Time to progression will also be evaluated in patients who have a CR, regardless of MRD status. This provides another way to identify and describe the value of maintenance therapy for patients with MM.

1.4.4.2 Rationale for Mutational Analyses

The heterogeneity of clinical results with MM therapeutics is partly related to variation in the molecular subtypes of MM and the complex interaction of each tumor with the biology of the host. Several clinical studies have shown that tumor biology can be directly related to the clinical efficacy of either multidrug combinations in MM (a validated gene expression model of high-risk MM is defined by deregulated expression of genes mapping to chromosome 1)[55-57] or to outcome after single-agent VELCADE therapy.[58,59] A recent whole genome sequencing study of MM patients reported the presence of mutations in known cancer genes that had either not previously been reported in MM, such as *BRAF*, or that were present at much higher frequency in MM than previously reported (*KRAS*, *NRAS*).[60] Similar studies with samples from VELCADE clinical trials highlighted the link between mutations in these pathways and response to the PI.[61] Mutational analysis of tumor samples from patients with RRMM highlights the prevalence of RAS/RAF pathway mutations and their potential impact on clinical outcomes.[61,62]

In this clinical study, the link between the presence of specific gene mutations in key pathways, such as RAF/RAS, and the maintenance of clinical response will be tested using archival tumor samples and (if available) a portion of BMA samples used for MRD assessment and those obtained after PD. These hypotheses will be tested in all patients. Additional analyses of tumor molecular characteristics may be performed to identify biomarkers that may be clinically meaningful in this study.

1.4.5 Rationale for Blood-Based Biomarkers and Antibody Titers

1.4.5.1 Single-Nucleotide Polymorphism Analyses

Recent data identify host variation, specifically germline DNA variants in proteasome subunits and the nuclear factor kappa-light chain enhancer of activated B-cells (NFκB) pathway, as factors that might contribute to VELCADE clinical activity. For example, in retrospective analyses of 2 independent VELCADE MM studies (internal unpublished data), an increased long-term clinical benefit in patients positive for P11A single-nucleotide polymorphism (SNP) in the *PSMB1* gene has been observed. In this study, a blood sample will be collected at baseline for the assessment of P11A SNP and other SNPs potentially associated with differential benefit:risk ratios during treatment with ixazomib.

1.4.5.2 Antibody Levels Against Common Pathogens, and Lymphocyte Phenotyping

Patients undergoing antineoplastic therapy are immunocompromised and may be at high risk for infection with common pathogens. Additionally, by interfering with intracellular protein homeostasis, PIs may be cytotoxic not only to malignant plasma cells but also potentially to normal plasma cells and lymphocytes, contributing to the loss of protective antibodies. The proposed study includes an exploratory endpoint of measuring antibody levels against 3 common pathogens that most patients have either been vaccinated against or have been exposed to: measles, varicella-zoster virus, and tetanus. Lymphocyte phenotyping will also be performed to study the effect of proteasome inhibition on lymphocyte subpopulations: B cells, T cells, and natural killer (NK) cells. Blood samples will be collected at screening; at Cycles 7, 13, and 19; at EOT; and every 6 months during the PFS Follow-up period.

1.5 Potential Risks and Benefits

As of 27 March 2014, 1287 patients make up the oral ixazomib Safety population. Clinical safety data include 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) indicates that the AEs reported with ixazomib are generally consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with bortezomib, though the frequency may slightly differ. 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 early 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.

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

2.0 STUDY OBJECTIVES

Note, assessment of several study objectives was completed at the time of the first interim analysis (IA). Upon implementation of Amendment 07, data collected after the first interim analysis will be used to assess OS, PFS2, patient reported outcomes, and safety only. The full list of study objectives is retained here for reference.

2.1 Primary Objective

The primary objective of this study is:

- To determine the effect of ixazomib maintenance therapy on PFS, defined as the time from randomization to PD or death from any cause, compared with placebo, in patients with NDMM who have had a major response—defined as CR, VGPR, or PR—to initial therapy and who have not undergone SCT

2.2 Key Secondary Objective

The key secondary objective is:

- To determine the effect of ixazomib maintenance therapy on OS compared with placebo

2.3 Other Secondary Objectives

The other secondary objectives are:

- To determine the effect of ixazomib maintenance therapy on improving best response for patients who enroll in the study at PR or VGPR and on maintaining best overall response for patients who enroll in the study at CR
- To determine the effect of ixazomib maintenance therapy on TTP
- To determine the effect of ixazomib maintenance therapy on progression-free survival 2 (PFS2), defined as the time from randomization to objective disease progression on next-line treatment or death from any cause
- To determine the effect of ixazomib maintenance therapy on the time to next-line therapy (TTNT)
- To determine the effect of ixazomib maintenance therapy on the time to end of next-line therapy
- To determine the effect of ixazomib maintenance therapy on duration of next-line therapy
- To assess the incidence of new primary malignancy in patients receiving ixazomib maintenance therapy
- To evaluate the frequency of conversion from MRD positive to MRD negative, or the maintenance of MRD negativity, using 8-color flow cytometry

- To assess the correlation between MRD status (detected using 8-color flow cytometry) and PFS and OS, using bone marrow aspirates.
- To determine the effects of ixazomib maintenance therapy on PFS and OS in high-risk cytogenetic patient groups characterized by individual or multiple cytogenetic abnormalities including, but not limited to, del17, t(4;14), and t(14;16)
- To determine the long-term safety and tolerability of 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

2.4 Exploratory Objectives

The exploratory objectives are:

- To determine the rate of increase in tumor burden, measured by M-protein level, after PD before the start of next-line therapy
- To determine the impact of mutations in the RAS/RAF pathway, and other key genes in MM, on the maintenance of response and on PFS and OS
- To determine the effects of ixazomib maintenance therapy on PFS and OS in patients with polymorphisms in proteasome and NFκB-related genes, such as *PSMB1* and *TRAF3*
- To evaluate the frequency of conversion from MRD positive to MRD negative, or the maintenance of MRD negativity, using sequencing
- To evaluate the concordance between MRD assessment using flow and sequencing methodologies
- To assess the correlation between MRD status (detected using next-generation sequencing) and PFS and OS, using bone marrow aspirates.
- To evaluate potential mechanisms of treatment-emergent resistance, such as somatic mutations in proteasome subunits and in key signaling pathways, or change in pathways activity, in tumors from patients who exhibit PD
- To determine the effect of ixazomib maintenance therapy on lymphocyte subpopulations (T, B, and NK cells) and on normal plasma cell function as measured by levels of antibodies against common pathogens, such as varicella-zoster virus (VZV), tetanus, and rubeola (measles), during the course of therapy

- To assess HRQL in patients who receive ixazomib maintenance therapy as measured by function and symptom domains of the EORTC QLQ-C30 instrument and by the EORTC QLQ-MY20 and EQ-5D-5L instruments
- To evaluate health utilization (HU) of ixazomib maintenance therapy

3.0 STUDY ENDPOINTS

Note, assessment of several study endpoints was completed at the time of the first IA. Upon implementation of Amendment 07, data collected after the first IA will be used to assess OS, PFS2, patient reported outcomes, and safety only. The full list of study endpoints is retained here for reference.

