Clinical Study Protocol

NCT Number: NCT02181413

Title: A Phase 3, Randomized, Placebo-Controlled, Double-Blind Study of Oral Ixazomib Citrate (MLN9708) Maintenance Therapy in Patients With Multiple Myeloma Following Autologous Stem Cell Transplant

Study Number: C16019

Document Version and Date: Amendment 4.0, 22 November 2021

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

CLINICAL STUDY PROTOCOL C16019 AMENDMENT 04

Ixazomib

A Phase 3, Randomized, Placebo-Controlled, Double-Blind Study of Oral Ixazomib Citrate (MLN9708) Maintenance Therapy in Patients With Multiple Myeloma Following Autologous Stem Cell Transplant

Protocol Number:	C16019
Indication:	Multiple myeloma
Phase:	3
Sponsor:	Takeda Development Center Americas, Inc
EudraCT Number:	2013-002076-41
Therapeutic Area:	Oncology

Protocol History

Original		08 January 2014
Amendment 1		05 April 2016
Amendment 2		21 April 2017
Amendment 3	Substantial	28 February 2019
Amendment 4	Substantial	22 November 2021

Takeda Development Center Americas, Inc
95 Hayden Avenue
Lexington, MA 02421 USA
Telephone: +1 (617) 349-0200

Approved by:

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

[redacted] MD	Signature	*Date DD Month YYYY*
(or designee)		
[redacted] PhD	Signature	*Date DD Month YYYY*
[redacted], Global Statistics		
(or designee)		

Rationale for Amendment 04

This document describes the changes in reference to the protocol incorporating Amendment No. 04. The primary reason for this amendment is to change the legal entity name from Millennium to Takeda Development Center Americas and to clarify some study procedures.

Additionally, this amendment clarifies other elements of the study procedures.

Descriptions of how to manage study procedures during the coronavirus disease 2019 (COVID-19) pandemic have been added. Finally, the Schedule of Events (SOE) has been streamlined to show only the assessments needed now that all patients have completed study therapy and are in follow-up (the original SOE is now in Section 15.10).

Changes in Amendment 04

1. Updated the legal entity name, address, and telephone of the sponsor.
2. Updated the email address for product complaints and medication errors.
3. Created Streamlined SOE to show only the assessments needed now that all patients are in follow-up, replacing the original SOE.
4. Clarified that new primary malignancy (NPM) reporting must be done through the end of the study.
5. Clarified timeframe for performing health care resource utilization, European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QLQ) Core 30-item (C30) Questionnaire, and EORTC QLQ Multiple Myeloma Module-20 (MY20) assessments.
6. Recorded a change in wording related to days of missed work that might affect the statistical analysis.
7. Changed PFS and PD Follow-up visits to be 12 weeks (+/-1 week) since the last completed Follow-up visit, rather than every 4 weeks.
8. Clarified that the collection of central laboratory assessments (except for investigator assessment of PFS2) has stopped now that the primary endpoint has been met.
9. Removed investigator assessment of disease response/status.
10. Added information about alternative monitoring approaches in the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic.
11. Added language regarding alternative methods for administering study procedures/assessments when it is not possible for the patient to come to the study site due to the COVID-19 pandemic.
12. Clarified that when a patient experiences disease progression, the investigator is encouraged to unblind the patient and take this information into account in planning the next line of therapy.
13. Added death as a reason for a patient's withdrawal from the study.

14. Updated signatories for the study.
15. Clarified how health care resource data are collected from patients.
16. Clarified the monitoring of adverse events.

PROTOCOL SUMMARY

Study Title: A Phase 3, Randomized, Placebo-Controlled, Double-Blind Study of Oral Ixazomib Citrate (MLN9708) Maintenance Therapy in Patients With Multiple Myeloma Following Autologous Stem Cell Transplant

Number of Patients: Approximately 652 patients with newly diagnosed multiple myeloma (NDMM) following induction therapy and autologous stem cell transplant (ASCT)

Study Objectives

Primary:

- To determine the effect of ixazomib maintenance therapy on progression-free survival (PFS), compared to placebo, in patients with NDMM who have had a response (complete response [CR], very good partial response [VGPR], or partial response [PR]) to induction therapy followed by high-dose therapy (HDT) and ASCT.

Key Secondary:

- To determine the effect of ixazomib maintenance therapy on overall survival (OS) compared to 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, as well as 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 (TTP).
- To determine the effect of ixazomib maintenance therapy on progression-free survival 2 (PFS2), defined as time from the date of randomization to the date of objective disease progression on next-line treatment or death from any cause, whichever occurs first.
- To determine the effect of ixazomib maintenance therapy on time to start of the next line of treatment, defined as the time from the date of randomization to the date of the first dose of the next line of antineoplastic therapy for any reason.
- To determine the effect of ixazomib maintenance therapy on time to end of the next line of treatment, defined as the time from the date of randomization to the date of the last dose of the next line of antineoplastic therapy for any reason.
- To determine the effect of ixazomib maintenance therapy on duration of the next line of antineoplastic therapy.
- To assess the incidence of new primary malignancies in patients receiving ixazomib maintenance therapy compared with placebo following ASCT.
- To evaluate the frequency of conversion from minimal residual disease (MRD) positive to MRD negative, or the maintenance of MRD negativity, after 1 and 2 years of therapy in patients treated with ixazomib compared to placebo, using bone marrow aspirates and 8-color flow cytometry or next-generation sequencing.
- To assess the correlation between MRD status (assessed by 8-color flow cytometry and next-

generation sequencing) 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 such as del17, t(4;14), t(14;16), ampl 1q, del13, and del1p
- To determine the long-term safety and tolerability of ixazomib administration to multiple myeloma patients following ASCT.
- To assess overall health-related quality of life (HRQL), as measured by the global health domain of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).
- 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 (PN), if it occurs, by grading at each subsequent monthly visit until 1) resolution of PN, 2) the start of an alternative antineoplastic treatment, or 3) 6 months after progression has occurred, whichever occurs first.

Overview of Study Design: This is a randomized, placebo-controlled, double-blind, phase 3 study in patients with NDMM who have undergone induction therapy according to regional standard of care (SoC), followed by a conditioning regimen containing high-dose melphalan (200 mg/m^2) and ASCT. Induction therapy must include proteasome inhibitor (PI) and/or immunomodulatory drug (IMiD)-based regimens. Vincristine, Adriamycin (doxorubicin), and dexamethasone is not an acceptable induction therapy for this trial.

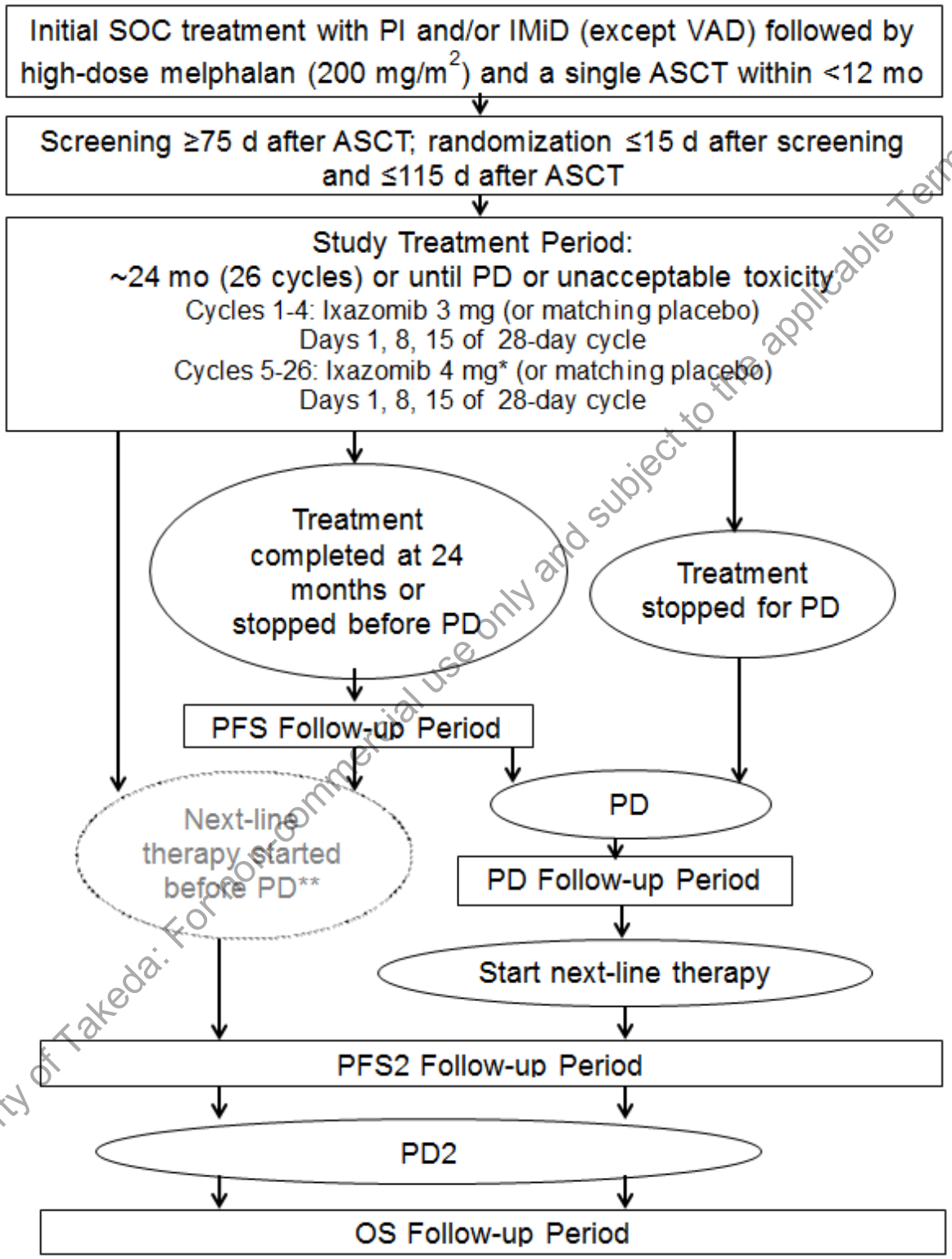
Patients who have achieved clinical and hematologic recovery following induction, HDT, and ASCT will initiate screening for study eligibility no earlier than 75 days after transplant, complete screening within 15 days, and be randomized no later than 115 days after transplant. Eligible patients (those whose CR, VGPR, or PR has been documented during screening and who have met all inclusion/exclusion criteria) will be enrolled and randomized in a 3:2 ratio to ixazomib or placebo. Stratification is based on induction regimen (PI without an IMiD vs IMiD without a PI vs PI and IMiD); pre-induction International Staging System (ISS) (stage 1 vs stage 2 or 3); and response after transplantation, defined as the response following induction, HDT, and ASCT measured during screening (CR or VGPR vs PR) on the basis of the International Myeloma Working Group (IMWG) uniform response criteria, version 2011.

Patients will receive blinded study drug (ixazomib capsules or matching placebo capsules) orally on Days 1, 8, and 15 of every 28-day cycle, for a maximum duration of approximately 24 months (to the nearest complete cycle [if there are no treatment delays, this would be 26 cycles]), or until documented disease progression (on the basis of the IMWG uniform response criteria, version 2011) or intolerable toxicities, whichever occurs first. The initial dose of study drug will be 3 mg of ixazomib or matching placebo, which will be increased to 4 mg on Cycle 5 Day 1 if tolerated during the first 4 cycles. Clinical, laboratory, disease response, and HRQL with an emphasis on tolerability and symptom burden, as well as MRD assessments will be made. Following documented disease progression, 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 are 5 planned interim analyses (IAs) and 1 final analysis (FA) in the study. The first IA will be the primary analysis (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.

Study Population: Patients with NDMM who have had a response (defined as CR, VGPR, or PR) to SoC induction therapy, high-dose melphalan (200 mg/m^2), and single ASCT will be eligible for this study. Patients must receive no further myeloma consolidation therapy after ASCT.
Duration of Study: Patients will be treated for a maximum duration of approximately 24 months (to the nearest complete cycle [if there are no treatment delays, this would be 26 cycles]), or until documented disease progression or intolerable toxicity, whichever occurs first. Subsequent to the 24 month active treatment period, or removal from study therapy due to disease progression or toxicity, patients will be followed in 4 follow-up periods—PFS, Progressive Disease, PFS2, and OS—for disease status, subsequent therapies, HRQL, new primary malignancies, and survival.

Study Overview Diagram

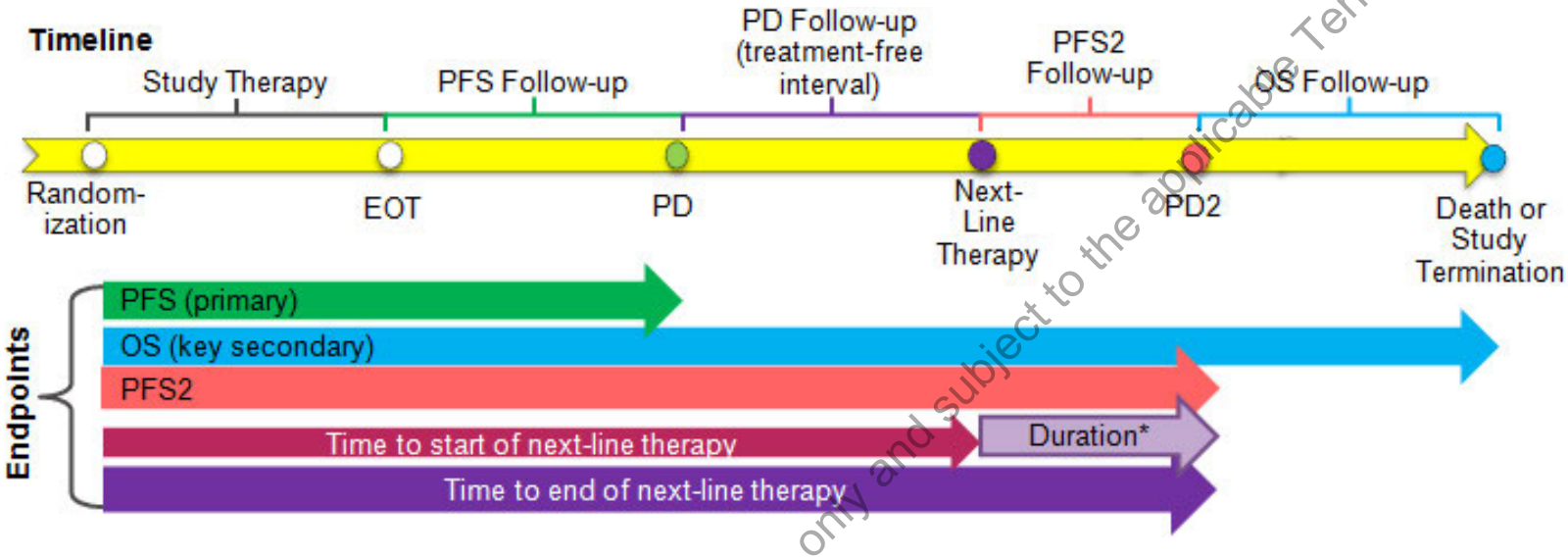


Abbreviations: ASCT=autologous stem cell transplant; IMiD=immunomodulatory drug; OS=overall survival; PD=progressive disease; PD2=second PD (on next-line therapy); PFS=progression-free survival, defined as time from randomization to PD or death from any cause; PFS2=time from the date of randomization to the date of objective disease progression on next-line treatment or death from any cause, whichever occurs first; PI=proteasome inhibitor; SOC=standard of care; VAD=vincristine, Adriamycin (doxorubicin), and dexamethasone.

* 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, Criteria for Dose Escalation at Cycle 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 will enter directly into the PFS2 Follow-up period.

Study Periods and Corresponding Endpoints 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 next-line therapy, and duration of next-line therapy, other secondary and exploratory endpoints.

* Duration=duration of next-line therapy. This duration starts with the onset of next-line therapy and ends when PD2 occurs or whenever the therapy is stopped for any other reason, whichever occurs first.

Streamlined Schedule of Events

Study Procedures	Follow-up			
	PFS	**PD**	**PFS2**	**OS**
Cycle	**Before PD, Every 12 wk**	**After PD but Before Next-Line Therapy, Every 12 wk**	**After Next-Line Therapy but Before PD on Next-Line Therapy, Every 12 wk**	**After PD on Next-Line Therapy, Every 12 wk**
Days				
Window	**±1 wk**			
Symptom-directed physical examination [a]	X	X		
ECOG performance status	X	X		
EORTC QLQ-C30 [b]	X	X	X (1st 2 visits)	
EORTC QLQ-MY20 [b]	X	X	X (1st 2 visits)	
EQ-5D [b]	X	X	X	X
HU assessment (also for unscheduled visits) [b]	X	X	X (1st 2 visits)	
Investigator assessment of disease response/status			X	
New primary malignancy assessment		Continuous from the start of study drug regimen administration until death or termination of the study by the sponsor		
Survival				X
Subsequent therapy/disease status			X	X

Abbreviations: C=study cycle; COVID-19=coronavirus disease 2019; CR=complete response; D=study day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC=European Organization for Research and Treatment of Cancer; EOT=End of Treatment (visit); EQ-5D=EuroQol 5-Dimensional Health Questionnaire; HU=healthcare resource utilization; Ig=immunoglobulin; MRD=minimal residual disease; OS=overall survival; PD=progressive disease; PFS=progression-free survival; PFS2=time from the date of randomization to the date of objective disease progression on next-line treatment or death from any cause, whichever occurs first; PN=peripheral neuropathy; QLQ-C30=Quality of Life Core 30-item Questionnaire; QLQ-MY20=Quality of Life Multiple Myeloma Module 20; SPEP=serum protein electrophoresis; UPEP=urine protein electrophoresis.

Tests and procedures should be performed on schedule, but, unless otherwise specified, occasional changes are allowable within a 2-day window for holidays, vacations, and other administrative reasons or a longer window after discussion with the 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] Includes evaluation for PN.

