Title: A Phase 2, Open-Label, Multicenter Study of Ixazomib Plus Lenalidomide and Dexamethasone in Adult Japanese Patients With Relapsed and/or Refractory Multiple Myeloma

NCT Number: NCT02917941

Protocol Approve Date: 25-NOV-2016

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If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

Note; This document was translated into English as the language on original version was Japanese.

PROTOCOL

A Phase 2, Open-Label, Multicenter Study of Ixazomib Plus Lenalidomide and Dexamethasone in Adult Japanese Patients With Relapsed and/or Refractory Multiple Myeloma

Sponsor:	Takeda Pharmaceutical Company Limited. 4-1-1 Doshomachi, Chuo-ku, Osaka 540-8645		
Study Number:	C16028		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Compound:	MLN9708, ixazomib citrate		
Date:	25 November 2016 (English version: 27 December 2016)	**Amendment Number:**	Amendment 01

Amendment History

Date	Amendment Number	Region
5 August 2016	Original	All sites
25 November 2016	Amendment 01	All sites

Note: This study will be continued as a post-marketing clinical study after a marketing approval of ixazomib was obtained in Japan. In the protocol, the term "study" will be replaced by "post-marketing clinical study" as appropriate, and the protocol is continuously used.

1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

See the protocol annex.

1.2 Principles of Clinical Studies

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

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

1.3 Protocol Amendment 01 Summary of Changes

The primary purpose of this amendment is to describe the procedures to be changed in order to continue this study as a post-marketing clinical study after a marketing approval of ixazomib was obtained in Japan, and to correct typographical errors and inconsistencies found in the protocol before this amendment. Further details of this amendment are provided in Appendix J.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Pharmaceutical Company Limited.	**Compound:** Investigational Drug Code: MLN9708 Generic Name: ixazomib citrate	
Title of Protocol: A Phase 2, Open-Label, Multicenter Study of Ixazomib Plus Lenalidomide and Dexamethasone in Adult Japanese Patients With Relapsed and/or Refractory Multiple Myeloma	**IND No.:** Not Applicable	**EudraCT No.:** Not Applicable
Study Number: C16028	**Phase:** 2	

Study Design:

This is a phase 2, open label, single arm, multicenter study to evaluate the efficacy and safety of ixazomib plus lenalidomide and dexamethasone (LenDex) in Japanese patients with relapsed and/or refractory multiple myeloma (MM). The patient population will consist of adult men and women who have a confirmed diagnosis of MM, who have received 1 to 3 prior lines of therapy, and who meet other outlined eligibility criteria.

Patients will receive study drug (ixazomib 4.0 mg) on Days 1, 8, and 15 plus lenalidomide (25 mg) on Days 1 through 21 and dexamethasone (40 mg) on Days 1, 8, 15, and 22 of a 28-day cycle. Patients may continue to receive treatment until progressive disease (PD) or unacceptable toxicity, whichever comes first. Dose modifications may be made based on toxicities. Patients with a low creatinine clearance < 60 mL/min will receive a reduced lenalidomide dose of 10 mg once daily on Days 1 through 21 of a 28-day cycle. The lenalidomide dose may be escalated to 15 mg once daily after 2 cycles if the patient is not responding to treatment and is tolerating the treatment. If renal function normalizes (ie, creatinine clearance ≥ 60 mL/min) and the patient continues to tolerate this treatment, lenalidomide may then be escalated to 25 mg once daily.

Patients will be seen at regular treatment cycle intervals while they are participating in the study: four times a treatment cycle for the first 2 cycles, twice a treatment cycle for the 3rd cycle, and then once a treatment cycle for the remainder of their participation in the active treatment and, if applicable, the PFS and OS follow-up phases of the study.

Response will be assessed by investigator according to the International Myeloma Working Group (IMWG) criteria for all patients every 4 weeks until PD. Central laboratory data will be used for serum M-protein, urine M-protein and serum free light chain. All patients will be followed for survival after progression. Patients will be contacted every 12 weeks until death or termination of the study by the sponsor.

The study will be closed at 24 months from the enrollment of the last patient.

Primary Objective:

- To determine very good partial response (VGPR) or better (VGPR + complete response [CR]) rate in response-evaluable analysis set*.
  *Defined as patients who received at least one dose of ixazomib and had measurable disease at baseline, and at least one post baseline response assessment.

Secondary Objectives:

- To determine progression-free survival (PFS)
- To determine overall response rate (ORR) (partial response [PR] or better)
- To determine duration of response (DOR)
- To determine time to progression (TTP)
- To determine safety
- To determine overall survival (OS)

Subject Population:

Japanese adult patients with a confirmed diagnosis of symptomatic MM and relapsed and/or refractory disease will be enrolled in this study.