3.1 Primary Endpoint

The primary endpoint is:

- Progression-free survival, defined as the time from randomization to the first occurrence of PD, as evaluated by an independent review committee (IRC), or death from any cause, whichever occurs first

3.2 Key Secondary Endpoint

The key secondary endpoint is:

- Overall survival, measured as the time of randomization to the date of death

3.3 Other Secondary Endpoints

The other secondary endpoints are:

- 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 randomization to the date of first documented PD
- Progression-free survival 2, defined as the time from randomization to objective disease progression on next-line treatment or death from any cause
- TTNT
- Time to end of next-line therapy
- Duration of next-line therapy
- Incidence of new primary malignancies
- Conversion rate from MRD positive to MRD negative, or the maintenance of MRD negativity, using 8-color flow cytometry
- Correlation of MRD status (detected using 8-color flow cytometry) with PFS and OS
- Overall survival and PFS in high-risk cytogenetic populations characterized by individual or multiple cytogenetic abnormalities including, but not limited to, patients carrying del17, t(4;14), or t(14;16)
- 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

- 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

3.4 Exploratory Endpoints

The exploratory endpoints are:

- Rate of increase in tumor burden, measured by M-protein level, after PD before the start of next-line therapy
- Maintenance of response, PFS, and OS in patients with mutations in the RAS/RAF pathway or other key genes in MM
- Progression-free survival and OS in patients with polymorphisms in proteasome and NFκB-related genes, such as *PSMB1* and *TRAF3*
- Frequency of conversion from MRD positive to MRD negative, or the maintenance of MRD negativity, using sequencing
- Concordance between MRD assessment using flow and sequencing methodologies
- Correlation of MRD status (detected using next-generation sequencing) with PFS and OS
- Identification of mechanisms of treatment-emergent resistance in tumors from patients who exhibit PD
- Lymphocyte subpopulations (T, B, and NK cells) and antibody levels against common pathogens, such as VZV, tetanus, and rubeola
- Health-related quality of life in patients, as measured by the function and symptom domains of the EORTC QLQ-C30 instrument and by the EORTC QLQ-MY20 and EQ-5D-5L questionnaires
- Assessment of HU by collecting the number of medical encounters

4.0 STUDY DESIGN

4.1 Overview of Study Design

This is a phase 3, randomized, double-blind, placebo-controlled, multicenter study in patients with NDMM who have not undergone SCT. Patients who have not undergone SCT have not done so because of frailty due to advanced age (eg, ≥65 years) or comorbidity or because they decline SCT for other reasons. The Study Overview Diagram depicts the study design.

Screening and Randomization

The purpose of the study is to evaluate the role of maintenance therapy with ixazomib (compared with matching placebo) 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 also have had a documented PR, VGPR, or CR at screening and met all additional inclusion/exclusion criteria. A Takeda project clinician or designee will confirm patient eligibility before randomization by the investigator and will ensure that the documentation adequately captures the reasons for not proceeding to SCT. The initial therapy permitted is any standard of care MM therapy.

Eligible and consenting patients are to be randomized no later than 60 days after the last dose of the initial therapy. Randomization will occur in a 3:2 ratio to ixazomib or matching placebo. Approximately 700 patients are planned to be enrolled in this study at approximately 200 sites worldwide. Because this is a global study, during the conduct of the trial the sponsor may choose to limit patient enrollment in specific regions or countries to maintain adequate representation across the regions participating in the study.

There are 4 stratification factors: initial therapy (PI-containing or not); International Staging System (ISS) stage before initial therapy (stage I or II vs stage III); age at time of randomization (<75 vs ≥75 years); and response to initial therapy, as measured during screening (CR or VGPR vs PR).

Study Treatment

Patients will receive blinded ixazomib or matching placebo capsules (both 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. In addition, an IRC will assess disease response and PD for every cycle through the first PD. Independent review committee response evaluations are for endpoint determinations only and will not be shared with investigators. 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.

The first IA has been conducted (data cutoff date 12 August 2019) and the primary endpoint of PFS was statistically significant. As such, upon implementation of Amendment 07, all central laboratory efficacy measures of disease response/progression are discontinued. No further IRC response or progression evaluations will be performed. Investigators should continue to assess disease response/progression according to IMWG criteria using local efficacy laboratory measures for documentation of initial disease progression and PFS2.

Patients will receive study 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. 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 4 Follow-up periods: PFS, PD, PFS2, 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. After PD occurs, the date and characteristics of PD2, and disease status, will be assessed by the treating physician/investigator according to the IMWG criteria, and reported.

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

If a patient completes 24 months of study 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 12 weeks until PD occurs. After PD occurs during the PFS Follow-up period, the

patient enters the PD Follow-up period and continues to be followed every 12 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 12 weeks until initiation of next-line therapy by the investigator/treating physician.

Progression-Free Survival 2 Follow-up and Overall Survival Follow-up

Patients who start next-line therapy (regardless of when) will enter the PFS2 Follow-up period. During the PFS2 Follow-up period, follow-up will occur every 12 weeks until PD2 occurs.

After patients in the PFS2 Follow-up period have PD2 on next-line therapy, they 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

The primary endpoint of PFS will be supported by prespecified evidence of clinical benefit as measured by the key and other secondary endpoints. There will be 2 IAs and 1 final analysis (FA) in the study. The first IA will be the FA (and the only analysis) for PFS for statistical testing purposes. If PFS is significant at the first IA, then OS will be tested at this first IA and at subsequent analyses. Additionally, for patients who have not yet had progressive disease at the first IA, central efficacy and investigator assessments for protocol purposes will be stopped and not recorded in the electronic case report form (eCRF). However, investigator assessment of response will continue to be collected for patients who have initiated next line therapy, for the purpose of supporting the PFS2 endpoint (see Schedule of Events).

An independent data monitoring committee (IDMC) will review safety and efficacy data at the IA and safety data at regularly scheduled meetings. An IRC will assess disease response and PD. Upon implementation of Amendment 07, the IRC will no longer assess disease response and PD. See Section 9.0 for more information.

The Schedule 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; and MRD assessments.

For HRQL, the focus is on tolerability and symptom burden, but the instruments also elucidate the effects of disease on physical, social, psychological/emotional, and cognitive functioning.

Eastern Cooperative Oncology Group Performance Status and AEs will be assessed, and laboratory values, vital signs, and electrocardiograms (ECGs) 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.[63]

4.2 Number of Patients

Approximately 700 patients will be enrolled in this study from approximately 200 study centers globally. Enrollment is defined as being randomized to a study drug. Randomization is 3:2 treatment:control, so approximately 420 patients are expected to be enrolled in the ixazomib arm and approximately 280 patients in the placebo arm.

4.3 Duration of Study

Patients will be treated for 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. 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, subsequent therapies, HRQL, new primary malignancy, and survival.

It is anticipated that this study will last for approximately 78 to 106 months, including a 42-month Enrollment period, a 24-month Treatment period, and an additional 12- to 40-month Follow-up period from the time at which the last patient has the opportunity to complete study therapy, depending on the death events for the final OS analysis.

5.0 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
   - Cytogenetics assessment at diagnosis (cytogenetic assessment performed after diagnosis must be approved by a Takeda 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 randomization.
    - 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 Cockcroft-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 randomization.

4. Diagnosed or treated for another malignancy within 5 years before randomization 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 randomization.

7. Central nervous system involvement.

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

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 randomization.

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 randomization.

6.0 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.

Patients will receive oral ixazomib or matching placebo 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 Schedule of Events. During the first cycle of treatment, all patients will receive doses of ixazomib or placebo 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 Test Article (Ixazomib Capsules and Matching Placebo Capsules)

Ixazomib capsules will be supplied as single capsules containing 0.5, 2.3, 3.0, or 4.0 mg of ixazomib. Placebo capsules will be identical in shape, size, and color to the ixazomib capsules. Both the active and placebo capsules will be provided by the sponsor.