[b] Patient-reported outcomes and HU assessments (ie, medical encounters) should be completed before any other study procedures are performed or study drug is administered. During the PFS2 Follow-up period only, EORTC QLQ-C30, EORTC QLQ-MY20, and HU assessments should be done ideally at the first 2 visits (or at least within the first 4 visits). Patient-reported outcome questionnaires are preferred to be completed by patients in the clinic, but if needed (eg, due to the COVID-19 pandemic), the EORTC QLQ-C30 and EORTC QLQ-MY20 questionnaires may be completed at the patient's home using paper versions of the questionnaires; as a last resort, these patient-reported outcomes can be collected via telephone using EORTC telephone interview administration scripts. At time points when a clinic visit is not required, or if needed due to the COVID-19 pandemic, the EQ-5D questionnaire may be administered over the telephone. HU data may be obtained over the telephone and/or via patient medical records, as needed.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
AE	adverse event
AL	light-chain
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ampl	amplification
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
BCRP	breast cancer resistance protein
BM	bone marrow
BMA	bone marrow aspirate
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CHMP	Committee for Medicinal Products for Human Use
CL	clearance, IV dosing
CR	complete response
CT	computed tomography
CYP	cytochrome P450
del	deletion
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DOR	duration of response
DVT	deep vein thrombosis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QLQ) Core 30-item (C30) Questionnaire
EOT	End of Treatment (visit)
EQ-5D	EuroQol 5-Dimensional Health Questionnaire
EQ VAS	EQ visual analogue scale
ESMO	European Society for Medical Oncology
EU	European Union
FA	final analysis
FDA	United States Food and Drug Administration
FISH	fluorescence in situ hybridization

Abbreviation	Term
GCP	Good Clinical Practice
GI	gastrointestinal
HDT	high-dose therapy
HRQL	health-related quality of life
HU	health care resource 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 drug
IMWG	International Myeloma Working Group
IRB	institutional review board
IRC	independent review committee
ISS	International Staging System
ITT	intent-to-treat
IV	intravenous; intravenously
IXRS	interactive web/voice response system
LenDex	lenalidomide+dexamethasone
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MP	melphalan prednisone
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRP2	multidrug resistance associated protein
MTD	maximum tolerated dose
MY20	Multiple Myeloma Module-20
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDMM	newly diagnosed multiple myeloma
NEC	not elsewhere classified
NFKB	nuclear factor kappa-light-chain-enhancer of activated B cells
NPM	new primary malignancy
OS	overall survival
PAD	bortezomib, Adriamycin (doxorubicin), and dexamethasone
PD	progressive disease
PE	pulmonary embolism

Abbreviation	Term
PFS	progression-free survival
PFS1	progression-free survival on study therapy or before the next line of therapy if discontinued before progression
PFS2	time from the date of randomization to the date of objective disease progression on next-line treatment or death from any cause, whichever occurs first
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PN	peripheral neuropathy
PO	*per os*; by mouth (orally)
PR	partial response
PSMB1	proteasome (prosome, macropain) subunit, beta type, 1
QOL	quality of life
RP2D	recommended phase 2 dose
RRMM	relapsed and/or refractory multiple myeloma
SAE	serious adverse event
sCR	stringent complete response
SCT	stem cell transplant/therapy
SD	stable disease
SMA	Safety Management Attachment (to the Investigator's Brochure)
SNP	single-nucleotide polymorphism
SoC	standard of care
SPEP	serum protein electrophoresis
SPM	second primary malignancies
$t_{1/2}$	terminal disposition half-life
TEAE	treatment-emergent adverse event
TMA	thrombotic microangiopathy
T_{max}	first time of occurrence of maximum (peak) concentration
TRAF-3	TNF receptor-associated factor 3
TTP	time-to-progression
Tx	treatment
ULN	upper limit of the normal range
UPEP	urine protein electrophoresis
US	United States
VAD	vincristine, Adriamycin (doxorubicin), and dexamethasone
VGPR	very good partial response
WHO	World Health Organization

1.0 BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

Multiple myeloma (MM), a B-cell tumor of malignant plasma cells within the bone marrow, remains incurable despite advances in novel therapies with proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and stem cell transplant (SCT) therapy. Multiple myeloma is characterized by the accumulation of plasma cells in the bone marrow (and other organs) and can result in bone marrow failure, bone destruction, hypercalcemia, and renal failure. It constitutes approximately 1% of all reported neoplasms and approximately 13% of hematologic cancers worldwide.[1] In the Americas, Canada, and Western European countries, approximately 5 to 7 new cases of MM are diagnosed per 100,000 people each year.[1-3] Although less common in Asian countries, incidences of MM 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.[4,5]

Multiple myeloma is sensitive to many cytotoxic drugs including alkylating agents, anthracyclines, and corticosteroids for both initial treatment and relapsed disease. Over the past decade, significant achievements have been made in expanding treatment options for MM with novel therapies such as thalidomide, bortezomib, and lenalidomide. These regimens have extended PFS and/or time-to-progression (TTP).[6-10] The introduction of novel therapies and the increased use of high-dose therapy (HDT) significantly improved OS in patients with newly diagnosed myeloma (NDMM) who were eligible for autologous stem cell transplant (ASCT).[11-13]

Despite more therapeutic options, MM remains incurable, and there is 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 (DOR). Patients become refractory to approved therapies and ultimately are left with no alternative treatment options. In an effort to expand the therapeutic armamentarium against MM with agents that target the proteasome, 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 and subcutaneous bortezomib (VELCADE), the first-in-class, small molecule proteasome inhibitor (PI) developed by Takeda. Building on the efficacy seen with bortezomib in MM and other hematologic malignancies, Takeda has subsequently developed oral ixazomib citrate to improve the pharmacology of the agent and provide a more convenient mode of drug administration.

Like VELCADE, ixazomib citrate is a modified peptide boronic acid. Ixazomib citrate is the citrate ester of ixazomib, the biologically active form that potently, reversibly, and selectively inhibits the proteasome. Ixazomib citrate was formulated to improve the chemical properties of ixazomib for clinical delivery. Ixazomib citrate rapidly hydrolyzes to ixazomib upon contact with either plasma or aqueous solutions. In contrast to bortezomib, ixazomib demonstrates a

faster dissociation rate from the proteasome, possibly resulting in enhanced tumor penetration, exhibits antitumor activity in a broader range of tumor xenografts, and has more prolonged tissue penetration.

Ixazomib preferentially binds the β5 site of the 20S proteasome with a concentration producing 50% inhibition (IC_{50}) of 3.4 nM. At higher concentrations, it also inhibits the activity of the β1 and β2 sites. Ixazomib was selective for the proteasome when tested against a panel of proteases (IC_{50} values between 20 and 100 μM), kinases (IC_{50} values > 10 μM), and receptors (IC_{50} values > 10 μM). Ixazomib and bortezomib have different β5 proteasome dissociation half-lives ($t_{1/2}$), reflecting differences in their on-off binding kinetics (the β5 proteasome dissociation [$t_{1/2}$] for ixazomib citrate and bortezomib is 18 and 110 minutes, respectively). On the basis of these favorable characteristics, ixazomib citrate (henceforth called simply "ixazomib") is anticipated to be effective against MM.

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 has been evaluated as an oral single agent in phase 1 studies that have included patients with advanced solid tumors, lymphoma, relapsed/refractory MM (RRMM), and relapsed or refractory light-chain (AL) amyloidosis and demonstrated early signs of activity. Ongoing studies continue to investigate both single-agent ixazomib and ixazomib in combination with standard treatments. On the basis of encouraging preliminary data observed in patients with MM requiring systemic treatment, 2 phase 3 trials in patient populations with NDMM (C16014) and RRMM (C16010) are currently evaluating ixazomib in combination with lenalidomide and dexamethasone (LenDex) versus placebo/LenDex. Both trials are combining ixazomib at a weekly dose of 4 mg (as ixazomib) on Days 1, 8, and 15 in a 28-day cycle to a standard dose of lenalidomide with a weekly dexamethasone dose of 40 mg. In addition, a recently concluded clinical pharmacology study evaluated drug-drug interactions (DDIs) with ketoconazole, rifampin, and clarithromycin, effect of food, and relative bioavailability.[14] Studies evaluating the safety and PK of ixazomib alone (in Japanese patients) and in combination with lenalidomide and dexamethasone in Asian adult patients (including Japanese patients) with a diagnosis of RRMM are ongoing.

As of 27 March 2013, preliminary clinical data are available for a total of 653 patients across 13 studies. The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy (PN), is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

Fatigue was the most common AE reported among 384 patients treated in the oral (PO) studies (47%). Other common AEs reported in the pooled intravenous (IV) and PO safety populations

include nausea, thrombocytopenia, diarrhea, and vomiting. Rash is also a commonly reported TEAE; however, there is some variety in its characterization and causality, resulting in different preferred terms to describe it. A high-level term outline of rash events includes rashes, eruptions and exanthems not elsewhere classified (NEC); pruritus NEC; erythemas; papulosquamous conditions; and exfoliative conditions. The dose escalation phases of most trials reported in the IB have now completed enrollment, and gastrointestinal (GI) symptoms were the common dose-limiting toxicities (DLTs) when the use of prophylactic anti-emetics was not permitted per protocol. In the expansion cohorts or phase 2 cohorts (as per each study), the incidence and severity of GI symptoms was mitigated by the use of the lower maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) (as per each study) and standard clinical usage of anti-emetics and/or antidiarrheal medications as deemed appropriate. Prophylactic use of anti-emetics has not been required as with other agents but (as outlined in Section 6.9) has been used according to standard practice and is effective.

The most frequent (at least 20%) treatment-emergent adverse events (TEAEs) reported with the PO formulation pooled from single-agent studies (n=201) irrespective of causality to ixazomib citrate, include nausea (53%), fatigue (51%), diarrhea (44%), thrombocytopenia (34%), vomiting (38%), decreased appetite (32%), fever (21%), and anemia (21%). The most frequent (at least 20%) TEAEs reported with the PO formulation pooled from combination trials, irrespective of the combination or causality to ixazomib (n=173), include diarrhea (47%), fatigue (44%), nausea (38%), peripheral edema (35%), constipation (33%), insomnia (29%), thrombocytopenia (28%), anemia (26%), vomiting (26%), neutropenia (25%), back pain (24%), pyrexia (23%), cough (20%), hypokalemia (20%), and upper respiratory tract infection (20%). Overall, rash of all grades is 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.

Additional detailed information regarding the clinical experience of ixazomib may be found in the IB, including information on the IV formulation.

1.3.1 Pharmacokinetics and Drug Metabolism

Clinical IV and PO PK data show that ixazomib (measured as the biologically active boronic acid form of ixazomib) has multi-exponential disposition with a rapid initial phase that is largely over by 4 hours. Oral ixazomib is rapidly absorbed with a median single-dose first time of occurrence of maximum (peak) ixazomib concentration (T_{max}) of approximately 0.5 to 2.0 hours and a terminal disposition half-life ($t_{1/2}$) after multiple dosing of approximately 5 to 7 days.[15] Results of a population PK analysis (N=137) show that there is no relationship between body surface area (BSA) or body weight and clearance (CL). Also, on the basis of stochastic simulations for fixed dose, exposures are independent of the individual patient's BSA.[16] 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. Please refer to the current IB and Safety Management Attachment (SMA) for information on the PK for IV doses of ixazomib.

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 cytochrome P450s (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 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) [14]; 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 DDI study, co-administration of ixazomib with rifampin decreased ixazomib C_{max} by 54% and AUC by 74% (Study C16009, Arm 4).[14] 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

Multiple myeloma is generally considered an incurable disease. However, high-dose chemotherapy incorporating ASCT has been found to prolong PFS and OS in patients who are sufficiently fit to undergo the procedure. In addition, the introduction of modern agents, including IMiDs and PIs, has improved the survival of both transplant patients and those who are transplant ineligible.

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 survival or improving quality of life (QOL) without shortening survival, and a favorable benefit:risk ratio. Although there is emerging evidence for the clinical benefit of maintenance therapy following SCT, a positive benefit:risk balance is yet to be established in existing therapies, no therapy has been approved for this indication, and a true standard of care (SoC) has not been adopted.[17] A recent review regarding the European perspective on Multiple Myeloma Treatment Strategies reveals that "although recent trials have provided important results regarding the utility and benefit of consolidation and maintenance in the post-ASCT setting, further studies are needed to provide answers to questions, such as duration of treatment, the impact on subsequent therapies, and who should receive post-ASCT treatment.[18] In addition, the measurement of QOL data in the maintenance setting is of importance to thoroughly assess the benefit of long-term therapy."

The role of maintenance therapy in both the posttransplant and nontransplant settings has been extensively explored. A detailed review of the history of the clinical trials of maintenance therapy was published in 2012 by the International Myeloma Working Group (IMWG).[17] Initially, trials of maintenance therapy consisted of continuation of chemotherapy with melphalan and prednisone (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 due to the unfavorable safety profile. The immunomodulatory agent thalidomide has been extensively studied as a single agent or in combination maintenance therapy in both posttransplant and transplant-ineligible settings. Progression-free survival benefit was generally observed across studies. Overall survival benefits were observed in some studies,[19] whereas a decrement in OS was observed in others.[20] High rates of discontinuation were observed in all studies due to toxicity. In addition, patients with high-risk cytogenetics had no incremental benefit with thalidomide maintenance therapy,[21,22] and in 1 study patients experienced a decrement in benefit.[22]

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 bortezomib have been conducted, both as part of a combination maintenance regimen and in direct comparison with thalidomide.[23-25] In the GIMEMA trial, maintenance with bortezomib and thalidomide showed a PFS benefit over no maintenance therapy.[23]

The phase 3 HOVON/GMMG study investigated induction therapy leading to ASCT and subsequent maintenance therapy in patients with MM.[24] Induction therapy with the regimen of bortezomib, Adriamycin (doxorubicin), and dexamethasone (PAD), followed by bortezomib maintenance was evaluated and compared with induction therapy using vincristine, doxorubicin, and dexamethasone (VAD) 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 del(17)p13. However, the induction regimens in the 2 arms were different such that only the bortezomib maintenance arm received bortezomib during induction therapy, and thus the benefit of bortezomib as maintenance alone could not be not independently assessed.

Additionally, lenalidomide has been assessed as maintenance therapy in 3 placebo controlled trials.[26-28] While all studies demonstrated a significant PFS advantage with lenalidomide maintenance therapy, only the CALGB trial showed a possible OS benefit, and data regarding the impact of lenalidomide maintenance on DOR to subsequent therapy were limited.[27] In addition, offsetting the potential clinical benefit of lenalidomide maintenance was the increased incidence of secondary primary malignancies (SPMs). Therefore, positive risk:benefit could not be established during the Committee for Medicinal Products for Human Use (CHMP) review to date.[29] To understand whether ixazomib maintenance therapy impacts the incidence of SPMs, as was observed in the lenalidomide trials, a secondary endpoint assessing the incidence of new primary malignancies is incorporated in the proposed trial.

There is currently limited use of maintenance and no universal standard of care (SoC) regarding maintenance therapy post ASCT. This is likely due to the lack of an evidence-based positive benefit:risk profile for drugs in the maintenance setting. The most recent European Society for Medical Oncology (ESMO) guidelines for the treatment of MM point out that thalidomide maintenance increases complete response (CR) rate and prolongs PFS and OS on the basis of 3 randomized studies, "but the optimal duration of treatment and the respective impact of short consolidation versus prolonged maintenance is not yet known."[30] The guidelines also point out that the role of other novel agents in this setting is currently under evaluation. In Western Europe, only about 37% of patients with MM receive maintenance therapy following ASCT, with approximately equal usage of lenalidomide, VELCADE™ and thalidomide, and older agents such as interferon less frequently used.[31] The 2012 IMWG "Consensus on Maintenance Therapy in Multiple Myeloma" notes that in their considerations for clinical practice, a wait-and-see strategy remains a "valuable alternative" to maintenance therapy.[17] This position was reinforced in the 2013 "International Myeloma Working Group Recommendations for Global Myeloma Care," which stated, "Still, at the current time, the panel does not recommend the routine use of maintenance therapy."[32] In the US, current National Comprehensive Cancer Network (NCCN) guidelines (Version 2.2013) support the use of bortezomib, lenalidomide, and thalidomide maintenance therapies, while pointing out concerns regarding cumulative toxicity with thalidomide and increased incidence of secondary primary malignancies with lenalidomide; bortezomib maintenance was considered to be well tolerated. Although lenalidomide is approved by the United States Food and Drug Administration (FDA) for treatment of patients with RRMM, the drug is currently prescribed off-label as maintenance therapy for about 50% of patients after ASCT.

In conclusion, maintenance therapy has not yet been proven to be a superior treatment strategy compared to the current paradigm of a post-ASCT treatment-free interval followed by salvage therapy at relapse. Together with the lack of a universal maintenance SoC and an evidence-based comparator with a demonstrated survival benefit for maintenance therapy post-ASCT, a strong justification is provided to conclude that a phase 3, placebo-controlled trial is an appropriate approach for determining the efficacy of single-agent ixazomib maintenance therapy.

1.4.1 Rationale for Ixazomib Schedule and Dose

1.4.1.1 Schedule Rationale

The balance of benefit versus risk is paramount in this phase 3 maintenance study. The study will administer ixazomib on a weekly dosing schedule, which is consistent with the other ixazomib pivotal trials.

The 24-month duration of therapy was chosen on the basis of the favorable results from the HOVON-65/GMMG-HD4 trial.[24] In that study, 1 of the 2 study arms included a 2-year maintenance therapy period with VELCADE following induction therapy that contained VELCADE, and ASCT. Significant PFS and OS advantages were seen in this arm compared to the alternative arm, which included 2 years of thalidomide maintenance following a non-PI-containing induction therapy and ASCT. Because ixazomib is a boron-based PI similar to VELCADE (having a similar site of action on the proteasome), the HOVON-65/GMMG-HD4 study provides the basis for the sponsor's position that 24 months of maintenance therapy is an acceptable duration for the ixazomib trial.

In addition, in support of a fixed duration of therapy, it is possible that the incremental clinical benefit of prolonged maintenance therapy diminishes as the duration of maintenance continues. For example, in the HOVON-50 trial,[33] which studied the addition of thalidomide to induction in transplant-eligible MM patient followed by posttransplant thalidomide maintenance until progressive disease (PD) (compared to α-interferon maintenance in the control arm), investigators found a significant PFS benefit for patients receiving thalidomide-containing induction therapy and thalidomide maintenance therapy. However, OS was not improved; survival following relapse was significantly shorter for patients receiving thalidomide. The investigators concluded that prolonged exposure to thalidomide may have been responsible for the decrement in survival after progression. They also concluded that a "limited duration of postinduction/intensification therapy until maximal response is preferable to avoid resistant relapse and to minimize the side effects of prolonged thalidomide exposure."