Number of Subjects: approximately 30	**Number of Sites:** approximately 20
Dose Level(s): Patients will receive study drug (ixazomib 4.0 mg) on Days 1, 8, and 15 plus lenalidomide (25 mg) on Days 1 through 21 and dexamethasone (40 mg) on Days 1, 8, 15, and 22 of a 28-day cycle.	**Route of Administration:** oral
Duration of Treatment: Patients may continue to receive treatment until PD or unacceptable toxicity, whichever comes first (The maximum treatment period will be 24 months after the last patient is enrolled).	**Period of Evaluation:** The duration of the study, including enrollment, treatment, and follow-up, will be approximately 30 months.

Main Criteria for Inclusion:

Male or female Japanese patients 20 years of age or older, who have diagnosed MM and have received 1 to 3 prior therapies. Patients must have measurable disease defined by at least 1 of the following 3 measurements based on central laboratory data: 1) Serum M-protein: ≥ 1 g/dL (≥10 g/L). 2) Urine M-protein: ≥ 200 mg/24 hours. 3) Serum free light chain assay: involved free light chain level ≥ 10 mg/dL (≥100 mg/L) provided that the serum free light chain ratio is abnormal.

Main Criteria for Exclusion:

Patients who were refractory to lenalidomide or proteasome inhibitor-based therapy at any line, who experienced rash or pruritus requiring systemic medication within 14 days before enrollment, or who are diagnosed with Waldenstrom's macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, plasma cell leukemia, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome.

Main Criteria for Evaluation and Analyses:

The primary endpoint for this study is VGPR or better (CR + VGPR) rate in response-evaluable analysis set. Secondary endpoints for this study are PFS, ORR, DOR, TTP, safety (adverse events, laboratory tests and vital signs), and OS.

Statistical Considerations:

VGPR or better rate and the 2-sided 95% confidence interval (CI) in response-evaluable analysis set will be evaluated as primary analysis of the primary endpoint. Primary analysis is estimated to occur approximately 12 months from the enrollment of the last patient. Final analysis is estimated to occur approximately 24 months from the enrollment of the last patient.

Sample Size Justification:

The sample size of CCI will provide CCI % probability of the point estimate of VGPR or better rate over the threshold rate, assuming expected CR + VGPR rate of CCI % and threshold rate of CCI %. The target number of patients is estimated to be 30, assuming a drop-out rate of CCI %.

Note: This study will be continued as a post-marketing clinical study after a marketing approval of ixazomib was obtained in Japan. In the protocol, the term "study" will be replaced by "post-marketing clinical study" as appropriate, and the protocol is continuously used.

3.0 LIST OF ABBREVIATIONS

5-HT3	5-hydroxytryptamine 3 serotonin receptor
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CO_2	carbon dioxide
CR	complete response
CRO	contract research organization
CT	computed tomography
CYP	cytochrome P450
Del	deletion
DNA	deoxyribonucleic acid
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	End of Treatment (visit)
FAS	full analysis set
FCBP	female patients of childbearing potential
FDA	United States Food and Drug Administration
FLC	free light chain
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GVHD	graft-versus-host disease
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IMiD	immunomodulatory drugs
IMWG	International Myeloma Working Group
IRB	institutional review board
IUD	intrauterine device
IV	intravenous; intravenously
LenDex	lenalidomide and dexamethasone
LDH	lactate dehydrogenase

MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MM	multiple myeloma
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDMM	newly diagnosed multiple myeloma
ORR	overall response rate
OS	overall survival
PD	progressive disease (disease progression)
PET	positron emission tomography
PFS	progression-free survival
PMDA	Pharmaceuticals and Medical Devices Agency
PML	progressive multifocal leukoencephalopathy
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PTE	pretreatment event
RNA	ribonucleic acid
RRMM	relapsed and/or refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
sCR	stringent complete response
SD	stable disease
SPEP	serum protein electrophoresis
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
T_{max}	time to first occurrence of maximum (peak) concentration
TSH	thyroid stimulating hormone
TTP	time to progression
ULN	upper limit of the normal range
UPEP	urine protein electrophoresis
VGPR	very good partial response
WBC	white blood cell
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

Multiple myeloma (MM) is a malignant disease where monoclonal plasma cells proliferate mainly in the bone marrow. MM causes hematopoietic deterioration, increase of monoclonal immunoglobulin (M-protein) produced in myeloma cells, bone destruction, hypercalcemia, and results in renal failure, which is one of the major causes of death. It constitutes approximately 1% of all reported neoplasms and approximately 13% of hematologic cancers worldwide [1]. The

American Cancer Society estimates that there will be 26,850 new cases of MM, with approximately 11,240 deaths, in the United States in 2015 [2]. In Europe, the estimated annual incidence is 38,900 new cases of MM, with approximately 24,300 deaths in 2012 [3]. Although less common in Asian countries, MM is a growing health problem with an incidence that is approaching that of Western countries and a larger population base [4][5]. The National Cancer Center Japan estimates that there will be 8,600 new cases of MM, with approximately 4,200 deaths, in Japan in 2015 [6]. MM is generally regarded as incurable at present, although some data have suggested an increasing cure-fraction in front-line patients [7]. Responses to currently available therapies are transient, despite the marked improvement in treatment options, and most patients receive multiple lines of therapy, including combination regimens, over the course of their disease [8].