Ixazomib capsules and matching placebo capsules will be hereafter referred to as “study drug” when detailing blinded study procedures.

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 Schedule of Events. Toxicity will be evaluated according to the NCI CTCAE, Version 4.03, effective 14 June 2010.[63] These criteria are provided in the Study Manual.

Further clarification can be obtained in consultation with the Takeda 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 6-1. When a dose reduction of study drug is required due to toxicity, no dose re-escalation will be permitted.

Table 6-1 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 6-2 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 6-1.

Table 6-2 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/ placebo 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 6-1.
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 6.4.1: • 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 6-1. 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 6-4 for criteria for re-treatment and cycle delays.

6.4.4 Study Drug Dose Modification for Nonhematologic Toxicities

Please refer to Table 6-3 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 6-1.

Table 6-3 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 6-1.	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 6-1. 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 6-4 for criteria for retreatment and cycle delays. Dose level reductions should be made in accordance with those outlined in Table 6-1.

Table 6-4 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 6-1 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 Takeda 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 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 Takeda 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 (TMA), 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. TMA 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 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 to a patient receiving ixazomib, the possibility that ixazomib may have contributed to the transverse myelitis cannot be excluded. Transverse myelitis should be managed according to standard medical practice.

Overdose

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

6.10 Blinding and Unblinding

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.

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 Takeda 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 or to treat an AE, the investigator will contact the Takeda project clinician or designee (contact information is in the Study Manual). In these cases, a decision to break the blind must be reached by the Takeda project clinician or designee and the investigator. The investigator, or designee, may break the blind through the IXRS independent of the Takeda project clinician or designee in the following 2 situations:

a) If the patient experiences an AE/safety issue that is considered to be an emergency by the investigator that requires specific knowledge of the blinded study treatment to properly treat. If the treatment of the AE/safety issue is the same regardless of the study drug assignment, the blind should not be broken. In addition, the patient will be discontinued from further study drug administration in this study.

b) When a study patient has documented disease progression, the investigator should unblind the patient to determine the study treatment assignment and take this information into account in planning the patient's second-line therapy. The Takeda project clinician or designee does not need to be contacted to break the blind to inform decisions for subsequent therapy when a patient has disease progression.

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). Matching placebo will be identical in size, shape, and color to the corresponding ixazomib capsule. The dose strengths are differentiated by both capsule size and color, as described in the Table 6-5.

Table 6-5 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 Takeda. 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. See the Pharmacy Manual for more information.

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 study drug should be stored as indicated on the drug label. All excursions that occur during 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 Takeda. 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. Patients are permitted to transport study drug from the site to home at room temperature. If circumstances due to the COVID-19 pandemic prevent a patient from attending the study site, sites may use alternative strategies to deliver study drug to patients (eg, via courier or site staff), per local standard practice and regulations, and with prior approval from the investigator and sponsor's project clinician/designee. Comprehensive instructions should be provided to the patient to ensure compliance with dosing procedures. Patients who are receiving take-home medication ordinarily should 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 (note: patients in France are only permitted to receive 1 cycle of medication at a time). Patients should be instructed to store the medication according to the storage conditions that are indicated on the drug label. 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 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 immediately 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.

7.0 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: Consolidated Guideline.
- 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 Takeda 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 Takeda project clinician or designee before randomization by the investigator into the study. A centralized randomization using the IXRS will be used. Patients will be randomized strictly sequentially at a center as they become eligible for randomization. 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.

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. Investigators are expected to evaluate the impact to the safety of the study participants and site personnel for patients to continue. In evaluating such requests, the investigator/study site staff will give the highest priority to the safety and welfare of the patients. Patients must be willing and able to continue taking study medication and remain compliant with the protocol. For patients who are impacted by these unavoidable

circumstances, any procedures not conducted per the study protocol will be documented in the eCRF.

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

Patients will be evaluated at scheduled visits over 4 study periods: Screening, Treatment, EOT, and Follow-up (PFS, PD, PFS2, and OS).

Tests and procedures should be performed on schedule, but, unless otherwise specified, occasional changes are allowable within a 7-day window for holidays, vacations, and other administrative reasons or a longer window after discussion with the Takeda 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 7-day window also is permissible for study days not specified in this Schedule of Events.

Refer to the Schedule 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.

As of Amendment 07, patients remaining on study treatment will need to be reconsented before dosing on Day 1 of the next full treatment cycle. Patients 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/IEC, 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 Takeda 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 randomization for symptomatic bone lesion or >5 years before randomization for another malignancy), and the patient's current smoking status.

Refer to the Schedule 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 Schedule 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 Schedule 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 Schedule 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.[7,8]

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 Schedule 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 Schedule of Events. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

7.4.11 Enrollment

A patient is considered to be enrolled in the study when the patient has been randomized to study treatment.

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

7.4.12 Electrocardiogram

A 12-lead ECG 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 randomization, local laboratory results may be used as long as samples are also sent to the central laboratory before the patient is randomized. 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 Takeda project clinician or designee. The Takeda 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 Takeda 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 Takeda 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.

Upon implementation of Amendment 07, centralized clinical laboratory assessments of response and progression are no longer required and local laboratories are to be used. Safety laboratory evaluations will also be performed by a local laboratory.

Clinical Chemistry, Hematology, Urinalysis, Serology, and Lymphocyte Phenotyping

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 Schedule 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

Serology and Lymphocyte Phenotyping

- Measles
- VZV
- Tetanus
- Quantification of B cells, T cells, and NK cells

7.4.14 Health Utilization Data Collection

During the Treatment and Follow-up periods indicated in the Schedule of Events, all medical care encounters since the previous collection will be collected from all patients, regardless of the reason for the medical care encounter. Examples of data to be collected are number and duration of medical care encounters, such as inpatient/outpatient admissions, homecare, and time of work loss.

If needed due to the COVID-19 pandemic, HU data may be obtained over the telephone and/or via patient medical records, as needed.

7.4.15 Quality of Life Assessment (European Organization for Research and Treatment of Cancer)

The HRQL assessments (EORTC QLQ-C30 and EORTC QLQ-MY20; see Sections 15.9 and 15.10) will be completed by the patient as specified in the Schedule 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 item scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

The EORTC QLQ-MY20 multiple myeloma module (20-items) has 4 independent subscales: 2 functional subscales (body image, future perspective), and 2 symptoms scales (disease symptoms and side effects of treatment). This will be administered subsequent to the EORTC QLQ-C30.

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 50 items 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. During the PFS2 Follow-up period only, the EORTC QLQ-C30, EORTC QLQ-MY20, and HU are to be done twice—ideally once approximately 12 weeks after the start of next-line therapy and again 12 weeks later, as specified in the Schedule of Events.

These patient-reported outcome questionnaires are preferred to be completed by patients in the clinic but, if needed due to 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 Takeda or ordered from the publisher may be used.

7.4.16 Utility Measurement

The EQ-5D-5L (see Section 15.11) consists of 2 pages: the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises 5 dimensions (mobility, self care, usual activities, pain/discomfort, and anxiety/depression), each rated on 5 levels. The EQ VAS records the respondent's self-rated health on a 20-cm, vertical, visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

The EQ-5D-5L will be administered as specified in the Schedule of Events; at time points when a clinic visit is not required, or if needed due to the COVID-19 pandemic, the EQ-5D-5L questionnaire may be administered over the telephone, and site staff may enter the data from the patient.