It is also possible that prolonged therapy may negatively affect the duration of effectiveness of a subsequent therapy after progression due to the emergence of resistant disease while on continuous maintenance therapy—an important consideration for this newly diagnosed population that will inevitably experience relapse as part of the natural course of their disease.[34] A finite treatment period of 24 months aims to reduce the risk of developing resistant disease. In addition, a secondary endpoint of PFS2 (time from the date from randomization to the date of objective disease progression on next-line treatment or death from any cause, whichever occurs first) will evaluate whether relapse following ixazomib maintenance is followed by a shorter response to the next line of antineoplastic therapy.

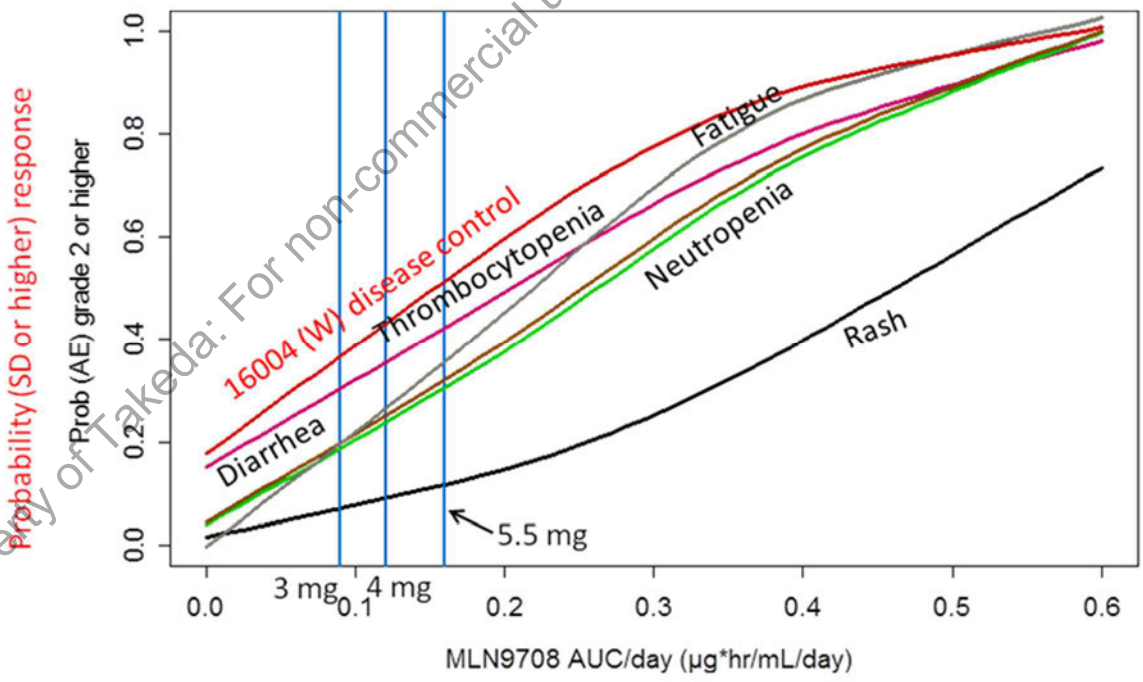
1.4.1.2 Dose Rationale

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 in RRMM patients) were used in a preliminary exposure/response (safety/efficacy) analysis. Data were available over a wide dose range (0.5-3.95 mg/m^2; N=44), corresponding to a dose range of approximately 1 to 8.9 mg. The metric of exposure was AUC 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: fatigue, rash, PN, diarrhea, anemia, thrombocytopenia, and neutropenia. The highest grade of toxicity over the treatment duration was used for each patient in the logistic regression analysis. The toxicity-graded data were then separated into 2 groups for the purposes of the analysis: Grade 2 or higher versus Grade 1 or lower. The data were categorized in this way because patients on maintenance therapy will be receiving drug for a long duration and at a time when they are likely to be asymptomatic from their disease; therefore, an important component of a good maintenance treatment would be a tolerable adverse effect profile to contribute to an overall reasonable QOL. Under these conditions, even Grade 2 toxicities (particularly nonhematologic toxicities) may be a significant burden to the patient. Results from 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) as shown in Figure 1-1.

Primary logistic regression analysis was also performed for efficacy. For this analysis, efficacy data were separated into 2 groups: stable disease (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 AUC. The dose/response curves indicate that a favorable benefit:risk may be achieved at doses of 3 mg and 4 mg, below the MTD.

Figure 1-1 Relationship Between Response (≥ Stable Disease) to Single-Agent Ixazomib and Adverse Events (≥ Grade 2) and AUC (N=44) in Patients With Relapsed and/or Refractory Multiple Myeloma



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

Currently, there are 2 ongoing phase 3 trials with ixazomib citrate, co-administered 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 proposed maintenance study. Patients entering Study C16019 will already have had a clinical response to HDT, will likely be symptom free from their disease, and at the time they start maintenance therapy will have not have been previously exposed to ixazomib citrate. 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, increase the dose to 4 mg to provide maximum possible clinical benefit.

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 AEs are reduced by approximately 10% to 20% compared to 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 or NDMM settings.

Nonetheless, to provide patients the opportunity to derive maximum clinical benefit, 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 ≥ 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 reduction will not dose escalate. The selection of the time point for dose escalation in patients tolerating ixazomib was based on the observation that subjects' 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.

1.4.2 Rationale for Minimal Residual Disease Assessment

The assessment of residual tumor cells persisting after therapy, or minimal residual disease (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.[35-42] As a result, molecular MRD analysis is currently used for risk stratification, as well as assessment of therapy-induced reduction in tumor burden and regrowth after chemotherapy in these indications.[43] Recent studies have suggested that MRD assessment may also play a role in the MM treatment paradigm. Numerous reports have shown that molecular MRD status is predictive of progression-free and OS in MM patients.[44-46] These studies have primarily assessed the bone marrow for the presence of MRD, and in this study the classical flow cytometry methodology will be employed for the assessment of normal/abnormal immunophenotype using bone marrow aspirates, as well as a novel sequencing-based approach, for the assessment of MRD present in the blood of MM patients.

1.4.2.1 Timing and Methods of MRD Assessment

MRD assessment will be conducted using bone marrow aspirate (BMA) and blood samples collected for all patients with a VGPR or CR at screening, at Cycle 13 and at EOT (approximately 24 months [to the nearest complete cycle; if there are no treatment delays, this would be 26 cycles]). In addition, patients whose response improves to CR during the trial will be requested to submit a BMA and a blood sample, and the BMA sample may be collected during the BMA procedure for CR confirmation.

MRD assessment in BMA samples will be done at the central laboratory using an immunophenotype-based methodology. This flow cytometry assay will assess the presence or absence or expression levels of 8 markers that differ between normal plasma cells and tumor plasma cells. The assay results will establish whether the patient who has a CR is MRD positive or negative (on the basis of a prespecified cutoff). Leftover plasma cells from the BMA samples will be used for the assessment of MRD using next-generation sequencing. The sequencing-based method identifies myeloma cells in peripheral blood or bone marrow samples on the basis of the cells' unique immunoglobulin gene rearrangements.[47,48] The sequencing assay can detect residual disease at levels of 1 in 1 million leukocytes, which provides higher sensitivity than standard flow-cytometric methods.[49] This methodology will be used to assess MRD in blood samples as well.

1.4.2.2 MRD Analyses

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. This provides another way to identify and describe the value of maintenance therapy for patients with MM.

The correlation between the MRD status in bone marrow and in peripheral blood samples and their correlation with long-term clinical benefits, such as PFS and OS, could provide a clear practical advantage for the recurrent assessment of MRD during and after treatment.

1.4.3 Rationale for Mutational Analyses

The heterogeneity of clinical results with myeloma therapeutics is partly related to variation in the molecular subtypes of myeloma 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 myeloma (a validated gene expression model of high-risk MM is defined by deregulated expression of genes mapping to chromosome 1[50-52] or to outcome after single-agent VELCADE therapy).[53,54] 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).[55] Similar studies with samples from VELCADE clinical trials highlighted the link between mutations in these pathways and response to proteasome inhibitor.[56] Mutational analysis of tumor samples from patients with RRMM highlights the prevalence of RAS/RAF pathway mutations and their potential impact on clinical outcomes.[56,57]

In this clinical study, the link between clinical outcomes and the presence of specific gene mutations in key pathways, such as RAF/RAS, will be tested using archival tumor samples as well as a portion of bone marrow aspirates that are MRD positive (if available). These hypotheses will be tested in all patients. Additional analyses of tumor molecular characteristics may be done to identify biomarkers determined to be clinically meaningful in this study.

1.4.4 Rationale for Blood-Based Biomarkers

1.4.4.1 Circulating Proteasome Levels and Single-Nucleotide Polymorphism Analyses

Circulating proteasome levels have been demonstrated to be an independent prognostic factor in MM patients with increasing circulating proteasome levels correlating with advanced disease.[58] Given that ixazomib directly targets the 20S proteasome, this leads to the possibility that pretreatment circulating proteasome levels may be relevant for prediction of patient response to therapy. Retrospective analysis of baseline serum proteasome levels from clinical trial samples for patients treated with bortezomib in combination with melphalan and prednisone demonstrated that circulating proteasome levels were associated with both OS and PFS only for bortezomib-containing therapy leading to the possibility that high-circulating proteasome levels could be both a poor prognostic and also a specific marker of poor outcome with bortezomib. These data point to the potential value of further exploring the relationship between predose circulating proteasome levels and response to ixazomib citrate. In this study, a blood sample will be collected at screening to test the levels of circulating proteasome and its association to ixazomib efficacy. Recent data identify host variation, specifically germline DNA variants in proteasome subunits, and the nuclear factor kappa-light chain enhancer of activated B-cells (NFKB) pathway, as factors that might contribute to VELCADE clinical activity. For example, in the 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 proteasome (prosome, macropain) subunit, beta type, 1 (PSMB1) gene has been observed. In this study, a blood sample will be collected at baseline for the assessment of P11A SNP as well as other SNPs potentially associated to responsiveness or resistance to proteasome inhibition.

1.5 Potential Risks and Benefits

As of 27 March 2013, preliminary clinical data are available for a total of 653 patients across 13 studies. Clinical safety data includes 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 and SMA) 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. It is possible that ixazomib 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 citrate, patients are monitored closely for anticipated toxicities. Guidance for the management of AEs and procedures for modifying doses are provided in the protocols, and drug dosage can be modified by either reducing the dose administered or by interruption of 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 oral ixazomib in MM or in the lymphoma trial of IV ixazomib at the corresponding oral doses after accounting for oral bioavailability.

Ixazomib shows 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. VELCADE's proven utility in the treatment of MM and mantle cell lymphoma (MCL) and ixazomib citrate's increased tissue distribution and activity in several xenograft models against the same components of the ubiquitin proteasome system support the further clinical investigation of ixazomib citrate.

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

2.1 Primary Objective

The primary objective of this study is:

- To determine the effect of ixazomib maintenance therapy on PFS, compared to placebo, in patients with NDMM who have had a response (CR, very good partial response [VGPR], or partial response [PR]) to induction therapy followed by HDT and ASCT.

2.2 Key Secondary Objective

The key secondary objective is:

- To determine the effect of ixazomib maintenance therapy on OS compared to 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, as well as 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 time from the date of randomization to the date of objective disease progression on next-line treatment or death from any cause, whichever occurs first.
- To determine the effect of ixazomib maintenance therapy on time to start of the next line of treatment, defined as the time from the date of randomization to the date of the first dose of the next line of antineoplastic therapy for any reason.
- To determine the effect of ixazomib maintenance therapy on time to end of the next line of treatment, defined as the time from the date of randomization to the date of the last dose of the next line of antineoplastic therapy for any reason.

- To determine the effect of ixazomib maintenance therapy on duration of the next line of antineoplastic therapy.
- To assess the incidence of new primary malignancies in patients receiving ixazomib maintenance therapy compared with placebo following ASCT.
- To evaluate the frequency of conversion from MRD positive to MRD negative, or the maintenance of MRD negativity, after 1 and 2 years of therapy in patients treated with ixazomib compared to placebo, using bone marrow aspirates and 8-color flow cytometry or next-generation sequencing.
- To assess the correlation between MRD status (assessed by 8-color flow cytometry and next-generation sequencing) 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, such as del17, t(4;14), t(14;16), ampl 1q, del13, or del1p.
- To determine the long-term safety and tolerability of ixazomib administration to multiple myeloma patients following ASCT.
- To assess overall 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 (EORTC QLQ-C30).
- 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, by grading at each subsequent monthly visit until 1) resolution of PN, 2) the start of an alternative antineoplastic treatment, or 3) 6 months after progression has occurred, whichever occurs first.

2.4 Exploratory Objectives

- To measure 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 and response in patients with polymorphisms in proteasome and nuclear factor kappa-light chain enhancer of activated B-cells (NFκB)–related genes, such as *PSMB1* and *TRAF3* or circulating proteasome levels.
- To evaluate the correlation between MRD readouts, using sequencing, in bone marrow aspirates and blood samples.
- To evaluate the correlation between MRD readouts in BMA samples using flow and MRD readouts in BMA samples using sequencing.

- 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 that exhibit PD.
- 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 instrument.
- To evaluate health care resource utilization (HU) and calculate utility values using the EuroQol 5-Dimensional Health Questionnaire (EQ-5D).

3.0 STUDY ENDPOINTS

3.1 Primary Endpoint

- PFS, defined as the time from the date of randomization to the date of first documentation of disease progression, as evaluated by an independent review committee (IRC), or death due to any cause, whichever occurs first.

3.2 Key Secondary Endpoint

- OS, measured as the time from the date of randomization to the date of death.

3.3 Other Secondary Endpoints

- Best response achieved or maintained (including PR, VGPR, and CR) prior to PD or subsequent therapy.
- TTP, measured as the time from randomization to the date of first documented progression.
- PFS2, defined as time from the date from randomization to the date of objective disease progression on next-line treatment or death from any cause, whichever occurs first.
- Time to start of the next line of therapy.
- Time to end of the next line of therapy.
- Duration of the next line of therapy.
- Development of new primary malignancy.
- The conversion rate from MRD positive to MRD negative, or the maintenance of MRD negativity, after 1 and 2 years of therapy in patients treated with ixazomib compared to placebo, using bone marrow aspirates and 8-color flow cytometry or next-generation sequencing.
- Correlation between MRD status (assessed by 8-color flow cytometry and next-generation sequencing) and PFS and OS, using bone marrow aspirates.
- OS benefits in high-risk population, such as patients carrying del17, t(4;14), t(14;16), ampl 1q, del13, or del1p.
- PFS benefits in high-risk population, such as patients carrying del17, t(4;14), t(14;16), ampl 1q, del13, or del1p.

- Eastern Cooperative Oncology Group (ECOG) performance status.
- AEs.
- Serious adverse events (SAEs).
- Assessments of clinical laboratory values.
- Collection of overall HRQL data from the Global Health Status/QOL subscale of the EORTC QLQ-C30.
- Ixazomib plasma concentration-time data.
- Time to resolution and time to improvement of PN events.

3.4 Exploratory Endpoints

- The rate of increase in tumor burden, measured by M-protein level, after PD before the start of next-line therapy.
- Association between mutations in key signaling pathways, such as RAS/RAF, and response, PFS, and OS, using archival materials.
- Association between polymorphisms in proteasome and NFKB-related genes, such as PSMB1 and TRAF-3, or circulating proteasome levels, and response, TTP, PFS, and OS using blood samples.
- Correlation between MRD readouts, using sequencing, in bone marrow aspirates and blood samples.
- Correlation between MRD readouts in BMA samples using flow and MRD readouts in BMA samples using sequencing.
- Detection of somatic mutations in proteasome subunits and in key signaling pathways, or change in pathways activity, in tumors that exhibit PD.
- Collection of HRQL data from the function and symptom domains of the EORTC QLQ-C30 and the MY20 module.
- Assessment of HU by collecting the number of medical encounters and assessment of health utility values per the EQ-5D questionnaire.

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. The purpose of the study is to evaluate the role of maintenance therapy with ixazomib (compared to matching placebo) in patients who have undergone induction therapy according to regional SoC, followed by a conditioning regimen containing high-dose melphalan (200 mg/m^2) and a single ASCT. Induction therapy must include PI and/or IMiD-based regimens.

Vincristine, Adriamycin (doxorubicin), and dexamethasone (VAD) is not an acceptable induction therapy for this trial.

Screening and Randomization

Patients who have achieved clinical and hematologic recovery following induction, HDT, and ASCT will initiate screening for study eligibility no earlier than 75 days after transplant, complete screening within 15 days, and be randomized no later than 115 days after transplant. Eligible patients (those who have a documented CR, VGPR, or PR during screening and who have met all additional inclusion/exclusion criteria) will be enrolled and randomized in a 3:2 ratio to ixazomib or placebo. A Takeda project clinician or designee will confirm patient eligibility before randomization by the investigator. The stratification factors are induction regimen (PI without an IMiD vs IMiD without a PI vs PI and IMiD); pre-induction International Staging System (ISS) (stage 1 vs stage 2 or 3); and response after transplantation, defined as the response following induction, HDT, and ASCT measured during screening (CR or VGPR vs PR).

Study Treatment

Patients will receive blinded study drug (ixazomib or matching placebo) orally on Days 1, 8, and 15 of every 28-day cycle. Ixazomib capsules and matching placebo capsules will be subsequently referred to as study drug when detailing blinded study procedures. 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 any time a patient is receiving study drug, and will comprise 28-day treatment cycles. Patients will have study assessments performed at regular treatment cycle intervals while they are participating in the study: weekly (Days 1, 8, and 15) for the first cycle, twice a treatment cycle during the second cycle (Days 1 and 8), and then once a treatment cycle for the remainder of their participation in the treatment period for a maximum duration of approximately 24 months (to the nearest complete cycle; if there are no treatment delays, this would be 26 cycles) or until they experience PD, unacceptable toxicity, or discontinue for alternate reasons, whichever occurs first.

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; the response evaluations are for endpoint determinations only and will not be shared with investigators. Dose-modification guidelines are given in Section 6.4. Unscheduled visits may occur between treatment cycles as required (see Section 7.5). For example, symptomatic pain progression should result in an interim unscheduled visit, as would ongoing Grade 3 or worse AEs.

Patients will receive study treatment for a maximum duration of approximately 24 months (to the nearest complete cycle; if there are no treatment delays, this would be 26 cycles) 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.

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, and by the IRC. After PD occurs, the date and characteristics of PD2, and disease status, will be assessed by the treating physician/investigator only.

Progression-Free Survival Follow-up and PD Follow-up

If a patient completes 24 months of study treatment (to the nearest complete cycle; if there are no treatment delays, this would be 26 cycles) before PD 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, the patient enters the PD Follow-up period and continues to be followed every 12 weeks until initiation of the next line of 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 the next line of therapy by the investigator/treating physician.

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

Patients who start the next line of 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 5 IAs and 1 FA in the study. The first IA will be the primary analysis (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.

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. See Section 9.3 for more information.

If PFS is found to be significant at the first IA, then central efficacy laboratory data collection and investigator-assessed response for protocol purposes (along with IRC assessment of disease

response and PD) will cease and will not be recorded in the eCRF. Central laboratory samples are no longer collected since the primary endpoint was met. However, investigator assessment of response-based data may continue for the purpose of determining PFS2.

The original Schedule of Events (Section 15.10), Streamlined Schedule of Events, and the Study Periods and Corresponding Endpoints 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.

ECOG 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.[59]

4.2 Number of Patients

Approximately 652 patients will be enrolled in this study from approximately 230 study centers in North America, Asia Pacific, Europe, and Latin America. Enrollment is defined as being randomized to treatment in the study.

4.3 Duration of Study

Patients will be treated until documented disease progression, intolerable toxicity, or for a maximum duration of approximately 24 months (to the nearest complete cycle), whichever occurs first. If there are no treatment delays, this would be 26 cycles. Subsequent to the 24-month treatment period or removal from study therapy due to disease progression or toxicity, patients will be followed for disease status, subsequent therapies, HRQL, new primary malignancies, and survival.

5.0 STUDY POPULATION

Adult patients age 18 years or older with a confirmed diagnosis of MM who have had a response (CR, VGPR, or PR) to primary MM therapy consisting of SoC induction, a conditioning regimen containing high-dose melphalan (200 mg/m^2), and single ASCT will be eligible for this study.

5.1 Inclusion Criteria

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

1. Adult male or female patients 18 years or older with a confirmed diagnosis of symptomatic multiple myeloma according to standard criteria (see Section 15.2).
2. Documented results available for cytogenetics/fluorescence in situ hybridization (FISH) obtained at any time before transplant and for ISS staging at the time of diagnosis.
3. Underwent SoC induction therapy (induction therapy must include PI and/or IMiD-based regimens as primary therapy for multiple myeloma), followed by a single ASCT with a high-dose melphalan (200 mg/m^2) conditioning regimen, within 12 months of diagnosis.

Vincristine, Adriamycin (doxorubicin), and dexamethasone (VAD) is not an acceptable induction therapy for this trial.

4. Started screening no earlier than 75 days after transplant, completed screening within 15 days, and randomized no later than 115 days after transplant.
5. Patient must have not received post-ASCT consolidation therapy.
6. Documented response to ASCT (PR, VGPR, CR/stringent complete response [sCR]) according to IMWG criteria (as defined in Section 15.9).
7. ECOG performance status of 0 to 2.
8. Female patients who:
   - 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, AND
   - Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [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, AND
   - Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)
9. 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.
10. Suitable venous access for the study-required blood sampling.
11. Patient is willing and able to adhere to the study visit schedule and other protocol requirements.
12. Patients must meet the following clinical laboratory criteria at study entry:
    - Absolute neutrophil count (ANC) $\geq 1{,}000/mm^3$ and platelet count $\geq 75{,}000/mm^3$. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before randomization.
    - Total bilirubin $\leq 1.5 \times$ the upper limit of the normal range (ULN).

- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN.
- Calculated creatinine clearance ≥ 30 mL/min.

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 following primary therapy or is not responsive to primary therapy. For this study, SD following ASCT will be considered nonresponsive to primary therapy.
2. Double (tandem) ASCT.
3. Radiotherapy within 14 days before the first dose of study drug.
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, symptomatic 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 Ginkgo biloba or St. John's wort within 14 days before randomization in the study.
12. Active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.
13. Comorbid systemic illnesses or other severe concurrent disease which, 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 60 days before the first dose of the study drug regimen.

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 appropriate study drug should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of dose.

All doses must be taken as outlined in the original Schedule of Events (Section 15.10). During the first cycle of treatment, all patients will receive doses of ixazomib or placebo capsules in the clinic. Subsequent to the Cycle 2 Day 8 assessment and dose, patients will take the study drug at home as directed for the remainder of Cycle 2. 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) particular note, the Cycle 5 Day 1 dose will be taken in the clinic following determination of whether the study drug dose should be escalated from 3 mg to 4 mg. All other doses may be taken at home.

Refer to the study manuals for additional instructions regarding study drug administration.

6.2 Test Article (Ixazomib Capsules and Matching Placebo Capsules)

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

Ixazomib active capsules will be supplied as single capsules at 4 dose strengths, 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.

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 a 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 or no sooner than 2 hours after a meal. The capsule should be swallowed with water. 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.

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 original Schedule of Events (Section 15.10). Toxicities are to be assessed according to the NCI CTCAE, version 4.03. Before beginning the next cycle of treatment, refer to the guidelines in Section 6.4.

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 3 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 (ANC) ≥ 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 (eg, chronic anemia managed by intermittent transfusions and/or erythropoietic growth factor).

If the patient fails to meet the previously cited criteria for retreatment, initiation of the next cycle of treatment should be delayed for 1 week. At the end of that time, 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 for ≥ 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 ANC ≤ 0.75×10^9/L on an ixazomib citrate/placebo dosing day (other than Day 1)	Study drug dose should be withheld. Complete blood count (CBC) 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 6.4.2: • ANC < 1.0×10^9/L, platelet count < 75×10^9/L (Or other nonhematologic toxicities > Grade 1 or not to the patient's baseline condition.)	Hold study drug until resolution per criteria. Reduce study drug by 1 dose level as outlined in Table 6-1. 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 toxicity timing, ie, after Day 15 dosing thus a dose reduction was not required at that point in the cycle, 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.

Abbreviations: ANC=absolute neutrophil count; CBC=complete blood count.

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 & 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 & symptoms: moderate symptoms, limiting instrumental activities of daily living (ADL)
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 & symptoms: severe symptoms, limiting self care ADL, assistive device indicated
New or worsening Grade 4 peripheral neuropathy	Discontinue study drug	
Grade 2 Rash	Symptomatic recommendations as 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 based on within-cycle criteria or for a subsequent cycle criteria, but not for both for a same cycle.	
Grade 4 Nonhematologic Toxicities	Consider permanently discontinuing study drug, except in the case where the investigator determines the patient is obtaining a clinical benefit and has discussed this with the project clinician or designee.	

Abbreviations: ADL=activities of daily living.

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 Takeda 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 & nonhematologic event	Delay therapy × 1 week. Re-evaluate patient; if still not resolved, delay therapy × 1 additional week.
Hematologic & nonhematologic event 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 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 treatment period of 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 DDI 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 active 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 disease progression)
- Platelet transfusions to help patients meet eligibility criteria are not allowed

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 first dose of the study drug regimen 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 [GM-CSF]) 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.
- Erythropoietin will be allowed in this study.
- Patients should be transfused with red cells and platelets as clinically indicated.
- Patients who are receiving biphosphonates for previously identified lytic destruction of bone or with osteopenia may continue treatment according to the American Society of Clinical Oncology (ASCO) 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.
- Institutional guidelines for deep vein thrombosis (DVT)/pulmonary embolism (PE) prophylaxis should be followed.
- 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 (NSAIDs) should be avoided in patients with impaired renal function, given reported NSAID-induced renal failure 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 (ICF) 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. Unless there is a clinical contraindication, prophylactic antiviral therapy is required for every patient while receiving study treatment. Examples of acceptable antiviral therapy include acyclovir (eg, 400 mg given orally, 3 times a day), famcyclovir (eg, 125 mg given orally, twice a day), or valacyclovir (eg, 500 mg given orally, twice a day) or SoC/local practice.

Pneumonia and Respiratory Tract Infections

Pneumonia, including serious infections, is a known risk in patients with multiple myeloma, especially following ASCT. Therefore, it is recommended that careful monitoring for serious respiratory tract infections and complications is followed with prompt introduction of antibiotics and supportive therapies, such as IV immunoglobulin, instituted as clinically indicated.

Nausea and/or Vomiting

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

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 and/or small papular bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominately on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash is most commonly reported within the first 3 cycles of therapy. The rash is often transient and self-limiting and is typically Grade 1 to 2 in severity. As in any other oncology trial, rash may occur in patients receiving placebo as well as 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 15.5]) is permitted. Management of a Grade 3 rash may require IV antihistamines or corticosteroids. Administration of study drug (and/or other causative agent if given in combination) should be modified per protocol and re-initiated at a reduced level from where rash was noted (also per protocol).

In line with clinical practice, dermatology consult and biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a patient has previously developed a rash (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. Study drug administration should be modified as per 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. A rare risk is thrombotic thrombocytopenia purpura, a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. Thrombotic thrombocytopenic purpura should be managed symptomatically according to standard medical practice.

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. Study drug administration should be modified as per 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 since 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 GI 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 and/or diuretics to manage their blood pressure (for either hypo- or hypertension) should be managed according to standard clinical practice, including considerations for dose adjustments of their concomitant medications during the course of the trial. Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome, which ultimately resolved, has been reported with ixazomib citrate. This condition is characterized by headache, seizures, and visual loss, as well as abrupt increase in blood pressure. Diagnosis may be confirmed by magnetic resonance imaging (MRI) 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

One case of 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. When a patient experiences disease progression, the investigator is encouraged to unblind the patient and take this information into account in planning the next line of therapy.

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

6.11 Description of Investigational Agents

The ixazomib citrate 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 (as Ixazomib)	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 IB and Pharmacy Manual.

6.12 Preparation, Reconstitution, and Dispensation

The study drug is dispensed in blisters 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.

6.14 Storage, Handling, and Accountability

On receipt at the investigative site, study drug should remain in the blister and carton provided until use or dispensation. The container should be stored as directed by the label on the packaging. All excursions should 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 and stored as directed by the label on the packaging as noted previously until the point of use. Comprehensive instructions should be provided to the patient to ensure compliance with dosing procedures. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time. Patients should be instructed to store the medication as directed by the label on the packaging for the duration of each cycle. Patients should be instructed to return their empty 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. Any excursions in temperature should be reported and dealt with on a case-by-case basis.

Study drug dispensed to the patient for take-home dosing should remain in the blister packaging and carton and stored as directed by the label on the packaging as noted previously until the point of use. Comprehensive instructions should be provided to the patient to ensure compliance with dosing procedures. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time. Patients should be instructed to store the medication as directed by the label on the packaging for the duration of each cycle. Patients should be instructed to return their empty 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. Any excursions in temperature should be reported and dealt with on a case-by-case basis.

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

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

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

Please refer to the Pharmacy Manual for additional instructions.

6.15 Other Protocol-Specified Materials

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

7.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and ICH guidelines.

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 manuals. 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 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 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 randomization code will not be reused, and the patient will not be allowed to re-enter the study.

7.4 Study Procedures

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 2-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 collection of assessments is completed before dosing.

Refer to the original Schedule of Events (Section 15.10) and Streamlined Schedule of Events for timing of assessments. Additional details are provided as necessary in the sections that follow.

In acknowledgement of hospital, local, state, or national government restrictions, or other site-related factors caused by the coronavirus disease 2019 (COVID-19) pandemic that may prevent investigators from conducting the study according to the Streamlined Schedule of Events at the clinical study site, investigators may continue patients in the study despite departure from the Streamlined 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. For patients who are impacted by the COVID-19 pandemic, any procedures not conducted per the study protocol will be documented as a protocol deviation.

During contact with the patient, the study site physician or other qualified site staff should at minimum conduct AE collection. Other study assessments may be collected remotely as is feasible. Assessments/procedures that cannot be completed during the protocol-specified window because a site visit is done remotely (ie, symptom-directed physical examination, hematology, clinical chemistry) are waived.

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.

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:

- Diagnosis (Section 15.2) and initial staging (Section 15.4) of MM, including biochemistry (serum protein electrophoresis [SPEP], urine protein electrophoresis [UPEP], serum/urine immunofixation, free light chains), bone marrow results, ISS stage (based on serum albumin and β_2-microglobulin levels), and lactate dehydrogenase (LDH) levels.
- Cytogenetic evaluation should be performed before ASCT using FISH and/or conventional cytogenetics (karyotyping); if only 1 test is available, FISH is preferred. At a minimum, this should include testing for the presence or absence of at least 2 of the following 3 high-risk abnormalities, listed in order of preference: del(17p), 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 ICF will be developed to permit cytogenetic evaluation on BMA samples.
- MM-directed therapy including induction therapies and dates, transplant therapy including conditioning regimen and dates, along with clinically significant toxicities
- Disease response, including pre-and post-ASCT evaluation of disease status.
  NOTE: To minimize clinically redundant procedures, the investigator may choose to use the screening visit to serve as the clinical post-ASCT evaluation of disease status, as long as all requirements for screening are met.
- Review of all current medications, prior radiation (as permitted > 14 days before study therapy for symptomatic bone lesion or > 5 years before study therapy for another malignancy), and the patient's current smoking status.

Refer to the original Schedule of Events (Section 15.10) for specific time requirements and windows.

7.4.4 Physical Examination

A physical examination will be completed per SoC at the times specified in the original Schedule of Events (Section 15.10) and Streamlined Schedule of Events. Symptom-directed examinations should include examination of organ systems related to patient symptoms to document potential AEs, AE severity, AE resolutions, and verification of new primary malignancy (NPM). 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 original Schedule of Events (Section 15.10). Height will only be measured at the screening visit.

7.4.6 Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed using the ECOG performance scale at the time points specified in the original Schedule of Events (Section 15.10) and Streamlined Schedule of Events.

7.4.7 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at screening, within 3 days before dosing, 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 regimen 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 as per request of IEC/IRBs or if required by local regulations.

7.4.8 Concomitant Medications and Procedures

Concomitant medications and therapy will be recorded from the first dose of drug in the study drug regimen through 30 days after last dose of drug in the study drug regimen (see the original Schedule of Events [Section 15.10]). 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.

7.4.9 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the original Schedule of Events (Section 15.10) and Streamlined Schedule of Events. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

7.4.10 Enrollment

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

Procedures for completion of the enrollment information are described in the study manuals.

7.4.11 Electrocardiogram

A 12-lead ECG will be conducted at screening and at the times outlined in the original Schedule of Events (Section 15.10). It may be repeated as clinically indicated during the study at the discretion of the investigator. ECG data to be obtained include PR interval, QRS interval, and QT interval.

7.4.12 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed by a central laboratory until the primary endpoint of PFS is met. For dosing decisions, local hematology and chemistry laboratory results may be used; however, samples must also be sent to central labs. Hematology and chemistry panels may be collected up to 3 days before Day 1 dosing and (when required) 24 hours before Days 8 and 15 dosing.

The collection of samples by a central laboratory was stopped after the primary endpoint was met.

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 prior to starting the next cycle of treatment.

Local laboratory evaluations may be done more frequently at the investigator's discretion, such as 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 manuals.

Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the following clinical chemistry and hematological parameters and urine samples for urinalysis will be obtained as specified in the original Schedule of Events (Section 15.10).

Hematology

- Hemoglobin
- Hematocrit
- Platelet (count)
- Leukocytes with differential
- Neutrophils (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
- Microscopic analysis (only if macroscopic urinalysis parameters abnormal)

7.4.13 Health Care Resource Utilization Data Collection

During the treatment and the follow-up periods indicated in the original Schedule of Events (Section 15.10) and Streamlined Schedule of Events, all medical care encounters since the previous collection will be collected from patient charts and/or patients directly as needed, regardless of the reason for the needed medical care encounter. Examples of data to be collected

are number and duration of medical care encounters, such as inpatient/outpatient admissions, visit type and reasons, and time of work loss.

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

The HRQL assessments will be completed by the patient as specified in the original Schedule of Events (Section 15.10) and Streamlined Schedule of Events. The EORTC QLQ-C30 (30 items; see Section 15.8) incorporates 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status/QOL scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

The EORTC QLQ-MY20 multiple myeloma module (20 items; see Section 15.7) 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 takes about 15 minutes to administer. The instruments consist of a total of 50 items and have been validated and used in many countries.

Patient-reported outcomes and HU assessments (ie, medical encounters) should be completed before any other study procedures are performed or study drug is administered. During the PFS2 Follow-up period only, EORTC QLQ-C30, EORTC QLQ-MY20, and HU assessments should be done ideally at the first 2 visits (or at least within the first 4 visits). Patient-reported outcome questionnaires are preferred to be completed by patients in the clinic, but if necessary (eg, due to the COVID-19 pandemic), the EORTC QLQ-C30 and EORTC QLQ-MY20 questionnaires may be completed at the patient's home using paper versions of the questionnaires; as a last resort, these patient-reported outcomes can be collected via telephone using EORTC telephone interview administration scripts. At time points when a clinic visit is not required, or if needed due to the COVID-19 pandemic, the EQ-5D questionnaire may be administered over the telephone. HU data may be obtained over the telephone and/or via patient medical records, as needed.

7.4.15 Utility Measurement

The EQ-5D (see Section 15.6) consists of 2 pages: the EQ-5D 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). 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 will be administered as specified in the original Schedule of Events (Section 15.10) and Streamlined Schedule of Events; at time points when a clinic visit is not required, EQ-5D may be administered over the telephone and site staff may enter the data from the patient.