7.4.17 Bone Marrow Aspiration

7.4.17.1 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.

For patients with a confirmed or suspected CR at study entry, during the screening BMA procedure, an additional BMA specimen should be obtained for MRD evaluation by the central laboratory, as discussed below (Section 7.4.17.2).

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.

Upon implementation of Amendment 07, BMA is not required for central laboratory assessment of CR for protocol purposes. Investigators may continue to take BMA per standard of care for response assessment, per IMWG criteria.

7.4.17.2 Central Laboratory Evaluations

Minimal Residual Disease in Patients With a Complete Response

In patients with a confirmed or suspected CR at study entry, during the screening BMA procedure, an 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 a suspected CR, an additional BMA sample for MRD will be collected.

Eight-color flow cytometry will be performed to determine MRD. In addition, and if portions of the samples are available after flow cytometry, sequencing technology will also be used for the assessment of MRD. The concordance between flow and sequencing methodology readouts will be assessed.

Archival tumor material (BMA as unstained [preferred] or stained slides) from disease diagnosis and any other available 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. Bone marrow biopsy samples will not be accepted for this purpose. If not available at screening, the archival BMA sample may be submitted at any time during the study. These samples will be processed according to the Laboratory Manual, stored by the central lab, and analyzed in batches. Because these samples are consumed in the analysis, archival marrow material cannot be returned to the investigator.

All BMA MRD samples are required to be sent to the central laboratory immediately after collection.

Upon implementation of Amendment 07, BMA is not required for central laboratory assessment of CR or for MRD for protocol purposes. Investigators may continue to take BMA per standard of care for response assessment, per IMWG criteria.

Molecular Analyses

Mutations in key signaling pathways in MM, such as RAS/RAF, and other tumor molecular characteristics determined to be clinically meaningful for this study will be assessed in each patient using archival materials and tumor DNA from BMA samples originally used for the assessment of MRD, as available.

Unless otherwise noted, BMA samples for MRD or for molecular analysis are required to be sent to the central laboratory for processing immediately after collection.

Upon implementation of Amendment 07, BMA is not required for central laboratory assessment of MRD or molecular analysis for protocol purposes. Investigators may continue to take BMA per standard of care for response assessment, per IMWG criteria.

7.4.18 Blood-Based Biomarker Analyses

One blood sample will be collected at screening for testing the candidate biomarker relationship to response or resistance and to long-term clinical benefits, such as OS and PFS, of ixazomib therapy. Polymorphisms in mechanism- and pathway-related genes, including proteasome subunits and NFκB regulators, such as P11A, *NFKB1*, *TRAF3*, and IKB, will be assessed. Recent data have identified host variation, specifically germline DNA variants in proteasome subunits[64] and the NFκB pathway,[65] as potential important contributors to PI clinical activity.

Details regarding the preparation, handling, and shipping of samples are provided in the Study Manual.

7.4.19 Imaging Assessments

Skeletal survey of disease will be performed at screening (within 8 weeks before randomization 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.

7.4.20 Quantification of M-Protein

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

Upon implementation of Amendment 07, all central laboratory assessments of response and progression are discontinued. Investigators should continue to assess disease response/progression according to IMWG criteria (including use of local efficacy laboratory measures), as well as initial disease progression, PFS2, and start of subsequent therapies.

7.4.21 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 Schedule 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).

Upon implementation of Amendment 07, this sample is no longer needed.

7.4.22 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 Schedule of Events.

Upon implementation of Amendment 07, all central laboratory assessments of response and progression are discontinued. Investigators should continue to assess disease response/progression according to IMWG criteria (including use of local efficacy laboratory measures) for documentation of initial disease progression and PFS2.

7.4.23 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 Schedule 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.

Upon implementation of Amendment 07, all central laboratory assessments of response and progression are discontinued. Investigators should continue to assess disease response/progression according to IMWG criteria (including use of local efficacy laboratory measures) for documentation of initial disease progression and PFS2.

7.4.24 Disease Response Assessment

Patients will be assessed for disease response according to the IMWG uniform response criteria, version 2011 (see Section 15.12).[66]

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 Schedule of Events).

Upon implementation of Amendment 07, all central laboratory assessments of response and progression are discontinued. Investigators should continue to assess disease response/ progression according to IMWG criteria (including use of local efficacy laboratory measures) for documentation of initial disease progression and PFS2 (see the updated Schedule of Events for Amendment 07).

Response categories are as follows in Table 7-1:

Table 7-1 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.

As of Amendment 07, no central laboratory bone marrow assessment is required to document CR.

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).

7.4.25 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.

Upon implementation of Amendment 07, no further PK sample collection will be performed, as all ongoing patients have completed at least 10 cycles of treatment. The PK Sampling Schedule has been moved to Section 15.13 for reference.

7.4.26 Follow-up Assessment for Progression-Free Survival, Progressive Disease, Progression-Free Survival 2, and Overall Survival

At EOT, patients will enter a Follow-up period for PFS, PD, PFS2, and/or OS. See the Schedule 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 4 Follow-up periods.

7.4.26.1 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 12 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 12 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 12 weeks until initiation of next-line therapy by the investigator/treating physician.

Upon implementation of Amendment 07 in the PFS and PD Follow-up periods, the EORTC QLQ-C30, EORTC QLQ-MY20, and EQ-5D-5L questionnaires and the HU assessment will be administered every 12 weeks.

7.4.26.2 Progression-Free Survival 2 Follow-up and Overall Survival Follow-up

Patients who start next-line therapy (regardless of when) will enter the PFS2 Follow-up period. The next-line therapy will be recorded, including dates of initiation and termination (for progression or death), regardless of whether it is initiated before or after PD. Information about disease response/status should also be collected during the PFS2 Follow-up period. During the PFS2 Follow-up period, follow-up will occur every 12 weeks until PD2 occurs.

After patients in the PFS2 Follow-up period have PD2 on next-line therapy, they enter into 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.

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 social security indexes. Both the patient and the current treating physician will be contacted during the OS Follow-up period to provide information about all MM treatments (drug regimen, interval, dose, start/stop date).

Related SAEs must be reported to the Takeda 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 Takeda Department of Pharmacovigilance or designee.

Refer to Section 10.0 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 Takeda 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 Schedule of Events. Also refer to the Schedule 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 after all patients have completed the OS Follow-up period (ie, all patients have died or the study has been terminated) or withdrawn from the study (see Section 7.10).

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 Schedule of Events. The primary reason for study drug discontinuation will be recorded on the eCRF.

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

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.

8.0 STATISTICAL AND QUANTITATIVE ANALYSES

The first IA has been conducted (data cutoff date 12 August 2019) and the primary endpoint of PFS based on IRC assessment was statistically significant. The description of statistical methods and analyses presented below reflects the full design of the study so to retain all statistical considerations.

8.1 Statistical Methods

In general, summary tabulations will be presented by treatment arm and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage per category for categorical data. The Kaplan-Meier (K-M) survival curves and 25^{th}, 50^{th} (median), and 75^{th} percentiles will be provided along with their 2-sided 95% confidence intervals (CIs) for time-to-event data.

Details for the statistical analysis will be provided in the statistical analysis plan (SAP). The SAP will be written by Takeda and will be finalized before the first formal IA for OS, which is also the FA for PFS.

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 this study is to determine whether ixazomib improves PFS as compared with placebo. To obtain an adequate statistical power for OS, however, the study will not be stopped after the PFS analysis even if a significant PFS is observed.