7.4.16 Bone Marrow Aspiration

7.4.16.1 Local Laboratory Evaluations

Disease Assessment

A bone marrow aspirate (BMA) will be obtained at screening for disease assessment and, at any time, a BMA sample will be obtained to assess CR or to investigate suspected PD. This evaluation will be performed locally. A standard BMA drawn before consent is acceptable for the screening sample, provided this is collected within 42 days of the first dose and unless VGPR or CR are suspected (in which case another BMA sample for MRD is needed for screening, as discussed below).

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

Cytogenetics/FISH

Cytogenetic evaluation should be performed before ASCT using FISH and/or conventional cytogenetics (karyotype). At a minimum, cytogenetic markers should include at least 2 of these 3 high-risk abnormalities: del17, t(4;14) and t(14;16). Additional abnormalities (ampl 1q, del13, or del1p) may also be tested.

All cytogenetic evaluations will be performed locally by the site according to local standards. Prospective study patients at sites that do not routinely conduct cytogenetic evaluation at the time of disease diagnosis will be asked to sign a prescreening ICF to permit cytogenetic evaluation on bone marrow aspirate samples.

7.4.16.2 Central Laboratory Evaluations

Minimal Residual Disease

Bone marrow aspirate samples will be collected for MRD assessment at screening for all patients in CR and VGPR. A bone marrow aspirate sample for MRD will also be requested when a patient is having a bone marrow aspirate performed for confirmation of a suspected CR at any time on study. In addition, patients in VGPR or CR at Cycle 13 and at EOT (approximately 24 months [to the nearest complete cycle]; if there are no treatment delays, this would be 26 cycles) will have BMA and blood samples collected for MRD at those 2 time points (unless already done within the most recent 2 cycles); BMA and blood samples will also be obtained in patients in CR or VGPR who stop therapy before Cycle 26. All samples will be used for the assessment of MRD using 8-color flow cytometry technology. These samples will be sent to a specialty laboratory.

A portion of the bone marrow aspirates, if available, will also be used for the assessment of MRD using a sequencing methodology. The concordance between flow and sequencing methodology readouts may also be assessed.

MRD will be also assessed in blood samples using a sequencing technology for all patients for whom tumor archival material is available (unstained slides, bone marrow aspirate as a formalin-

fixed, paraffin-embedded block, or stained slides; biopsy samples will not be accepted). This material will be collected at screening and used for the identification of the MM tumor clone(s). The presence of the specific tumor clone(s) will then be assessed at screening, at Cycle 13, and at EOT (approximately 24 months [to the nearest complete cycle]; if there are no treatment delays, this would be 26 cycles). A blood sample will also be collected in patients suspected to have achieved CR at any time on study. These samples will be processed according to the Laboratory Manual, stored by the central laboratory, and analyzed in batches.

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/or tumor DNA from bone marrow aspirates, as available.

In addition, mechanisms of treatment-emergent resistance, such as somatic mutations in proteasome subunits and key signaling pathways or change in pathway activity, will be studied in tumors of patients who experience PD. For this purpose, an optional BMA sample will be collected at the time of PD. This sample may be collected at time of PD confirmation, at the EOT visit, or before starting a new therapy (as the second pull if a sample is collected for PD confirmation).

7.4.17 Blood-Based Biomarker Analyses

Two blood samples will be collected at screening for testing candidate biomarker relationship to response or resistance to ixazomib therapy. Polymorphisms in mechanism and pathway-related genes, including proteasome subunits and NFKB regulators, such as NFKB1, TRAF3, and IKB, will be assessed. Polymorphisms of NFKB family genes are associated with development of multiple myeloma and treatment outcome in patients receiving bortezomib-based regimens and may be relevant for the efficacy of proteasome inhibitors generally.[60] Relationship between response to ixazomib and circulating proteasome levels in serum will also be analyzed. Circulating proteasome levels have been demonstrated to be an independent prognostic factor in MM patients with increasing circulating proteasome levels correlating with advanced disease.[58] Given that ixazomib directly targets the 20S proteasome, this leads to the possibility that pretreatment circulating proteasome levels may be relevant for prediction of patient response to therapy. Retrospective analysis of baseline serum proteasome levels from clinical trial samples for patients treated with bortezomib in combination with melphalan and prednisone demonstrated that circulating proteasome levels were associated with both OS and PFS only for bortezomib-containing therapy[60] leading to the possibility that high-circulating proteasome levels could be both a poor prognostic and also a specific marker of poor outcome with bortezomib. These data point to the potential value of further exploring the relationship between predose circulating proteasome levels and response to ixazomib citrate. These have been linked to the efficacy of bortezomib. Polymorphisms of NFKB family genes are associated with development of MM and treatment outcome in patients undergoing bortezomib-based regimens.

Details regarding the preparation, handling, and shipping of samples are provided in the study manuals.

7.4.18 Imaging Disease Assessments

For patients with documented extramedullary disease at the time of diagnosis, other assessments and scans, such as a CT, positron emission tomography-computed tomography (PET-CT), or MRI scan, may be required to better delineate the sites and measurements of extramedullary disease at the time of screening. Follow-up scans should be obtained at EOT. Additional assessments can be done at the discretion of the investigator (ie, for suspected new lesions or PD). 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.

7.4.19 β_2-Microglobulin

A blood sample will be collected at screening for serum β_2-microglobulin testing and analyzed by a central laboratory. A local laboratory may additionally be used at the discretion of the investigator. The stratification will be by pretreatment ISS stage 1 vs stage 2 or 3, using local results obtained before initiation of induction therapy. Local and central results will be used for analysis.

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 original Schedule of Events (Section 15.10) until PFS significance has been claimed in this study.

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 outlined in the original Schedule of Events (Section 15.10). Quantitative IgD and IgE will be done at screening (and baseline if needed) only. For the rare patient with IgD or IgE MM, the quantitative test for that antibody will be followed at the same time points as quantitative Igs (in addition to IgM, IgG, and IgA).

7.4.22 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 original Schedule of Events (Section 15.10).

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 original Schedule of Events (Section 15.10). Undetectable M-protein by protein electrophoresis in both serum and urine will lead the Central Laboratory to perform immunofixation testing in both serum and urine.

7.4.24 Skeletal Survey

A complete skeletal survey, using roentgenography, will be performed at screening (within 8 weeks before randomization) and at EOT. If at any time the physician believes there are

symptoms or signs that suggest increased or new bone lesions, a repeat of the skeletal survey should be performed. For imaging of symptomatic sites, plain films may be obtained for additional clarity.

In certain circumstances and 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.

7.4.25 Disease Response Assessment

Patients will be assessed for disease response according to the IMWG uniform response criteria, version 2011 (see Section 15.9) [61]. Takeda or a designee will not be assessing responses in the PFS2 period.

Response assessments should be made every 12 weeks during the PFS follow-up period until disease progression (see the Streamlined Schedule of Events). At this time, the primary endpoint has been met; therefore, central efficacy assessments for protocol purposes have been stopped; all investigator assessments of response should be based on local laboratories per local clinical practice.

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

CR must be confirmed with follow-up assessments of SPEP, UPEP, immunofixation of blood and urine, and serum free light chains as outlined in Section 15.9. One bone marrow assessment (locally evaluated) has to occur to document CR; no second bone marrow confirmation of CR is needed.

Please note that to determine a response of sCR, bone marrow immunohistochemistry or immunofluorescence for kappa/lambda ratio should be performed for all patients suspected to be in CR to meet this response category's requirements.

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

7.4.26 Pharmacokinetic Measurements

Plasma concentrations of the complete hydrolysis product of ixazomib citrate (ixazomib) will be measured using a validated LC/MS/MS assay.

Details regarding the preparation, handling, and shipping of the pharmacokinetic samples are provided in the study manuals. Blood samples (3 mL) for the determination of plasma

concentrations of ixazomib (the complete hydrolysis product of ixazomib citrate) will be collected during Cycles 1 through 10. Samples are to be collected at the time points specified in the Ixazomib Pharmacokinetic Sampling Schedule

7.4.27 Follow-up Assessments for PFS, PD, PFS2, and OS

At EOT, patients will enter a Follow-up period for PFS, PD, or PFS2. See the Streamlined Schedule of Events for assessments during each period. See the Study Periods and Corresponding Endpoints 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. PFS and PD Follow-up visit is scheduled to be 12 weeks (+/-1 week) since the last completed Follow-up visit.

7.4.27.1 PFS Follow-up and PD Follow-up

Patients who complete 24 months (to the nearest complete cycle; if there are no treatment delays, this would be 26 cycles) 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 the next line of therapy by the investigator/treating physician.

In both the PFS and PD Follow-up periods, the EORTC QLQ-C30 and MY20 questionnaires, the HU assessment, and the EQ-5D questionnaire will be administered every 12 weeks.

7.4.27.2 PFS2 Follow-up and OS Follow-up

All patients who underwent maintenance therapy and then receive subsequent anticancer therapy will be transitioned to PFS2 period.

Patients who start the next line of therapy (regardless of when) will enter the PFS2 Follow-up period. The next line of 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.

During the PFS2 Follow-up period only, EORTC QLQ-C30, EORTC QLQ-MY20, and HU assessments should be administered ideally at the first 2 visits (or at least within the first 4 visits). The EQ-5D questionnaire should be administered every PFS2 visit. Patient-reported outcome questionnaires are preferred to be completed by patients in the clinic, but if needed (eg, due to the COVID-19 pandemic), the EORTC QLQ-C30 and EORTC QLQ-MY20 questionnaires may be completed at the patient's home using paper versions of the questionnaires; as a last resort, these patient-reported outcomes can be collected via telephone using EORTC telephone interview administration scripts. At time points when a clinic visit is not required, or if needed due to the COVID-19 pandemic, the EQ-5D questionnaire may be administered over the

telephone. HU data may be obtained over the telephone and/or via patient medical records, as needed.

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. In the OS Follow-up period, the EQ-5D questionnaire may be administered every visit, which occurs every 12 weeks, via telephone.

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 the patient's disease status and current MM treatments (drug regimen, interval, dose, start/stop date). Should an NPM be reported, unscheduled visits should be considered to assess the patient and update the eCRF.

NOTE: 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 the posttreatment follow-up. In addition, new primary malignancies that occur during the 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. At unscheduled visits, the HU data should be captured. Other 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 at least a maximum treatment duration of 24 months (to the nearest complete cycle). If there are no treatment delays, this would be 26 cycles.
- PD/death after the completion of Cycle 1.

A Takeda project clinician or designee and the investigator will review PD before taking the patient off treatment for PD. Patients will attend an EOT visit 30 days (+1 week) after receiving their last dose of the study drug regimen, and will continue to be followed for other follow-up assessments specified in the Streamlined Schedule of Events. Refer to the original Schedule of Events (Section 15.10) 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.

7.9 Discontinuation of Treatment With Study Drug, and Patient Replacement

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
- Lost to follow-up
- Other

Once study drug has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the original Schedule of Events (Section 15.10). 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:

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

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 percent per category for categorical data. The Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided 95% confidence intervals (CIs) for time-to-event data.

Details for the FA will be provided in the 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 if ixazomib improves PFS compared with placebo. The study will not be stopped after the PFS analysis. However, even if a significant PFS is observed, the trial will continue to obtain an adequate statistical power for OS.

The total sample size is calculated based on maintaining approximately 80% power to test the OS. The study is also adequately powered to test PFS. There are 5 planned IAs and 1 FA. The first IA will be the primary analysis (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 IA and subsequent analyses.

The primary analysis of PFS, which is also the first IA of OS, will be performed 25 months after the last patient has been enrolled or approximately 328 PFS events have been observed, whichever occurs later. With projected 328 PFS events, it will have 95% power to detect a hazard ratio of 0.67 (ie, median PFS of 26 months for control versus 39 months for treatment) using a 2-sided log-rank test at a 2-sided alpha level of 0.05 and assuming approximately 15% dropout rate at month 30. This IA is expected to occur at 45 months after the first patient is enrolled, including a 20-month enrollment period and an additional 25-month follow-up after the last patient enrolled. This will be the FA for PFS for statistical testing purposes, with the opportunity to claim PFS benefit. With a projected 328 PFS events, an observed hazard ratio of 0.802 or better (ie, median PFS of 26 months for control versus 32.4 months for treatment, 25% improvement) will likely lead to statistical significance for PFS at this analysis. If the test for PFS is not statistically significant, the study will be claimed as unsuccessful and no further formal testing will be conducted.

If the test for PFS is significant, OS will be tested.

The total event size calculation for OS is based on the adaptive sample size reassessment approach [62], which, in this study's setting, is an adaptive event size reassessment approach. The minimum event size of 260 death events is based on an optimistic assumption of a hazard ratio of 0.70 (ie, median OS of 70 months for control vs 100 months for treatment, 43% improvement) with approximately 80% power at a 2-sided level of significance. The O'Brien-Fleming alpha spending function (the Lan-Demets method) is used to calculate the significance boundary based on the observed number of death events in each IA with a total of 260 OS events for the FA.

The second IA will be performed when approximately 140 death events have been observed; the third IA will be performed at approximately 170 death events. The fourth IA for OS will be performed when approximately 200 death events have been observed. If OS significance is not claimed at the fourth IA, 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 350 death events. The fifth IA will be performed when approximately 230 death events have been observed. If the OS results are

statistically significant at any of the IAs (the first through fifth IAs), the study can be stopped early, and this analysis on OS will be the FA for formal hypothesis testing on OS. No futility analysis will be performed in the study.

The event size adaptation rule is a prespecified stepwise function to avoid the back calculation problem resulting from 1 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 study conduct.

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, a randomization number 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: induction therapy of PI without an IMiD vs IMiD without a PI vs PI and IMiD; pre-induction ISS (stage 1 vs stage 2 or 3); and response after transplantation, defined as the response to induction/ASCT 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 (PP) population: The PP population is a subset of the ITT population. The PP 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 PP population will be made before the unblinding of 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, primarily missing data imputation will be based on published instrument specific methods. Other missing data imputation method such

as Last Observation Carry Forward (LOCF) and multiple imputation method may be explored as sensitivity analyses for patient-reported outcomes data.

If there are missing values between visits for an individual AUC calculation for HRQL, a linear interpretation will be implemented to impute missing values.

For AUC calculations based on a prespecified time period, if the HRQL data are not collected before the end of the prespecified time period, the score 0 will be imputed from the last available visit to the end of the prespecified time period.

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, gender, 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 order: (1) PFS (primary endpoint) at the 1st IA. (2) OS (first key secondary endpoint) at the IAs or FA. PFS will be tested at a 2-sided alpha level of 0.05. 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). Because of the closed sequential testing property, the family-wise type I error is strongly controlled for both the primary endpoint and the key secondary endpoint.

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

PFS will be analyzed 25 months after the last patient has been enrolled or when approximately 328 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 0.05. 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 Kaplan Meier (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:

1. PFS assessed by the investigator will be analyzed in the ITT population.
2. PFS assessed by the IRC will be analyzed in the per protocol population.

PFS assessed by the IRC using different censoring mechanisms will be analyzed in the ITT population, for example, not censoring for patients who discontinue treatment and go on

alternative antineoplastic therapy. Details of different censoring approaches will be included in the SAP.

Subgroup analyses will be performed for PFS relative to baseline stratification factors, demographic data such as gender, race, and age. In addition, a stepwise Cox model will be implemented to identify potential predictive factors using relevant demographic or diagnostic covariates, with the entry level fixed at 0.25 and a stay level fixed at 0.10.

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 based on 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 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 treatment group.

Subgroup analyses will be performed for OS relative to baseline stratification factors, 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, with the entry level fixed at 0.25 and a stay level fixed at 0.10.

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 maintenance, duration of CR, time to progression (TTP), PFS2, time to end of the next line of therapy, and duration of the next line of therapy.

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

Best Response During Maintenance

The percentage of each response category (CR, VGPR, PR) and CR + VGPR will be determined. A chi-square test will be used to compare the best response during maintenance between those 2 arms.

Duration of CR

Duration of CR is defined as the time from the date of randomization for those who are CR at randomization or the date of CR for those who converted to CR during maintenance to the date of first documentation of PD. Responders without documentation of PD will be censored at the date of last response assessment that is CR. Duration of CR will be summarized descriptively using the Kaplan-Meier method.

TTP

TTP 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 last response assessment. TTP will be analyzed based on the ITT population using the similar method as PFS.

Progression-Free Survival 2

Progression-free survival 2 (PFS2) is defined as time from the date of randomization to the date of objective disease progression on next-line treatment or death from any cause, whichever occurs first. The second PD should occur during or after the second line of antineoplastic therapy but before the third line of therapy. Patients who do not have documented PD will be censored at the date of last response assessment which is SD or better. PFS2 will be analyzed by the treating physician/investigator based on the ITT population using the similar method as PFS.

Time to End of the Next Line of Therapy

Time to end of the next line of therapy is defined as the time from the date of randomization to the date of last dose of the next antineoplastic therapy or death due to any cause, whichever occurs first. Time to end of the next line of therapy will be analyzed based on the ITT population using the similar method as PFS. Patients who are still on treatment on the next line of therapy will be censored at the date of last response assessment that is SD or better.

Duration of the Next Line of Therapy

Duration of the next line of therapy is defined as the time from the date of the first dose of the next line of therapy to the date of the last dose of the next antineoplastic therapy or death due to any cause, whichever occurs first. Duration of the next line of therapy will be analyzed on those patients who actually received the next line of therapy following the study treatment using the ITT principle. Patients who are still on treatment on the next line of therapy will be censored at last visit. Duration of the next line of 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 EORTC QLQ-C30 and 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 minimal important difference (MID) 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 (CDF) figures. The subscale scores will also be analyzed using mixed models by incorporating the measurements across all available time points.

8.1.7.2 Average HRQL Score Based on Scores From the EORTC QLQ-C30 Global Quality of Life Domain

For each patient, an average HRQL score will be calculated from baseline to last measurement before disease progression.

Once the average score is measured at the individual level, a 2-sample t-test will be used to assess whether the mean average score in the ixazomib group is noninferior to that in the placebo group. The noninferiority margin is 12.

Analyses of the global QOL during the PD Follow-up period (following progression until start of next-line therapy) and the PFS2 Follow-up period (from the start of next-line therapy until PD2) may be conducted—such as descriptive statistics, linear regression, t-test, or linear mixed models. Comparisons of the average global QOL during the treatment period or follow-up periods may be also considered.

In addition, the AUC approach as a sensitivity analysis will be used to examine the differential effect of treatment throughout the study. The AUC approach aggregates the cumulative absolute HRQL score over time: the y axis represents the absolute EORTC QLQ-C30 global QOL score (range: 0-100); the x axis represents the time horizon.

For each individual patient, an AUC will be calculated from baseline to a prespecified time period, such as 24 months for the first IA, 36 months for the fourth IA, and 48 months for the FA. Missing data will be imputed using a linear mixed model. Once the AUC is measured at the individual level, a 2-sample t-test will be used to assess whether the mean AUC in the ixazomib arm is noninferior to that in the placebo arm. The noninferiority margin is set to be 12 × the time period for the AUC analysis. This is consistent with the average score approach, as the time period is fixed.

Additionally, the distribution of individual AUCs in the 2 treatment groups may be described by summary statistics, such as means, standard deviations, median, etc.

If the noninferiority test is statistically significant, then the superiority test will be performed to further examine the benefit of the differential effect of treatment.

The average score and AUC analyses described above will also apply to other scales of EORTC QLQ-C30 and MY20.

8.1.7.3 Health Economics Analysis Using Health Care Resource Utilization and Health Utility

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

HU data will be summarized in descriptive statistics of medical encounters (length of stay, inpatient, outpatient, and reason), or other activities for treatment arms.

8.1.8 PK/Pharmacodynamics/Biomarkers

8.1.8.1 PK Analysis

PK 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 MRD Analysis

MRD negativity is defined as absence of MRD and MRD positivity is defined as presence of MRD. The conversion rate from MRD positive to MRD negative as well as the maintenance of MRD negativity will be assessed and reported in both arms. MRD negativity will also be reported in all patients who achieve a CR, regardless of whether they receive ixazomib or placebo during the study. The MRD assessment will be performed using BMA samples and flow cytometry, and sequencing may also be performed on BMA and/or blood samples from the patients. Degree of correlation between these 2 methodologies will be assessed as well. Association between MRD status with PFS and OS will be evaluated independently from the methodology used for the assessment. 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.

8.1.8.3 Biomarker Analysis

PFS, 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 NFKB regulatory genes, such as NFKB1, TRAF3, and IKB. PFS, OS; and response will also be examined in patients defined by different levels of circulating proteasome.

OS and PFS in High-Risk Population

OS and PFS in a high-risk population, defined as patients carrying cytogenetic abnormalities, such as del17, t(4;14), t(14;16), ampl 1q, del13, or del1p, will be analyzed using the 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 treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher drug-related treatment-emergent AEs
- The most commonly reported treatment-emergent AEs (ie, those events reported by ≥ 10% of all patients)
- SAEs

A listing of treatment-emergent AEs 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. ECOG performance scores will be summarized using a shift table.

Shift tables for laboratory parameters will be generated based on 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 first dose of study drug through the study period will be classified to generic terms according to the World Health Organization (WHO) drug dictionary.

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

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; and
- Incidence rates, defined by 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, were 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).

Due to the distinct nature of hematologic and nonhematologic neoplasms, as well as 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 PN Events

PN is defined as the treatment-emergent adverse event in the high-level term of peripheral neuropathies NEC according to MedDRA.

A PN event is considered as resolved if its final outcome is resolved with no subsequent PN event of the same preferred term occurring on the resolution date or the day before and after. A PN event is considered as improved if the event improves from the maximum grade. That is, all the grades recorded after the maximum grade is 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 event, 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 permits.

8.1.10 Interim Analysis

There are 5 planned IAs. The first IA will be performed when approximately 328 PFS events have occurred or 25 months after the last patient has been enrolled, whichever occurs later. The first IA will be the primary analysis and the only analysis for the primary endpoint of PFS for statistical testing purposes. 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). The second, third, fourth, and fifth IAs will be conducted for OS when approximately 140, 170, 200, and 230 death events have occurred, respectively.

The test significance for the IAs of OS will be determined using O'Brien-Fleming boundaries (the Lan-DeMets method) with a total of 260 death events.

On the basis of OS results in the fourth IA, the planned number of OS events may be increased to up to 350 death events if the observed treatment effect is promising but not large enough to yield the likely conclusion of statistical significance at the end of the study using the original planned number of OS events. It is also possible for the entire study design to remain unchanged as a result of the IAs. The Cui-Hung-Wang test statistic [63] will be used in the FA of OS to protect the type I error.

The IAs will be conducted by the independent statistical center and presented for review to the IDMC. During the closed session of the IDMC meeting at the fourth IA, 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 to the sponsor executive committee the final adaptation decision. 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 PFS Follow-up period; does not apply to PFS2 assessment) from the study and determine disease status (response and progression). Data from the IRC will not be provided back to the investigator during the conduct of the study.

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. In the event that 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 undergone 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 serious AEs, 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.

At the fourth IA, if OS significance is not claimed, the conditional power based on OS will be calculated. During the closed session of the IDMC meeting at the fourth IA, the IDMC will compare the conditional power for OS based on the interim results with the prespecified effect size adaptation rules and recommend to the sponsor executive committee the final adaptation decision. This recommendation will be documented in the IDMC closed meeting minutes.

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 AE Definition

An AE refers to 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 SAE Definition

An SAE refers to 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.

In this study, intensity for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010.[59] Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Department of Pharmacovigilance or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Takeda, will be provided to each clinical study site. A sample of the SAE Form may be found in the study manuals. 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.

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 laboratory abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010.[59] The criteria are provided in the study manuals.

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 AEs and Period of Observation

AEs, 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.
- 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 and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Department of Pharmacovigilance or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or

chronic condition or intercurrent illness(es). In addition, NPMs that occur during the follow-up periods must be reported, irrespective of causality to the study drug, from the first dose of study drug through death or termination of the study by the sponsor.

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female patient occurring while the patient is on study drug, or within 90 days of the patient's last dose of study drug, are considered immediately reportable events. Study drug is to be discontinued immediately. The sponsor must also be contacted immediately by 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, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Department of Pharmacovigilance or designee. 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 electronic data capture (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 eCRF Completion

Takeda, or its 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.

eCRFs 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 its designee, will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk (CD) 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 due to the COVID-19 pandemic, alternative monitoring approaches, such as 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. Remote monitoring and site staff interviews for consistency check of data can be used.

11.5 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. 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 the patient or his/her 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.

Patients in the PFS and PD Follow-up periods may need to be reconsented upon implementation of Amendment 4, according to IRB/IEC standards. Reconsenting should be done in person, where possible. Remote reconsenting is permitted as long as the process adheres to site, IRB/IEC, and GCP standards and local 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 its 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 its designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

11.9 On-site Audits/Inspection

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 its 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 Overdose)

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 or medication errors in and of themselves are not AEs. If a product complaint results in an SAE, an 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 of 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 of 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 byTakeda 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 C16019 Amendment 04: A Phase 3, Randomized, Placebo-Controlled, Double-Blind Study of Oral Ixazomib Citrate (MLN9708) Maintenance Therapy in Patients With Multiple Myeloma Following Autologous Stem Cell Transplant

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

Principal investigator printed name

Principal investigator signature Date

Investigational site or name of institution and location (printed)

14.0 REFERENCES

1. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med 2011;364(11):1046-60.
2. Landgren O, Weiss BM. Patterns of monoclonal gammopathy of undetermined significance and multiple myeloma in various ethnic/racial groups: support for genetic factors in pathogenesis. Leukemia 2009;23(10):1691-7.
3. Harousseau JL, Dreyling M, Group EGW. Multiple myeloma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2008;19 Suppl 2:ii55-7.
4. Huang SY, Yao M, Tang JL, Lee WC, Tsay W, Cheng AL, et al. Epidemiology of multiple myeloma in Taiwan: increasing incidence for the past 25 years and higher prevalence of extramedullary myeloma in patients younger than 55 years. Cancer 2007;110(4):896-905.
5. Qiu L, Wang Y, Qi P, Zou D, Zhao Y, Qi J. Clinical Epidemiological Study on Multiple Myeloma in China: A 18-Year Retrospective Study in a Representative Center. Blood (ASH Annual Meeting Abstracts) 2008;112(11):abstr 2723.
6. Palumbo A, Rajkumar SV, Dimopoulos MA, Richardson PG, San Miguel J, Barlogie B, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia 2008;22(2):414-23.
7. Mateos MV, Richardson PG, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. J Clin Oncol 2010;28(13):2259-66.
8. Gay F, Larocca A, Petrucci M. Achievement of Complete Remission is a Strong Prognostic Factor in 895 Elderly Myeloma Patients Treated With Melphalan-Prednisone Based-Regimens: Results of 3 Multicenter Italian Trials. Haematologica 2010;94:0507.
9. Richardson P, Mitsiades C, Schlossman R, Ghobrial I, Hideshima T, Chauhan D, et al. The treatment of relapsed and refractory multiple myeloma. Hematology 2007:317-23.
10. Dimopoulos MA, Chen C, Spencer A, Niesvizky R, Attal M, Stadtmauer EA, et al. Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia 2009;23(11):2147-52.
11. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood 2008;111(5):2516-20.
12. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. Blood 2008;111(5):2521-6.
13. Libby E, Ebaid A, Quintana D, Wiggins C. Declining myeloma mortality rates in the United States following introduction of novel therapies International Myeloma Workshop 3-6 May 2011; Paris, France.
14. NINLARO (ixazomib) capsules, for oral use [prescribing information]. Cambridge, MA: Takeda Pharmaceutical Company Limited, 2015.

15. Gupta N, Liu G, Berg D, Kalebic T, Gomez-Navarro J. Clinical Pharmacokinetics of Intravenous and Oral MLN9708, An Investigational Proteasome Inhibitor: An Analysis of Data From Four Phase 1 Monotherapy Studies. Blood 2010;116(21):abstr 1813.
16. Gupta N, Saleh M, Venkatakrishnan K. Flat-Dosing Versus BSA-Based Dosing for MLN9708, An Investigational Proteasome Inhibitor: Population Pharmacokinetic (PK) Analysis of Pooled Data From 4 Phase-1 Studies Blood 2011;118(21):abstr 1433.
17. Ludwig H, Durie BG, McCarthy P, Palumbo A, San Miguel J, Barlogie B, et al. IMWG consensus on maintenance therapy in multiple myeloma. Blood 2012;119(13):3003-15.
18. Ludwig H, Avet-Loiseau H, Blade J, Boccadoro M, Cavenagh J, Cavo M, et al. European perspective on multiple myeloma treatment strategies: update following recent congresses. Oncologist 2012;17(5):592-606.
19. Spencer A, Prince HM, Roberts AW, Prosser IW, Bradstock KF, Coyle L, et al. Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. J Clin Oncol 2009;27(11):1788-93.
20. Stewart AK, Trudel S, Bahlis NJ, White D, Sabry W, Belch A, et al. A randomized phase 3 trial of thalidomide and prednisone as maintenance therapy after ASCT in patients with MM with a quality-of-life assessment: the National Cancer Institute of Canada Clinicals Trials Group Myeloma 10 Trial. Blood 2013;121(9):1517-23.
21. Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood 2006;108(10):3289-94.
22. Morgan GJ, Gregory WM, Davies FE, Bell SE, Szubert AJ, Brown JM, et al. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. Blood 2012;119(1):7-15.
23. Palumbo A, Bringhen S, Rossi D, Cavalli M, Larocca A, Ria R, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. J Clin Oncol 2010;28(34):5101-9.
24. Sonneveld P, Schmidt-Wolf IG, van der Holt B, El Jarari L, Bertsch U, Salwender H, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. J Clin Oncol 2012;30(24):2946-55.
25. Mateos M-V, Oriol A, Teruel A-I, Bengoechea E, Pérez M, López J, et al. Maintenance Therapy with Bortezomib Plus Thalidomide (VT) or Bortezomib Plus Prednisone (VP) In Elderly Myeloma Patients Included In the GEM2005MAS65 Spanish Randomized Trial. Blood (ASH Annual Meeting Abstracts) 2011;118(21):abstr 477.
26. Attal M, Lauwers-Cances V, Marit G, Caillot D, Moreau P, Facon T, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med 2012;366(19):1782-91.

27. McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med 2012;366(19):1770-81.

28. Palumbo A, Hajek R, Delforge M, Kropff M, Petrucci MT, Catalano J, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med 2012;366(19):1759-69.

29. Revlimid (Lenalidomide) European Public Assessment Report. European Medicines Agency Committee for Medicinal Products for Human Use. 21 June 2012. Publication No. EMA/432817/2012.

30. Harousseau JL, Dreyling M. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21 Suppl 5:v155-7.

31. Kantar Health. Treatment Architecture: Western Europe Multiple Myeloma. CancerMPact® Western Europe 2012.

32. Ludwig H, Miguel JS, Dimopoulos MA, Palumbo A, Garcia Sanz R, Powles R, et al. International Myeloma Working Group recommendations for global myeloma care. Leukemia 2013.

33. Lokhorst HM, van der Holt B, Zweegman S, Vellenga E, Croockewit S, van Oers MH, et al. A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone, and high-dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma. Blood 2010;115(6):1113-20.

34. Badros AZ. Lenalidomide in myeloma--a high-maintenance friend. N Engl J Med 2012;366(19):1836-8.

35. Bruggemann M, Pott C, Ritgen M, Kneba M. Significance of minimal residual disease in lymphoid malignancies. Acta Haematol 2004;112(1-2):111-9.

36. Foroni L, Coyle LA, Papaioannou M, Yaxley JC, Sinclair MF, Chim JS, et al. Molecular detection of minimal residual disease in adult and childhood acute lymphoblastic leukaemia reveals differences in treatment response. Leukemia 1997;11(10):1732-41.

37. Moreton P, Kennedy B, Lucas G, Leach M, Rassam SM, Haynes A, et al. Eradication of minimal residual disease in B-cell chronic lymphocytic leukemia after alemtuzumab therapy is associated with prolonged survival. J Clin Oncol 2005;23(13):2971-9.

38. Mortuza FY, Papaioannou M, Moreira IM, Coyle LA, Gameiro P, Gandini D, et al. Minimal residual disease tests provide an independent predictor of clinical outcome in adult acute lymphoblastic leukemia. J Clin Oncol 2002;20(4):1094-104.

39. Pott C, Hoster E, Delfau-Larue MH, Beldjord K, Bottcher S, Asnafi V, et al. Molecular remission is an independent predictor of clinical outcome in patients with mantle cell lymphoma after combined immunochemotherapy: a European MCL intergroup study. Blood 2010;115(16):3215-23.

40. Liu H, Johnson JL, Koval G, Malnassy G, Sher D, Damon LE, et al. Detection of minimal residual disease following induction immunochemotherapy predicts progression free survival in mantle cell lymphoma: final results of CALGB 59909. Haematologica 2012;97(4):579-85.

41. Andersen NS, Pedersen LB, Laurell A, Elonen E, Kolstad A, Boesen AM, et al. Pre-emptive treatment with rituximab of molecular relapse after autologous stem cell transplantation in mantle cell lymphoma. J Clin Oncol 2009;27(26):4365-70.

42. Geisler CH, Kolstad A, Laurell A, Andersen NS, Pedersen LB, Jerkeman M, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. Blood 2008;112(7):2687-93.

43. Pott C. Minimal residual disease detection in mantle cell lymphoma: technical aspects and clinical relevance. Semin Hematol 2011;48(3):172-84.

44. Paiva B, Vidriales MB, Cervero J, Mateo G, Perez JJ, Montalban MA, et al. Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation. Blood 2008;112(10):4017-23.

45. Sarasquete ME, Garcia-Sanz R, Gonzalez D, Martinez J, Mateo G, Martinez P, et al. Minimal residual disease monitoring in multiple myeloma: a comparison between allelic-specific oligonucleotide real-time quantitative polymerase chain reaction and flow cytometry. Haematologica 2005;90(10):1365-72.

46. Martinez-Sanchez P, Montejano L, Sarasquete ME, Garcia-Sanz R, Fernandez-Redondo E, Ayala R, et al. Evaluation of minimal residual disease in multiple myeloma patients by fluorescent-polymerase chain reaction: the prognostic impact of achieving molecular response. Br J Haematol 2008;142(5):766-74.

47. Faham M, Zheng J, Moorhead M, Carlton VE, Stow P, Coustan-Smith E, et al. Deep-sequencing approach for minimal residual disease detection in acute lymphoblastic leukemia. Blood 2012;120(26):5173-80.

48. Gawad C, Pepin F, Carlton VE, Klinger M, Logan AC, Miklos DB, et al. Massive evolution of the immunoglobulin heavy chain locus in children with B precursor acute lymphoblastic leukemia. Blood 2012;120(22):4407-17.

49. Rawstron AC, Orfao A, Beksac M, Bezdickova L, Brooimans RA, Bumbea H, et al. Report of the European Myeloma Network on multiparametric flow cytometry in multiple myeloma and related disorders. Haematologica 2008;93(3):431-8.

50. Shaughnessy JD, Jr., Zhan F, Burington BE, Huang Y, Colla S, Hanamura I, et al. A validated gene expression model of high-risk multiple myeloma is defined by deregulated expression of genes mapping to chromosome 1. Blood 2007;109(6):2276-84.

51. Nair B, van Rhee F, Shaughnessy JD, Jr., Anaissie E, Szymonifka J, Hoering A, et al. Superior results of Total Therapy 3 (2003-33) in gene expression profiling-defined low-risk multiple myeloma confirmed in subsequent trial 2006-66 with VRD maintenance. Blood 2010;115(21):4168-73.

52. Broyl A, Hose D, Lokhorst H, de Knegt Y, Peeters J, Jauch A, et al. Gene expression profiling for molecular classification of multiple myeloma in newly diagnosed patients. Blood 2010;116(14):2543-53.

53. Mulligan G, Mitsiades C, Bryant B, Zhan F, Chng WJ, Roels S, et al. Gene expression profiling and correlation with outcome in clinical trials of the proteasome inhibitor bortezomib. Blood 2007;109(8):3177-88.

54. Keats JJ, Fonseca R, Chesi M, Schop R, Baker A, Chng WJ, et al. Promiscuous mutations activate the noncanonical NF-kappaB pathway in multiple myeloma. Cancer Cell 2007;12(2):131-44.