A total of approximately 700 patients will need to be randomized in a 3:2 ratio into the 2 treatment arms, assuming an average enrollment rate of approximately 9 patients/month for the first 12 months and approximately 20 patients/month thereafter. The total sample size is calculated on the basis of maintaining 80% power to test the OS. The study is also adequately powered to test PFS. There are 2 planned IAs and 1 FA. The first IA will be the FA (and the only analysis) for PFS for statistical testing purposes. If the test for PFS is significant at the first IA, then OS will be tested at this first IA and at the subsequent IA, and at the FA if needed.

The first IA for OS (FA for PFS) will be performed when approximately 392 IRC-assessed PFS events have been observed or approximately 10 months after the last patient has been enrolled, whichever occurs later. The PFS will be tested in the ITT population with a 2-sided alpha = 0.04. In addition, PFS will be tested in parallel with 2-sided alpha = 0.01, using the Hochberg testing approach, in 3 prespecified subgroups: 1) ISS stage III, 2) patients aged ≥75 years, and 3) patients who had a CR or VGPR to initial therapy.

With 392 IRC-assessed PFS events, the study will have 90% power to detect a hazard ratio for PFS of 0.71 (median PFS of 11 months for control vs 15.5 months with treatment) using a 2-sided log-rank test at a 2-sided alpha level of 0.04 and assuming a drop-out rate of approximately 20% at Month 20. This will be the FA for PFS for statistical testing purposes, with the opportunity to claim PFS benefit. If the test for PFS is not statistically significant in any population (in the ITT population or any of the 3 subgroups), the study will be deemed unsuccessful, and no further testing will be conducted.

If the test for PFS is significant at the first IA, OS will be tested. If the OS results are statistically significant at either the first or second IA, the study can be stopped early, and this OS analysis will be the FA for formal hypothesis testing of OS. Otherwise, determination of whether the final number of OS events might increase will occur at the second IA.

The total event size calculation for OS is based on the adaptive sample size reassessment approach, which, in this study, is an adaptive event size reassessment approach. The minimum event size of 295 death events is based on an optimistic assumption of a hazard ratio of 0.71 (ie, median OS of 70 months for the ixazomib arm vs 50 months for the placebo arm, for a 41% improvement with ixazomib), with 80% power at a 2-sided level of significance of 0.04. The O'Brien-Fleming alpha spending function (the Lan-Demets method) is used to calculate the significance boundary on the basis of the observed number of death events at each IA, with a total of 295 OS events for the FA.

The second IA for OS will be performed when approximately 206 death events have been observed. If OS significance is not claimed, the conditional power based on OS will be calculated. If the conditional power falls in the promising zone, the event size will be determined according to a prespecified event size adaptation rule, with an event cap of approximately 393 death events. No futility analysis will be performed in the study.

The event size adaptation rule is a prespecified stepwise function to avoid the problem of back calculation resulting from an event size corresponding to either barely promising or highly promising interim results. The event size adaptation rule will be designed by the sponsor's independent design statistician and approved by the sponsor's head of biostatistics. Neither the independent design statistician nor the head of biostatistics is involved in the conduct of this study.

The adaptation rules will be outlined in a separate document and will not be accessible to the sponsor's study team until completion of the study. The rules will be available only to the sponsor's independent design statistician, the sponsor's head of biostatistics, the IDMC, and the statistics representative on the sponsor's executive committee (if different from the sponsor's head of biostatistics).

8.1.2 Randomization and Stratification

The randomization scheme will be generated by an independent statistician at Takeda who is not on the study team. Before dosing, an enrollment code will be assigned to each patient. The randomization assignment will be implemented by an IXRS.

Eligible patients will be randomized in a 3:2 ratio to ixazomib or placebo treatment arms, stratified by 4 factors: initial therapy (PI-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age at time of randomization (<75 vs ≥75 years), and best response to initial therapy, as measured during screening (CR or VGPR vs PR).

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

Safety population: The Safety population is defined as all patients who receive at least 1 dose of study drug. Patients will be analyzed according to the treatment they actually received.

Intent-to-Treat (ITT) population: The ITT population is defined as all patients who are randomized. Patients will be analyzed according to the treatment they are randomized to receive, regardless of any errors of dosing.

Per-Protocol population: The Per-Protocol population is a subset of the ITT population. The Per-Protocol population consists of all patients who do not have major protocol violations, as determined by the study clinician, who is blinded to study drug assignment. All decisions to exclude patients from the Per-Protocol population will be made before unblinding the 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 Efficacy Analysis

A closed sequential-testing procedure will be used to test the primary endpoint of PFS and the key secondary endpoint of OS, with the following testing order:

1. At the first IA—PFS as assessed by the IRC in the ITT population (primary endpoint) (see Section 8.1.1) and PFS as assessed by the IRC in 3 prespecified subgroups: a) ISS stage III; b) patients aged ≥75 years; and c) patients with a response of CR or VGPR to initial therapy;
2. OS (key secondary endpoint) at the IAs or FA.

OS will be tested at the IAs or FA at the significance level determined by the O'Brien-Fleming alpha spending function (the Lan-DeMets method). Due to the closed sequential

testing property, the family-wise type I error is strongly controlled for both the primary endpoint and key secondary endpoints (see Section 8.1.10).

All other efficacy endpoints will be tested at a 2-sided alpha level of 0.05.

8.1.6.1 Analyses for Primary Efficacy Endpoints

The analysis of the primary endpoint, PFS, will be based on the ITT population using IRC-assessed progression data. Progression-free survival is defined as the time from the date of randomization to the 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 approximately 10 months after the last patient has been enrolled or when approximately 392 IRC-assessed PFS events have occurred, whichever occurs later. A 2-sided, stratified log-rank test will be used to compare the treatment groups with respect to PFS at a 2-sided alpha level of 0.04. In addition, an unadjusted stratified Cox model will be used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors. The K-M survival curves and K-M medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

Sensitivity analyses for PFS include:

- Progression-free survival as assessed by the investigator will be analyzed in the ITT population.
- Progression-free survival as assessed by the IRC will be analyzed in the Per-Protocol population if more than 5% patients are excluded from this analysis.

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

Subgroup analyses will be performed for PFS relative to baseline stratification factors and demographic data such as sex, race, and age. In addition, a stepwise Cox model will be implemented to identify potential predictive factors using relevant demographic or diagnostic covariates.

8.1.6.2 Analyses of Key Secondary Efficacy

The primary endpoint of PFS will be supported by prespecified evidence of clinical benefit as measured by the key secondary endpoint, OS. Overall survival will be analyzed on the basis of the ITT population and is defined as the time from the date of randomization 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.

A 2-sided, stratified log-rank test will be used to compare the treatment and control groups with respect to OS. In addition, an unadjusted stratified Cox model will be used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors. The

K-M survival curves and K-M medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each study group.

To adjust for the potential effects of subsequent therapies after patients discontinued study treatment, the following 2 methods may be used:

- Marginal Structural Models (MSM) by Robins et al [67]
- Inverse Probability of Censoring Weighted (IPCW) method by Robins and Finkelstein [68]

Subgroup analyses will be performed for OS relative to baseline stratification factors and demographic data such as sex, race, and age. Also, a stepwise Cox model will be implemented to identify potential predictive factors using relevant demographic or diagnostic covariates.

8.1.6.3 Analyses of Other Secondary Efficacy Endpoints

The primary endpoint of PFS will be supported by prespecified evidence of clinical benefit as measured by other secondary endpoints. Other secondary efficacy parameters include the best response during the study, duration of CR, TTP and PFS2, TTNT, the time to the end of next-line therapy, and duration of the next line of therapy.