55. Chapman MA, Lawrence MS, Keats JJ, Cibulskis K, Sougnez C, Schinzel AC, et al. Initial genome sequencing and analysis of multiple myeloma. Nature 2011;471(7339):467-72.

56. Mulligan G, Lichter D, Di Bacco A, Blakemore S, Berger A, Koenig E, et al. Mutational Analysis of Tumor Samples From Patients with Relapsed or Refractory Multiple Myeloma (MM) Highlights the Prevalence of RAS/RAF Pathway Activation and Demonstrates Previously Unreported Mutations in Known Cancer Genes. Blood (ASH Annual Meeting Abstracts) 2011;118(21):abstr 1377.

57. Mulligan G, Lichter DI, Di Bacco A, Blakemore SJ, Berger A, Koenig E, et al. Mutation of NRAS but not KRAS significantly reduces myeloma sensitivity to single-agent bortezomib therapy. Blood 2014;123(5):632-9.

58. Jakob C, Egerer K, Liebisch P, Turkmen S, Zavrski I, Kuckelkorn U, et al. Circulating proteasome levels are an independent prognostic factor for survival in multiple myeloma. Blood 2007;109(5):2100-5.

59. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. U.S. Department of Health and Human Services National Cancer Institute. 14 June 2010.

60. Du J, Huo J, Shi J, Yuan Z, Zhang C, Fu W, et al. Polymorphisms of nuclear factor-{kappa}B family genes are associated with development of multiple myeloma and treatment outcome in patients receiving bortezomib-based regimens. Haematologica 2011;96(5):729-37.

61. Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20(9):1467-73.

62. Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Stat Med 2011;30(28):3267-84.

63. Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. Biometrics 1999;55(3):853-7.

64. 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.

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

66. 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.

67. Knoben J, Anderson P. Handbook of Clinical Drug Data, 6th ed.: Drug Intelligence Pub, Inc.; 1988.

68. Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011;117(18):4691-5.

69. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia 2009;23(1):3-9.

15.0 APPENDICES

15.1 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

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

Source: Oken 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. [64]

15.2 Multiple Myeloma Diagnostic Criteria

IMWG 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.

15.3 Cockcroft-Gault Equation

For males:

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

For females:

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

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.[65]

15.4 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 or 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.[66]

Abbreviations: ISS=International Staging System.

a There are two categories for stage II: serum β_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.

15.5 Steroid Equivalent Doses

Approximate equivalent doses:

Steroid	Glucocorticoid Anti-inflammatory (mg)	Mineralicorticoid (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.[67]

15.6 EQ-5D

Health Questionnaire

(English version for the US)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some 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 with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

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

Anxiety/Depression

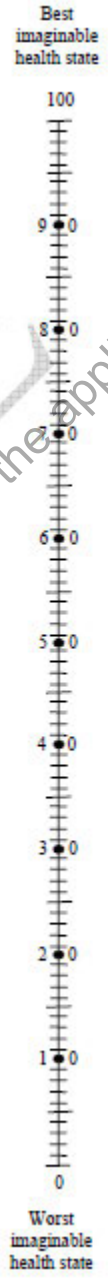
I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

 2

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



3

15.7 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

15.8 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

15.9 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.[68] (adapted from Durie et al.[61] and Kyle et al.[69] with permission).

15.10 Previous, Full Schedule of Events and PK Sampling Schedule (Schedules Before Implementation of Amendment 4)

Study Procedures	**Screening**	**Treatment Period**								**EOT[a]**	**Follow-up[b]**			
		28-Day Cycles[b]									**PFS**	**PD**	**PFS2**	**OS**
Cycle		**C1**			**C2**		**C3**	**C4-C5**	**C6-C26**		**Before PD, Every 4 wk**	**After PD but Before Next-Line Therapy, Every 4 wk**	**After Next-Line Therapy but Before PD on Next-Line Therapy, Every 12 wk**	**After PD on Next-Line Therapy, Every 12 wk**
Days	**-15 to -1**	**1**	**8**	**15**	**1**	**8**	**1**	**1**	**1**					
Window		**±2 days**								**+1 wk**	**±1 wk**			
Informed consent	X													
Inclusion/exclusion criteria[c]	X													
Demographics	X													
Complete medical history and disease staging	X													
Complete physical examination[d]	X									X				
Symptom-directed physical examination[d]		X			X		X	X	X		X	X		
ECOG performance status	X				X		X	X	X	X	X	X		
Vital signs	X	X			X		X	X	X	X	X	X		
Height (cm)	X													
Weight (kg)	X	X			X		X	X	X	X				
Pregnancy test (serum)[e]	X	X								X				
12-lead ECG	X									X				
Hematology laboratory[f]	X	X	X	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**	**C6-C26**		**Before PD, Every 4 wk**	**After PD but Before Next-Line Therapy, Every 4 wk**	**After Next-Line Therapy but Before PD on Next-Line Therapy, Every 12 wk**	**After PD on Next-Line Therapy, Every 12 wk**
Days	**-15 to -1**	**1**	**8**	**15**	**1**	**8**	**1**	**1**	**1**					
Window		**±2 days**								**+1 wk**	**±1 wk**			
Chemistry laboratory[f]	X	X			X		X	X	X	X				
Urinalysis	X													
EORTC QLQ-C30[g]	X	X			X		X	X	X	X	X	X	X (twice only)	
EORTC QLQ-MY20[g]	X	X						X (C4)	X (C7, 10, 13,16, 19, 22, 25)	X	X	X	X (twice only)	
EQ-5D[g]	X	X						X (C4)	X (C7, 10, 13,16, 19, 22, 25)	X	X (every 3 months)	X (every 3 months)	X	X
HU assessment (also for unscheduled visits)[g]		X			X		X	X	X	X	X	X	X (twice only)	
Skeletal survey[h]	X									X				
Imaging disease assessment[i]	X									X				
Investigator assessment of disease response/status					X		X	X	X	X	X		X	
β_2-microglobulin	X													
M-protein measurements (SPEP)	X[j]	X[j]			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**	**C6-C26**		**Before PD, Every 4 wk**	**After PD but Before Next-Line Therapy, Every 4 wk**	**After Next-Line Therapy but Before PD on Next-Line Therapy, Every 12 wk**	**After PD on Next-Line Therapy, Every 12 wk**
Days	**-15 to -1**	**1**	**8**	**15**	**1**	**8**	**1**	**1**	**1**					
Window		**±2 days**								**+1 wk**	**±1 wk**			
M-protein measurements (UPEP [24 hour Urine collection])	X[j]	X[j]			X		X	X	X	X	X	X		
Serum free light chain assay	X[j]	X[j]			X		X	X	X	X	X	X		
Immunofixation - serum and urine[k]	X[j]	X[j]			X		X	X	X	X	X	X		
Quantification of Ig[l]	X[j]	X[j]			X		X	X	X	X	X	X		
Bone marrow aspiration (BMA)														
Disease assessment BMA[m]	X													
MRD BMA—scheduled[n]	X								X (C13)	X				
MRD BMA—unscheduled		Additional MRD BMA specimen requested at the time of first CR (may be collected during the BMA procedure for CR confirmation)												
Archival tumor sample	X[o]													
PD BMA[p]										X	X			
Blood samples for biomarker analysis														
MRD Peripheral blood specimen[n]	X								X (C13)	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**	**C6-C26**		**Before PD, Every 4 wk**	**After PD but Before Next-Line Therapy, Every 4 wk**	**After Next-Line Therapy but Before PD on Next-Line Therapy, Every 12 wk**	**After PD on Next-Line Therapy, Every 12 wk**
Days	**-15 to -1**	**1**	**8**	**15**	**1**	**8**	**1**	**1**	**1**					
Window		**±2 days**								**+1 wk**	**±1 wk**			
MRD Peripheral blood specimen—unscheduled		Additional MRD peripheral blood specimen requested at the time of first CR (may be collected during the BMA procedure for CR confirmation)												
Plasma biomarker (proteasome level)	X													
Blood sample for germline DNA	X													
Adverse event reporting		Recorded from the first dose of drug in the study drug regimen through 30 days after last dose of drug in the study drug regimen[q]												
	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 drug in the study drug regimen													
Concomitant medications/ procedures		Recorded from the first dose of drug in the study drug regimen through 30 days after last dose of drug in the study drug regimen												
New primary malignancy assessment		Continuous from the start of study drug regimen administration until death or termination of the study by the sponsor												
Herpes zoster prophylaxis		Required, unless medically contraindicated, throughout treatment period												
Survival														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**	**C6-C26**		**Before PD, Every 4 wk**	**After PD but Before Next-Line Therapy, Every 4 wk**	**After Next-Line Therapy but Before PD on Next-Line Therapy, Every 12 wk**	**After PD on Next-Line Therapy, Every 12 wk**
Days	**-15 to -1**	**1**	**8**	**15**	**1**	**8**	**1**	**1**	**1**					
Window		**±2 days**								**+1 wk**	**±1 wk**			
Subsequent therapy/disease status													X	X
Study Drug Regimen Administration[r]														
Ixazomib/placebo		Single dose on Days 1, 8, and 15 of each cycle												
Determination of dose escalation								X^r (C5)						

Abbreviations: C=study cycle; CR=complete response; D=study day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End of Treatment (visit); FFPE=formalin-fixed, paraffin-embedded; HU=healthcare resource utilization; Ig=immunoglobulin; MRD=minimal residual disease; OS=overall survival; PD=progressive disease; PFS=progression-free survival; PFS2=time from the date of randomization to the date of objective disease progression on next-line treatment or death from any cause, whichever occurs first; VGPR=very good partial response; SPEP=serum protein electrophoresis; UPEP=urine protein electrophoresis.

Tests and procedures should be performed on schedule, but, unless otherwise specified, occasional changes are allowable within a 2-day window for holidays, vacations, and other administrative reasons or a longer window after discussion with the Takedaproject 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 Takeda project clinician or designee.

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

c Confirmation of patient eligibility by Takeda project clinician or designee is required before randomization.

d Includes evaluation for peripheral neuropathy.

e 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 serum pregnancy test may be collected up to 3 days before dosing. The results must be available and negative before the study drug regimen is administered.

Study Procedures	Screening	Treatment Period								EOT[a]	Follow-up[b]			
		28-Day Cycles[b]									PFS	PD	PFS2	OS
Cycle		C1			C2		C3	C4-C5	C6-C26		Before PD, Every 4 wk	After PD but Before Next-Line Therapy, Every 4 wk	After Next-Line Therapy but Before PD on Next-Line Therapy, Every 12 wk	After PD on Next-Line Therapy, Every 12 wk
Days	-15 to -1	1	8	15	1	8	1	1	1					
Window		±2 days								+1 wk	±1 wk			

f 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 still be sent to the central laboratory as well. Hematology and chemistry panels may be collected up to 3 days before Day 1 dosing and 24 hours before Days 8 and 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).

g Patient-reported outcomes and HU assessment (ie, 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, 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 questionnaire may be administered over the telephone.

h Skeletal survey will be performed at screening (within 8 weeks before randomization) and at EOT for all patients. Additional assessments can be done at the discretion of the investigator (ie, for suspected increased or new bone lesions). In certain circumstances and at the discretion of the investigator, a computed tomography (CT) scan, a positron emission tomography (PET)-CT scan, or whole body magnetic resonance imaging (MRI) may be done at screening in place of a skeletal survey, provided that the same modality for assessment is used throughout the study.

i Patients with documented extramedullary disease at diagnosis should have imaging disease assessment by CT, PET-CT, or MRI performed at screening and at EOT. Additional assessments can be done at the discretion of the investigator (ie, for suspected new lesions or progressive disease). The modality is at the discretion of the investigator, but should be kept consistent throughout.

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

k Immunofixation 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).

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

m To be evaluated at a local laboratory to assess disease status at screening. To be repeated if the patient is considered to possibly have CR (eg, resolution of serum and urine M-protein), or to investigate suspected PD if applicable.

n For all patients in CR or ~~very good partial response (~~VGPR~~)~~ at screening, an additional bone marrow aspirate aliquot and a peripheral blood specimen will be collected and sent to the central laboratory for MRD. For patients achieving suspected CR during study therapy, a portion of the bone marrow aspirate obtained to document the CR should be sent to the central laboratory for MRD. In addition, patients in VGPR or CR at Cycle 13 and at EOT (approximately 24 months [to the nearest complete cycle; if there are no treatment delays, this would be 26 cycles]) will have BMA and blood samples

Study Procedures	Screening	Treatment Period								EOT[a]	Follow-up[b]			
		28-Day Cycles[b]									PFS	PD	PFS2	OS
Cycle		C1			C2		C3	C4-C5	C6-C26		Before PD, Every 4 wk	After PD but Before Next-Line Therapy, Every 4 wk	After Next-Line Therapy but Before PD on Next-Line Therapy, Every 12 wk	After PD on Next-Line Therapy, Every 12 wk
Days	-15 to -1	1	8	15	1	8	1	1	1					
Window		±2 days								+1 wk	±1 wk			

collected for MRD at those 2 time points (unless already done within the most recent 2 cycles); BMA and blood samples will also be obtained in patients in CR or VGPR who stop therapy before Cycle 26. All bone marrow analyses for disease status are evaluated locally, with an aliquot of the bone marrow sent to the central laboratory for MRD analyses. Blood samples for MRD (processed accordingly to the laboratory manual) will be sent to the central laboratory for storage.

o Archival tumor material from the time of diagnosis and any available other prestudy time points (eg, postinduction response assessment) is to be used as a calibration sample for MRD assessment. The material should consist of (in order of preference) unstained slides; bone marrow aspirate as a FFPE-; or stained slides. Bone marrow biopsy samples will not be accepted.

p A BMA for patients who have PD is optional but highly recommended. This may be a second pull of the sampling already done at this time point to investigate suspected PD.

q When peripheral neuropathy occurs, each subsequent monthly evaluation will record the grade of peripheral neuropathy at that visit. (This is in contrast to other AEs where only increases in grade are recorded until the maximum grade is reached and then followed at that grade until complete resolution or return to baseline.) Peripheral neuropathy will be followed monthly until 1) resolution of peripheral neuropathy, 2) the start of a second-line alternative antineoplastic treatment, or 3) 6 months after progression has occurred, whichever occurs first.

r 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. If dose escalation was inadvertently missed at Cycle 5, escalation may be performed with permission from the Takeda project clinician or designee.

Ixazomib Pharmacokinetic Sampling Schedule

Cycle 1				Cycle 2		Cycles 3-10
Day 1		Day 8	Day 15	Day 1	Day 8	Day 1
1 hour postdose (±0.25 hr)	4 hours postdose (±0.75 hr)	Predose[a]	Predose[a]	Predose[b]	Predose[a]	Predose[b]
X	X	X	X	X	X	X

Note: 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 as per the protocol.

a If pharmacokinetics (PK) sample is taken on a dosing day (due to allowable ±2-day window of visits), PK sample must be taken within 4 hours before dose of study drug. If PK sample is taken on a nondosing day, ie, sample on Day 14 and dose on Day 15, PK sample can be taken at any time during the visit.

b Day 1 predose PK assessments should occur within 4 hours of dosing.

15.11 Amendment 04 Detailed Summary of Changes

The primary sections of the protocol affected by the changes in Amendment 04 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Updated the legal entity name, address, and telephone of the sponsor.

The primary change occurs on the cover page:

Initial wording:	Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited 40 Landsdome Street Cambridge, MA USA 02139 Telephone: +1 (617) 679-7000 Please note: Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium," "Sponsor," or "Takeda".
Amended or new wording:	~~Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited~~**Takeda Development Center Americas, Inc**. ~~40 Landsdome Street~~**95 Hayden Avenue** ~~Cambridge~~, **Lexington,** MA ~~USA 02139~~**02421 USA** Telephone: +1 (617) 679-7000 ~~Please note: Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium," "Sponsor," or "Takeda".~~

Rationale for Change:

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

The following sections also contain this change:

Section 1.1.1 Disease Under Treatment

Section 1.1.2 Ixazomib, Takeda's Next-Generation Proteasome Inhibitor

Section 1.4.1.2 Dose Rationale

Section 4.1 Overview of Study Design

Section 6.3 Dose-Modification Guidelines

Section 6.4.4 Study Drug Dose Modification for Nonhematologic Toxicities

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 7.4.25 Disease Response Assessment Section 7.4.27.2 PFS2 Follow-up and OS Follow-up Section 7.7 Completion of Treatment Section 8.1 Statistical Methods Section 8.1.2 Randomization and Stratification Section 9.1 Steering Committee Section 9.3 Independent Data Monitoring Committee Section 10.2 Procedures for Recording and Reporting AEs and SAEs Section 10.3 Monitoring of AEs and Period of Observation Section 10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events Section 11.2 Data Quality Assurance Section 11.3 eCRF Completion Section 11.4 Study Monitoring Section 11.8 Investigator Compliance Section 11.9 On-site Audits/Inspection Section 11.10 Investigator and Site Responsibility for Drug Accountability Section 11.11 Product Complaints and Medication Errors (Including Overdose) Section 11.12 Closure of the Study Section 11.13 Record Retention Section 12.0 USE OF INFORMATION Section 15.10 Previous, Full Schedule of Events and PK Sampling Schedule (Schedules Before Implementation of Amendment 4)
Change 2: Updated the email address for product complaints and medication errors.
The primary change occurs in Section 11.11 Product Complaints and Medication Errors (Including Overdose).