Disease response–related endpoints will be analyzed using IRC-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. A chi-square test will be used to compare the best response during the treatment period between those 2 arms.

Duration of Complete Response

Duration of CR is defined as the time from the date of randomization (for those who had a CR at randomization) 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 randomization 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 ITT population using methods similar to those used for PFS.

Progression-Free Survival 2

Progression-free survival 2 is defined as PFS on next-line therapy: the time from randomization to objective disease progression on next-line treatment or death from any cause. Patients who do not have documented PD while on next-line therapy will be censored

at the date of the last assessment of SD or better. Progression-free survival 2 will be determined by the treating physician/investigator, and the analysis of PFS2 will be based on the ITT population using methods similar to those used for PFS.

Time to Next-Line Therapy

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

Time to End of Next-Line Therapy

Time to end of next-line therapy is defined as the time from the date of randomization to the date of last dose of next-line antineoplastic therapy. Time to end of next-line therapy will be analyzed on the basis of the ITT population. Patients who are still receiving next-line therapy will be censored at the date of the last dose.

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

An unadjusted stratified Cox model including frailty status (fit, unfit, or frail) and treatment will be used to estimate the hazard ratio and 95% CIs for the treatment effect and frailty status using stratification factors for both PFS and OS. A status of fit will be compared with a status of unfit or frail.

Duration of the Next Line of Therapy

Duration of next-line therapy is defined as the time from the date of the first dose of the line of antineoplastic therapy coming after study treatment to the date of the last dose. Duration of next-line therapy will be analyzed for patients in the ITT population who actually received next-line therapy. Patients who are still receiving next-line therapy will be censored at the date of the last dose. Duration of next-line therapy will be summarized using the K-M method.

8.1.7 Analyses of Patient-Reported Outcomes and Health Economics

Analyses of patient-reported outcomes and health economics will be performed using the ITT population.

8.1.7.1 Patient-Reported Outcomes Analysis

The actual value and change from baseline of the subscale scores for the EORTC QLQ-C30 and EORTC QLQ-MY20 will be summarized using descriptive statistics and plotted by treatment group over time.

The number and percentage of patients with a meaningful change from baseline in subscale scores will be summarized by treatment group 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.

8.1.7.2 Health Economics Analysis Using Medical Resource Utilization and Utility

EQ-5D-5L scores will be summarized in descriptive statistics for treatment arms.

Health utilization data will be summarized in descriptive statistics of medical encounters (length of stay, inpatient, outpatient, and reason) and number of missing days from work or other activities by patient and caregiver for treatment arms.

8.1.8 Pharmacokinetics/Pharmacodynamics/Biomarkers

8.1.8.1 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.

8.1.8.2 Minimal Residual Disease Analysis

Minimal residual disease negativity is defined as the absence of MRD and MRD positivity is defined as the presence of MRD. The MRD assessment will be performed using BMA samples tested using both flow cytometry and sequencing methodologies. The conversion rate from MRD positive to MRD negative and the maintenance of MRD negativity will be assessed at Cycle 13 and at EOT (approximately 24 months [equivalent to 26 cycles, if no cycle delays]) and compared between the 2 arms. Minimal residual disease negativity will also be reported in all patients who achieve a CR, regardless of whether they receive ixazomib or placebo during the study. The rate of achievement of CR MRD negativity during maintenance will also be compared between the 2 treatment groups. The association between MRD status and PFS and OS will be evaluated in both study arms, and concordance between flow cytometry and sequencing readouts will be assessed in the subset of patients for whom both readouts are available.

8.1.8.3 Biomarker Analysis

Progression-free survival, OS, and disease response will be evaluated in the patients defined by mutations in key signaling pathways, such as RAS/RAF; polymorphisms in proteasome genes, such as polymorphism P11A in *PSMB1* or polymorphisms in NFκB regulatory genes such as *NFKB1*, *TRAF3*, and *IKB*.

Overall Survival and Progression-Free Survival in High-Risk Populations

Overall survival and PFS in high-risk populations, defined as patients carrying mutations including, but not limited to, del17, t(4;14), or t(14;16), will be analyzed using a similar method as PFS and OS in the ITT population. Cytogenetic characteristics will be documented by the site at the time of disease diagnosis and will not be reassessed during the course of the study.

8.1.9 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 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 ≥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.

8.1.9.1 New Primary Malignancy

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

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

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

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

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

8.1.9.2 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.

8.1.10 Interim Analyses

There are 2 planned IAs. The first IA will be performed when approximately 392 of the IRC-assessed PFS events have occurred or approximately 10 months after the last patient has been enrolled, whichever occurs later. This IA is expected to occur approximately 50

months after the first patient is enrolled. This is the primary analysis and the only analysis of PFS for statistical testing purposes and the first IA for OS.

At the first IA, PFS will be tested in both the ITT population and in 3 prespecified subgroups. The subgroup testing strategy includes 2 major components: a) preservation of the ability to detect the overall treatment effect using a reduced overall significance level of alpha = 0.04, which will be used for the ITT population; and b) test of treatment effect for the 3 prespecified subgroups: 1) ISS stage III, 2) patients aged ≥75 years, and 3) CR or VGPR to initial therapy. Subgroup testing will be conducted using the remaining alpha = 0.01 and the Hochberg procedure for multiplicity correction (refer to the SAP for proof of strong control of the Type I error rate). Because the size of the treatment effect may be substantially greater in a prespecified subgroup than in the overall study population, analysis of patients in each subgroup at a stringent significance level may still provide a statistically significant outcome.

After PFS is tested at the first IA, central efficacy and investigator assessments of disease response for protocol purposes will be discontinued (except for investigator assessment of PFS2).

If the test for PFS is not statistically significant in any population (the ITT or any of the 3 subgroups), the study will be stopped.

The second IA will be performed when approximately 206 deaths (approximately 70% of the total expected 295 deaths, the minimal number of events for the OS final analysis) have been observed.

For the testing of OS, alpha spending for the first and second IAs will always be based on the observed events (information fraction) and a total of 295 death events with a different adjustment of the critical value at OS FA testing (Cui, Hung, and Wang [CHW] test statistics [69] used for the primary analysis of OS at FA) based on the following scenarios:

- If PFS in the ITT population is significant, and PFS in at least 1 subgroup is not significant, then OS in the ITT population will be tested using a total alpha of 0.04.
- If PFS in the ITT is significant and PFS in all 3 subgroups is significant, then OS in the ITT population will be tested with a total alpha of 0.05.
- If PFS in the ITT population is not significant, and PFS in at least 1 subgroup is significant, then no formal ITT OS testing will be conducted.

The family-wise error rate for the 4 null hypotheses for PFS and the 1 hypothesis for OS for the overall study population is controlled using a prespecified, 2-sided 0.05 level of significance. The proof of strong control of the type I error rate for testing PFS and OS in the ITT population and PFS in the subgroup populations is shown in the SAP. Because of the closed sequential testing property, the family-wise error rate is strongly controlled for both the primary endpoint and the 3 key secondary endpoints.

The IAs will be conducted by the independent statistical center and will be presented for review to the IDMC. During the closed session of the IDMC meeting, the IDMC will compare the conditional power for OS based on the interim results with the prespecified event size and primary endpoint adaptation rules and recommend the final adaptation

decision to the sponsor's executive committee. This recommendation will be documented in the IDMC closed meeting minutes.

9.0 STUDY COMMITTEES

9.1 Steering Committee

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

9.2 Independent Review Committee

An IRC, blinded to treatment arm assignments, will review all disease evaluation data between screening and PD (including the PFS Follow-up period; does not apply to PFS2 assessment) from the study and determine disease status (response and PD). Data from the IRC will not be provided back to the investigators during the conduct of the study.

As of Amendment 07, analysis of the primary endpoint of PFS has been completed for this study and no further IRC review of disease evaluation data will take place.

9.3 Independent Data Monitoring Committee

An IDMC supported by an independent statistician will review safety and efficacy data at the planned IAs. The IDMC will provide a recommendation regarding study continuation based on the safety and efficacy parameters. If the study is terminated early based on the IDMC recommendation, Takeda will notify the appropriate regulatory authorities. In addition, the IDMC will periodically review safety data at regularly scheduled meetings prespecified in the IDMC charter.

The first formal safety review will occur after approximately 60 subjects have been randomized and receive at least 1 cycle of study treatment. Subsequently, periodic safety reviews will also occur as prespecified in the IDMC charter.

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

10.0 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 have to have 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.[63] 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 Takeda 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 Takeda, 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 Takeda. 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 email address on the fax cover sheet so that an acknowledgment of receipt can be returned via email within 1 business day. Email submission of paper SAE forms with a PDF attachment should only be used in the case where fax is not possible within 24 hours of receiving the event. In case of email, site personnel must confirm successful transmission by awaiting an acknowledgment of the receipt via email within 1 business day. If SAEs are reported via fax or by email, the EDC application must be updated as soon as possible with the appropriate information.

SAE Reporting Contact Information

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.[63] 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 Takeda 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 Takeda 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 Takeda 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, whichever occurs first. The IDMC will also receive reports of all cases of new primary malignancies occurring during the trial.

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 Takeda 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 Takeda Department of Pharmacovigilance or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11.0 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 EDC application. Takeda 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

Takeda 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.

Takeda, 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 Takeda 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 because of the COVID-19 pandemic, alternative monitoring approaches such as remote source data verification or telephone contact may be used to ensure data quality and integrity and maintain patient safety. Alternative monitoring approaches should be used only where allowed by 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. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

Upon implementation of Amendment 07, patients on study treatment must be reconsented before dosing on Day 1 of the next full treatment cycle. Patients 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 Takeda 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 Takeda. 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. Takeda, 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 Takeda, 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 Takeda 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 Takeda, or a designee (or disposal of the drug, if approved by Takeda) will be maintained by the clinical site. Takeda 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 Takeda 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 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 Takeda, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Takeda 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 Takeda once the site's participation in the study has concluded.

Within 15 days after premature closure, Takeda 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 Takeda notified.

12.0 USE OF INFORMATION

All information regarding ixazomib supplied by Takeda 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 Takeda. It is understood that there is an obligation to provide Takeda 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 Takeda, 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 Takeda 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 Takeda.

13.0 INVESTIGATOR AGREEMENT

I have read Protocol C16021 Amendment 09: A Phase 3, Randomized, Placebo-Controlled, Double-Blind 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)

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15.0 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.[70]

15.3 Cockcroft-Gault Equation

For males:

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

For females:

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

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.[71]

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.[72]

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.[73]

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 3. Weighted index of comorbidity

Assigned weights for diseases	Conditions
1	Myocardial infarct
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end organ damage
	Any tumor
	Leukemia
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS

Assigned weights for each condition that a patient has. The total equals the score. Example: chronic pulmonary (1) and lymphoma (2) = total score (3).

Source: Charlson et al. 1987.[9]

15.7 Activities of Daily Living Index

Katz Index of Independence in Activities of Daily Living

ACTIVITIES POINTS (1 OR 0)	**INDEPENDENCE:** (1 POINT) **NO** supervision, direction or personal assistance	**DEPENDENCE:** (0 POINTS) **WITH** supervision, direction, personal assistance or total care
BATHING POINTS:_____	**(1 POINT)** Bathes self completely or needs help in bathing only a single part of the body such as the back, genital area or disabled extremity.	**(0 POINTS)** Needs help with bathing more than one part of the body, getting in or out of the tub or shower. Requires total bathing.
DRESSING POINTS:_____	**(1 POINT)** Gets clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes.	**(0 POINTS)** Needs help with dressing self or needs to be completely dressed.
TOILETING POINTS:_____	**(1 POINT)** Goes to toilet, gets on and off, arranges clothes, cleans genital area without help.	**(0 POINTS)** Needs help transferring to the toilet, cleaning self or uses bedpan or commode.
TRANSFERRING POINTS:_____	**(1 POINT)** Moves in and out of bed or chair unassisted. Mechanical transferring aides are acceptable.	**(0 POINTS)** Needs help in moving from bed to chair or requires a complete transfer.
CONTINENCE POINTS:_____	**(1 POINT)** Exercises complete self control over urination and defecation.	**(0 POINTS)** Is partially or totally incontinent of bowel or bladder.
FEEDING POINTS:_____	**(1 POINT)** Gets food from plate into mouth without help. Preparation of food may be done by another person.	**(0 POINTS)** Needs partial or total help with feeding or requires parenteral feeding.

TOTAL POINTS = _____ 6 = High (*patient independent*) 0 = Low (*patient very dependent*)

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)

EORTC QLQ-C30 (version 3)

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

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

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

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

Please go on to the next page

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

15.10 European Organization for Research and Treatment of Cancer (EORTC) Multiple Myeloma Module (QLQ-MY20)

EORTC Multiple Myeloma Module (QLQ-MY20)

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

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

Please turn to next page

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

15.11 EQ-5D-5L

Health Questionnaire

English version for the UK

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

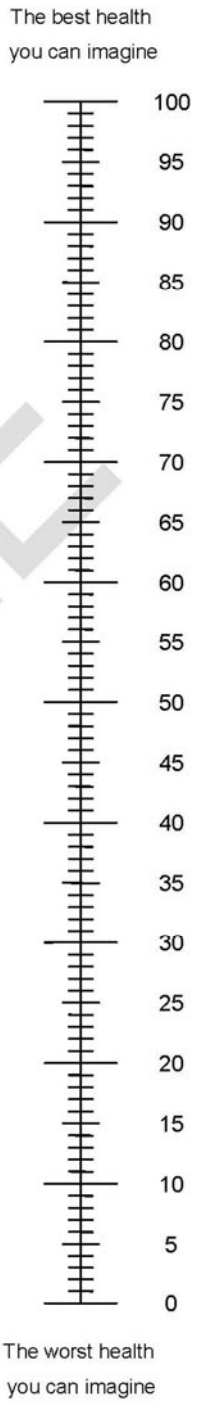
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY = ☐



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.[74] (adapted from Durie et al.[66] and Kyle et al.[75] with permission).