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, an 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: The email address for product complaints changed.	
Change 3: Created Streamlined Schedule of Events to show only the assessments needed now that all patients are in follow-up, essentially replacing the original Schedule of Events.	
Initial version:	See Section 15.10 Previous, Full Schedule of Events and PK Sampling Schedule (Schedules Before Implementation of Amendment 4)
Amended version:	See Streamlined Schedule of Events. Deleted central laboratory collection of samples. Removed investigator assessment of disease response/status through MBA rows for PFS Follow-up period but kept for PFS2. Removed footnotes c and d. Added missing abbreviations. Changed follow-up to 12 weeks from 4 weeks for PFS and PD. Removed empty rows. Changed to 1st 2 visits from twice only for PFS2 and OS.
Initial SOE footnotes	Patient-reported outcomes and HU assessment (ie, 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, EORTC QLQ-

	C30, EORTC QLQ-MY20 and HU assessments should be done ideally at the first 2 visits (or at least within the first 4 visits). Patient-reported outcome questionnaires are preferred to be completed by patients in the clinic, but if needed e.g.due to the 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; as the last resort, these PROs can be collected via telephone using EORTC telephone interview administration scripts. At time points when a clinic visit is not required, or if needed due to the COVID-19 pandemic, the EQ-5D questionnaire may be administered over the telephone. HU data may be obtained over the telephone and/or via patient medical records, as needed.
Amended SOE footnotes	Patient-reported outcomes and HU ~~assessment~~ **assessments** (ie, ~~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, EORTC QLQ-C30, EORTC ~~QLQ-MY20~~ **QLQ-MY20,** and HU assessments should be done ideally at the first 2 visits (or at least within the first 4 visits). Patient-reported outcome questionnaires are preferred to be completed by patients in the clinic, but if needed ~~e.g~~(**eg**, due to the 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; as ~~the~~**a** last resort, these ~~PROs~~**patient-reported outcomes** can be collected via telephone using EORTC telephone interview administration scripts. At time points when a clinic visit is not required, or if needed due to the COVID-19 pandemic, the EQ-5D questionnaire may be administered over the telephone. HU data may be obtained over the telephone and/or via patient medical records, as needed.
Rationale for Change: To reflect the current phase of study.	
Change 4: Clarified the timelines for new primary malignancy reporting in Section 10.3 of the protocol.	
The primary change occurs in Section 10.3.	
Initial wording:	In addition, new primary malignancies that occur during the follow-up periods must be reported, irrespective of causality to the study drug, from the first dose of study drug through death, termination of the study by the sponsor, or for a minimum of 3 years after the last dose of the investigational product, whichever occurs first.
Amended or new wording:	In addition, ~~new primary malignancies~~ **NPMs** that occur during the follow-up periods 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. ~~or for a minimum of 3 years after the last dose of the investigational product, whichever occurs first.~~
Rationale for Change: To reflect the current phase of study.	

Change 5: Clarified timeframes for performing HU and EORTC assessments.	
The primary change occurs in Sections 7.4.14 Quality of Life Assessment (European Organization for Research and Treatment of Cancer), 7.4.27.2 PFS2 Follow-up and OS Follow-up, and 15.10 Previous, Full Schedule of Events and PK Sampling Schedule (Schedules Before Implementation of Amendment 4).	
Initial wording in Section 7.4.14:	Patient-reported outcomes and HU assessment (ie, number of medical encounters) should be completed before any other study procedures are performed or study drug is administered. Patient-reported outcome questionnaires are preferred to be completed by patients in the clinic, but if needed due to the 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 questionnaire may be administered over the telephone. HU data may be obtained over the telephone and/or via patient medical records, as needed
Amended wording in 7.4.14:	Patient-reported outcomes and HU assessments (ie, ~~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, EORTC QLQ-C30, EORTC QLQ-MY20, and HU assessments should be done ideally at the first 2 visits (or at least within the first 4 visits).** Patient-reported outcome questionnaires are preferred to be completed by patients in the clinic, but if necessary **(eg,** due to the COVID-19 ~~pandemic restrictions~~ **pandemic),** the EORTC QLQ-C30 and EORTC QLQ-MY20 questionnaires may be completed at the patient's home using paper versions of the questionnaires**; as a last resort, these patient-reported outcomes can be collected via telephone using EORTC telephone interview administration scripts.** At time points when a clinic visit is not required, or if needed due to the COVID-19 pandemic, the EQ-5D questionnaire may be administered over the telephone. HU data may be obtained over the telephone and/or via patient medical records, as needed.
Initial wording in Section 7.4.27.2	In the PFS2 Follow-up period, the EORTC QLQ-C30 and MY20 questionnaires, the EQ-5D questionnaire, and the HU assessment should be administered twice, ideally once approximately 8 to 12 weeks after the start of next-line therapy and again 8 to 12 weeks later. 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. In the OS follow-up period, the EQ-5D questionnaire will be

	administered every 3 months.
Amended wording in 7.4.27.2	~~In~~ **During** the PFS2 Follow-up period **only**, ~~the EORTC QLO and~~ **EORTC QLQ-C30**, **EORTC QLQ-MY20** ~~questionnaire~~s, and ~~the~~ HU assessment**s** should be administered **ideally at the first 2** ~~PFS2~~**visits** (or at least within the first 4 ~~visits~~**visits). The EQ-5D questionnaire should be administered every PFS2 visit**. ~~Only, but the EQ-5D questionnaire assessment should be done every PFS2 visit.~~ **Patient-reported outcome questionnaires are preferred to be completed by patients in the clinic, but if needed** ~~(e.g.~~**(eg, due to the COVID-19 pandemic), the EORTC QLQ-C30 and EORTC QLQ-MY20 questionnaires may be completed at the patient's home using paper versions of the questionnaires; as** ~~the~~**a last resort, these patient-reported outcomes can be collected via telephone using EORTC telephone interview administration scripts. Time points when a clinic visit is not required, or if needed due to the COVID-19 pandemic, the EQ-5D questionnaire may be administered over the telephone. HU data may be obtained over the telephone and/or via patient medical records, as needed.** ~~Paper questionnaire completion (MY20/C30) can be done at home also in PFS and PD Follow-up.~~ 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. In the OS follow-up period, the EQ-5D questionnaire ~~will~~ **may** be administered every visit, which occurs every 12 weeks, **via telephone.**
Rationale for change: To clarify EORTC and HU assessments.	
Change 6: Recorded a change in wording related to days of missed work that might affect the statistical analysis.	
The primary change occurs in Section 8.1.7.3 Health Economics Analysis Using Health Care Resource Utilization and Health Utility.	
Initial wording:	EQ-5D scores will be summarized in descriptive statistics for treatment arms. HU data will be summarized in descriptive statistics of medical encounters (length of stay, inpatient, outpatient, and reason), number of missing days from work or other activities by patient and care-giver for treatment arms.
Amended or new wording:	EQ-5D scores will be summarized in descriptive statistics for treatment arms. HU data will be summarized in descriptive statistics of medical

	encounters (length of stay, inpatient, outpatient, and reason), ~~number of missing days from work~~ or other activities ~~by patient and care giver~~ for treatment arms.
Rationale for Change: To account for the deletion of "number of missing days from work" and "by patient and care giver," affecting the statistical analysis.	
Change 7: Clarified calculation of follow-up visits.	
The primary change occurs in Section 7.4.27 Follow-up Assessments for PFS, PD, PFS2, and OS.	
Initial wording:	At EOT, patients will enter a Follow-up period for PFS, PD, or PFS2. See the Schedule of Events for assessments during each period. See the Study Periods and Corresponding Endpoints 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. Calculation of Follow-up visits to be 12 weeks (+/-1 week) since the last completed Follow-up visit from visit, rather than every 4 weeks.
Amended or new wording:	At EOT, patients will enter a Follow-up period for PFS, PD, or PFS2. See the **Streamlined** Schedule of Events for assessments during each period. See the Study Periods and Corresponding Endpoints 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. Calculation of Follow-up visits to be 12 weeks (+/-1 week) since the last completed Follow-up visit from visit, rather than every 4 weeks. **PFS and PD Follow-up visit is scheduled to be 12 weeks (+/-1 week) since the last completed Follow-up visit.**
The following section also contains this change: 15.10 Previous, Full Schedule of Events and PK Sampling Schedule (Schedules Before Implementation of Amendment 4).	
Rationale for Change: Changed PFS and PD Follow-up visits to be 12 weeks (+/-1 week) since the last completed Follow-up visit, rather than every week.	
Change 8: Central laboratory is no longer collecting samples.	
The primary change occurs in Section 7.4.12 Clinical Laboratory Evaluations.	
Initial wording:	**7.4.12 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 central labs. Hematology and chemistry panels may be collected up to 3 days before Day 1 dosing and (when required) 24 hours before Days 8 and 15 dosing.
Amended or new wording:	Clinical laboratory evaluations will be performed by a central laboratory~~.~~ **until the primary endpoint of PFS is met.** For dosing decisions, local hematology and chemistry laboratory results may be used; however, samples must also be sent to central labs. Hematology and chemistry panels may be collected up to 3 days before Day 1 dosing and (when required) 24 hours before Days 8 and 15 dosing. **The collection of samples by a central laboratory was stopped after the primary endpoint was met.**
Rationale for Change: To clarify study procedures now that the primary endpoint has been met.	
Change 9: Remove investigator assessment of disease response/status.	
The primary change occurs in Section 7.4.25 Disease Response Assessment.	
Initial wording:	… this study. At that time, central efficacy and investigator assessments for protocol purposes will be stopped except for investigator assessment of PFS2. The Millennium project clinician or designee and investigator will review the assessment of PD before taking the patient off treatment. After PD, and during the PFS2 follow-up period; response assessments are made by the investigator (or treating physician) on the basis of local laboratory data.
Amended wording:	… **At** this ~~study.At that~~ time, **the primary endpoint has been met; therefore,** central efficacy ~~and investigator~~ assessments for protocol purposes ~~will be~~**have been** stopped ~~except for investigator assessment of PFS2. The Millennium project clinician or designee and investigator will review the assessment of PD before taking the patient off treatment. After PD, and during the PFS2 follow-up period,~~; **all investigator assessments** of response ~~assessments are made by the investigator (or treating physician) on the basis of~~**should be based on** local ~~laboratory~~ ~~**data**~~ **laboratories per local clinical practice.**
The following section also contains this change: Streamlined Schedule of Events	

Rationale for Change: Clarify study procedures now that the primary endpoint has been met.	
Change 10: Added information about alternative monitoring approaches in the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic.	
The primary change occurs in Section 11.4 Study Site Monitoring visits.	
Initial wording:	Monitoring and auditing procedures developed or approved by Millennium will be followed to comply with GCP guidelines. All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner that ensures that patient confidentiality is maintained.
Modified text:	Monitoring and auditing procedures developed or approved by ~~Millennium~~ **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 due to the COVID-19 pandemic, alternative monitoring approaches, such as 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 ~~H~~**h**ealth ~~A~~**a**uthority and permitted by the IRB/IEC.~~-~~**Remote monitoring and site staff interviews for consistency check of data can be used**.
Rationale for Change: Provides for alternative means of monitoring during the COVID-19 pandemic to account for unavoidable circumstances affecting study conduct.	

Change 11: Added language regarding alternative methods for administering study procedures/assessments when it is not possible for the patient to come to the study site due to the COVID-19 pandemic.	
The primary change occurs in Section 7.4 Study Procedures.	
Initial wording	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 2-day window for holidays, vacations, and other administrative reasons or a longer window after discussion with the Millennium Pharmaceuticals Inc. (Millennium) project clinician or designee. If the study schedule is shifted, assessments must be shifted to ensure collection of assessments is completed before dosing. Refer to the Schedule of Events for timing of assessments. Additional details are provided as necessary in the sections that follow.
Added new text:	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 2-day window for holidays, vacations, and other administrative reasons or a longer window after discussion with the ~~Millennium Pharmaceuticals Inc. (Millennium)~~ **Takeda** project clinician or designee. If the study schedule is shifted, assessments must be shifted to ensure collection of assessments is completed before dosing. Refer to the **original** Schedule of Events **(Section 15.10) and Streamlined Schedule of Events** for timing of assessments. Additional details are provided as necessary in the sections that follow. **In acknowledgement of hospital, local, state or national government restrictions, or other site-related factors caused by the coronavirus disease 2019 (COVID-19) pandemic that may prevent investigators from conducting the study according to the Streamlined Schedule of Events at the clinical study site, investigators may continue patients in the study despite departure from the Streamlined 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. For patients who are impacted by the COVID-19 pandemic, any procedures not conducted per the study protocol will be documented as a protocol deviation. **During contact with the patient, the study site physician or other qualified site staff should at minimum conduct AE collection. Other study assessments may be collected remotely as is feasible. Assessments/procedures that cannot be completed during the protocol-specified window because a site visit is done remotely (ie, symptom-directed physical examination, hematology, clinical chemistry) are waived.**
Rationale for Change: To account for the COVID-19 pandemic affecting study conduct.	
Change 12: Updated language regarding unblinding in patients experiencing disease progression.	
The primary change occurs in Section 6.10 Blinding and Unblinding.	
Initial wording	To maintain the blind, all study personnel including the investigators, site personnel, study clinicians, and the sponsor will be blinded to the treatment assignments for the duration of the study. When a patient is discontinued from the study, the investigator may request unblinding if it is necessary for determination of the patient's subsequent anticancer treatment. Treatment assignments will be obtained through the interactive voice/web response system (IXRS) according to the procedures outlined in the study manuals. Information regarding the treatment assignments will be kept securely at Millennium or its designee, per its standard operating procedures. Emergency unblinding, if necessary, will be conducted via the IXRS. Records of the patient number, the date each drug in the study drug regimen was dispensed, and the treatment assignment will be maintained by the study site. If the treatment assignment must be revealed for the safety of the patient, to treat an AE, or to inform decisions for subsequent therapy, the investigator will contact the Millennium project clinician or designee (contact information is in the study manuals). A decision to break the blind must be reached by the Millennium project clinician or designee and the investigator. The investigator, or designee, may break the blind through the IXRS independent of the Millennium project clinician or designee only if it is considered to be an emergency by the investigator that requires specific knowledge of the blinded study treatment to properly treat the AE/safety issue. If the treatment of the AE/safety issue is the same regardless of the study drug assignment, the blind should not

	be broken. In addition, the patient will be discontinued from further study drug administration in this study.
Amended or new wording:	To maintain the blind, all study personnel including the investigators, site personnel, study clinicians, and the sponsor will be blinded to the treatment assignments for the duration of the study. When a patient **experiences disease progression, the investigator is encouraged to unblind the patient and take this information into account in planning the next line of therapy**. ~~is discontinued from the study, the investigator may request unblinding if it is necessary for determination of the patient's subsequent anticancer treatment.~~ Treatment assignments will be obtained through the interactive voice/web response system (IXRS) according to the procedures outlined in the study manuals. Information regarding the treatment assignments will be kept securely at ~~Millennium~~ **Takeda** or its designee, per its standard operating procedures. Emergency unblinding, if necessary, will be conducted via the IXRS. ~~Records of the patient number, the date each drug in the study drug regimen was dispensed, and the treatment assignment will be maintained by the study site. If the treatment assignment must be revealed for the safety of the patient, to treat an AE, or to inform decisions for subsequent therapy, the investigator will contact the Millennium project clinician or designee (contact information is in the study manuals). A decision to break the blind must be reached by the Millennium project clinician or designee and the investigator. The investigator, or designee, may break the blind through the IXRS independent of the Millennium project clinician or designee only if it is considered to be an emergency by the investigator that requires specific knowledge of the blinded study treatment to properly treat the AE/safety issue. If the treatment of the AE/safety issue is the same regardless of the study drug assignment, the blind should not be broken. In addition, the patient will be discontinued from further study drug administration in this study.~~
Rationale for Change: Enables investigator to unblind a patient experiencing disease progression to plan next line of therapy.	
Change 13: Added death as a reason for a patient's withdrawal from the study.	
The primary change occurs in Section 7.10 Withdrawal of Patients From Study	
Initial wording:	**7.10 Withdrawal of Patients From Study** A patient may be withdrawn from the study for any of the following

	reasons: • Study terminated by sponsor • Withdrawal by patient • Lost to follow-up • Other
Added new text:	**7.10 Withdrawal of Patients From Study** A patient may be withdrawn from the study for any of the following reasons: • Study terminated by sponsor • Withdrawal by patient • **Death** • Lost to follow-up • Other
Rationale for Change: Adding additional reason for withdrawing from study.	
Change 14: Updated signatories for the study.	
The primary change occurs on the cover page.	
Description of Change:	Removed [redacted], MD, [redacted], Oncology Clinical Research (or designee) and [redacted], PhD, [redacted], Global Statistics as signatories; added [redacted], PhD, [redacted], [redacted], Global Statistics
Rationale for Change: To reflect current Takeda personnel responsible for approving the protocol.	
Change 15: Clarified how health care resource data are collected from patients.	
The primary change occurs in Section 7.4.13 Health Care Resource Utilization Data Collection.	
Initial wording:	**7.4.13 Healthcare Resource Utilization Data Collection** During the treatment and the 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.

Amended or new wording:	Health ~~e~~Care Resource Utilization Data Collection During the treatment and the follow-up periods indicated in the **original** Schedule of Events (Section 15.10) **and Streamlined Schedule of Events**, all medical care encounters since the previous collection will be collected from ~~all~~ **patient charts and/or** patients **directly as needed**, **regardless** of the reason for the **needed** medical care encounter. Examples of data to be collected are number and duration of medical care encounters, such as inpatient/outpatient admissions, ~~homecare,~~ **visit type and reasons**, and time of work loss.
Rationale for Change: To clarify how data are collected for health care resource utilization.	
Change 16: Clarified the monitoring of AEs	
The primary change occurs in Section 10.3 Monitoring of AEs and Period of Observation.	
Initial wording:	AEs, 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. 1. Serious pretreatment events will be reported to the Millennium Department of Pharmacovigilance or designee from the time of the signing of the ICF up to first dose of study drug, but will not be recorded in the eCRF. 2. Related and unrelated SAEs will be reported to the Millennium Department of Pharmacovigilance or designee from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Millennium Department of Pharmacovigilance or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). In addition, new primary malignancies that occur during the follow-up periods must be reported, irrespective of causality to the study drug, from the first dose of study drug through death, termination of the study by the sponsor, or for a minimum of 3 years after the last dose of the investigational product, whichever occurs first.

Amended or new wording:	AEs, 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. • Serious pretreatment events will be reported to the ~~Millenium~~ **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 ~~Millennium~~ **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 and recorded in the eCRF. After this period, only related SAEs must be reported to the ~~Millennium~~ **Takeda** Department of Pharmacovigilance or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). In addition, **NPMs**~~new primary malignancies~~ that occur during the follow-up periods 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**.** ~~or for a minimum of 3 years after the last dose of the investigational product, whichever occurs first.~~
Rationale for Change: Deleted the reporting of NPMs for a minimum of 3 years after last dose of investigational product, whichever occurs first.	

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Science Approval	25-Nov-2021 04:17 UTC
[redacted]	Biostatistics Approval	25-Nov-2021 05:25 UTC