15.13 Full Schedule of Events and PK Sampling Schedule (Schedules Prior to Implementation of Amendment 07)

SCHEDULE OF EVENTS

Study Procedures	**Screening**	**Treatment Period**									**EOT[a]**	**Follow-up[b]**			
		28-Day Cycles[b]										**PFS**	**PD**	**PFS2**	**OS**
Cycle		**C1**			**C2**		**C3**	**C4–C5**	**C5[c]**	**C6-C26**					
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**
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				

Study Procedures	**Screening**	**Treatment Period**								**EOT[a]**	**Follow-up[b]**			
		28-Day Cycles[b]									**PFS**	**PD**	**PFS2**	**OS**
Cycle		**C1**			**C2**		**C3**	**C4–C5**	**C5[c]**	**C6-C26**				
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**
12-lead ECG	X													
EORTC QLQ-C30[f]	X	X			X		X	X		X	X	X	X	X (twice only)	
EORTC QLQ-MY20[f]	X	X						X (C4)		X (C7, 10, 13, 16, 19, 22, 25)	X	X	X	X (twice only)	
EQ-5D-5L[f]	X	X						X (C4)		X (C7, 10, 13, 16, 19, 22, 25)	X	X	X (every 3 months)	X	X
HU assessment[f]		X			X		X	X		X	X	X	X	X (twice only)	
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 (C5)							
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		**C1**			**C2**		**C3**	**C4–C5**	**C5[c]**	**C6-C26**		**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														
Serology and lymphocyte phenotyping[m]	X									X (C7, 13, 19)	X	X (every 6 mo)			
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		**C1**			**C2**		**C3**	**C4–C5**	**C5[c]**	**C6-C26**		**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 (C13)	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		**C1**			**C2**		**C3**	**C4–C5**	**C5[c]**	**C6-C26**					
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**
Progressive disease BMA (local and central lab)[t]		Progressive disease BMA specimen is requested at any time of progressive disease confirmation													
Blood sample for germline DNA biomarker analysis	X														

Abbreviations: BMA=bone marrow aspirate; C=study cycle; CT=computed tomography; ECG=electrocardiography; ECOG=Eastern Cooperative Oncology Group; EORTC=European Organization for Research and Treatment of Cancer; EOT=End of Treatment; EQ-5D-5L=5-level classification system of the EuroQol 5 Dimensional Health Questionnaire; HU=health utilization; 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); QLQ-MY20=Quality of Life Questionnaire Multiple Myeloma Module (20 questions); SFLC=serum free light chain; SPEP=serum protein electrophoresis; UPEP=urine protein electrophoresis; wk=week(s).

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 Takeda Development Center Americas, Inc (Takeda) 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 Takeda 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 Takeda 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.[7-9]

f Patient-reported outcomes and HU assessment (ie, number of medical encounters) should be completed before any other study procedures are performed or

Study Procedures	Screening	Treatment Period								EOT[a]	Follow-up[b]			
		28-Day Cycles[b]									PFS	PD	PFS2	OS
Cycle		C1			C2		C3	C4–C5	C5[c]	C6-C26				
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

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 and QLQ-MY20 questionnaires may be completed at home. At time points when a clinic visit is not required, the EQ-5D-5L questionnaire may be administered over the telephone.

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 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 Takeda 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).

m Blood samples for serology will be used to measure antibody levels against measles, varicella-zoster virus, and tetanus and to quantify B cells, T cells, and natural killer cells.

Study Procedures	**Screening**	**Treatment Period**								**EOT[a]**	**Follow-up[b]**			
		28-Day Cycles[b]									**PFS**	**PD**	**PFS2**	**OS**
Cycle		**C1**			**C2**		**C3**	**C4–C5**	**C5[c]**	**C6-C26**				
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**

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 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, an 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. In addition, when this BMA is collected to investigate suspected PD, a second pull for molecular analysis should be made and sent to the central laboratory immediately after collection.

IXAZOMIB PHARMACOKINETIC SAMPLING SCHEDULE

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.

15.14 Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment 09 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Change the legal entity name of the sponsor.

The change occurs on the Cover Page:

Initial wording:	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited 40 Landsdowne Street Cambridge, MA 02139, USA Telephone: +1 (617) 679-7000
Amended or new wording:	**Takeda Development Center Americas, Inc**~~Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited~~ ~~40 Landsdowne Street~~**95 Hayden Avenue** ~~Cambridge~~**Lexington**, MA 02~~139~~**421**, USA Telephone: +1 (617) 679-7000

Rationale for Change: To reflect the new legal entity name for the sponsor of Takeda Development Center Americas rather than Millennium.

The following sections also contain this change:

- Schedule of Events.
- List of Abbreviations and Glossary of Terms.
- Section 1.1.1 Disease Under Treatment.
- Section 1.1.2 Ixazomib: Takeda's Next-Generation Proteasome Inhibitor.
- Section 1.4.3.2 Dose Rationale.
- Section 4.1 Overview of Study Design.
- Section 5.1 Inclusion Criteria.
- Section 6.3 Dose-Modification Guidelines.
- Section 6.5 Criteria for Dose Escalation at Cycle 5.
- Section 6.7 Permitted Concomitant Medications and Procedures.
- Section 6.10 Blinding and Unblinding.
- Section 6.13 Packaging and Labeling.
- Section 6.14 Storage, Handling, and Accountability.
- Section 7.1 Study Personnel and Organizations.
- Section 7.3 Treatment Group Assignments.
- Section 7.4 Study Procedures.

- Section 7.4.3 Medical History.
- Section 7.4.13 Clinical Laboratory Evaluations.
- Section 7.4.15 Quality of Life Assessment (European Organization for Research and Treatment of Cancer).

Change 2: Clarify language regarding procedures for reporting product complaints or medication errors.

The 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)

Fax at 1-800-881-6092

Email: GlobalOncologyMedinfo@takeda.com

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~~. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.~~**to ctmcomplaint@takeda.com**.

Product complaints in and of themselves are not AEs. If a product complaint is associated with an SAE, a Takeda 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-N1-POINT (1-844-617-6468)~~

~~Fax at 1-800-881-6092~~

~~Email: GlobalOncologyMedinfo@takeda.com~~

~~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 3: Clarify language in study conduct regarding the coronavirus disease 2019 (COVID-19) pandemic.

The 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. 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 use alternative strategies to deliver study drug to patients (eg, via courier or site staff), per local standard practice and regulations, and with prior approval from the investigator and sponsor's project clinician/designee. Comprehensive instructions should be provided to the patient to ensure compliance with dosing

	procedures. Patients who are receiving take-home medication ordinarily should 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 (note: patients in France are only permitted to receive 1 cycle of medication at a time). Patients should be instructed to store the medication according to the storage conditions that are indicated on the drug label. 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 immediately 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. Patients are permitted to transport study drug from the site to home at room temperature. ~~In case of extenuating~~**If** circumstances **due to the COVID-19 pandemic**~~that~~ prevent a patient from attending the study site ~~(eg, the coronavirus disease 2019 [COVID-19] pandemic)~~, sites may use alternative strategies to deliver study drug to patients (eg, via courier or site staff), per local standard practice and regulations, and with prior approval from the investigator and sponsor's project clinician/designee. Comprehensive instructions should be provided to the patient to ensure compliance with dosing procedures. Patients who are receiving take-home medication ordinarily should 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 (note: patients in France are only permitted to receive 1 cycle of medication at a time). Patients should be instructed to store the medication according to the storage conditions that are indicated on the drug label. 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 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 immediately 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:

- Schedule of Events.
- Section 7.4 Study Procedures.
- Section 7.4.14 Health Utilization Data Collection.
- Section 7.4.15 Quality of Life Assessment (European Organization for Research and Treatment of Cancer).
- Section 7.4.16 Utility Measurement.

Change 4: Clarify local laboratory assessment recordings.

The change occurs in the Schedule of Events:

Added text:	Added the following sentence to footnote "i": **Local laboratory assessments are not recorded in the electronic data capture (EDC).**

Rationale for Change: Clarified that local laboratory assessments are not recorded in the EDC.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Science Approval	18-Nov-2021 13:33 UTC
[redacted]	Biostatistics Approval	18-Nov-2021 23:21 UTC