The treatment of MM has undergone important changes over the recent past due to advances in understanding the disease biology and improvements in treatment strategies. While historic treatment approaches focused on cytotoxic drugs, such as alkylating agents, anthracyclines, and corticosteroids, the introduction of the first-in-class proteasome inhibitor, bortezomib, and the immunomodulatory drugs (IMiDs), thalidomide and lenalidomide, have improved treatment outcomes [9][10][11][12]. These agents, alone and in combination with steroids or cytotoxic agents, are now among the recommended standard of care throughout the MM treatment pathway [13][14]. As of July 2016, bortezomib and lenalidomide are available for the treatment for the both newly diagnosed multiple myeloma (NDMM) and relapsed and/or refractory multiple myeloma (RRMM) in Japan. In addition, pomalidomide, panobinostat and carfilzomib are approved for RRMM.

Despite the increase in the number of therapeutic options, MM remains incurable and there is a need for new and better agents. Patients who were refractory to the initial therapy or relapse demonstrate variable response to subsequent treatments with decreasing likelihood and duration of response (DOR). Patients ultimately become refractory to approved therapies and have no alternative treatment options. In an effort to further target the proteasome with increased activity in MM and other cancers, ixazomib has been developed, a small molecule 20S proteasome inhibitor.

Ixazomib refers to the biologically active boronic acid form of the drug substance. The drug substance is administered as a stable citrate ester, ixazomib citrate, a prodrug of ixazomib. In physiological conditions, ixazomib citrate rapidly hydrolyzes to the biologically active boronic acid, ixazomib, that potently, reversibly, and selectively inhibits the proteasome. In contrast to

bortezomib, ixazomib demonstrates a faster dissociation rate from the proteasome that may result in enhanced tumor penetration, exhibits antitumor activity in a broader range of tumor xenografts, and has more prolonged tissue penetration. The clinical benefit of ixazomib has been studied in Millennium-sponsored clinical studies and ixazomib is being developed globally for the treatment options for RRMM, NDMM, and systemic AL amyloidosis. In November 2015, ixazomib in combination with lenalidomide and dexamethasone received FDA approval for the treatment of patients with multiple myeloma who have received at least 1 prior therapy; therefore, ixazomib is available commercially in the United States.

The pivotal study for ixazomib in patients with RRMM is an ongoing phase 3 global, randomized, double-blind, placebo-controlled study (Study C16010). The objective of the study is to evaluate efficacy and safety of ixazomib in combination with lenalidomide + dexamethasone (LenDex) in comparison with placebo in combination with LenDex in patients with multiple myeloma who had received at least one prior therapy. The results of the primary analysis of efficacy for the overall population showed that there was a statistically significant and clinically meaningful prolongation of progression-free survival (PFS) as assessed by the independent review committee, the primary endpoint, in the ixazomib + LenDex regimen compared to the placebo + LenDex regimen. The median PFS was 20.6 months in the ixazomib + LenDex regimen and 14.7 months in the placebo + LenDex regimen (hazard ratio = 0.742; p = 0.012) [15]. In addition, the ixazomib + LenDex regimen provided clinical benefit in terms of better disease control (demonstrated by significant improvements in complete response (CR) and overall response rates) and longer disease control (demonstrated by significant improvement in time to progression and by longer duration of response). Ixazomib in combination with LenDex is a well-tolerated regimen, and ixazomib does not add clinically significant toxicity to the LenDex background therapy.

4.2 Rationale for the Proposed Study

In Study C16010, the results of the primary analysis of efficacy for the overall population showed that there was a statistically significant and clinically meaningful prolongation of PFS in the ixazomib + LenDex regimen compared to the placebo + LenDex regimen. In the Japanese subpopulation, the consistency of the results of PFS between overall population and Japanese subpopulation was not denied. However, it was proposed that an additional evaluation be necessary for the efficacy of ixazomib in Japanese RRMM patients.

This study, therefore, was planned to evaluate the efficacy and safety of ixazomib when administered with LenDex in Japanese patients with RRMM. The primary objective of this study is to determine the very good partial response (VGPR) or better rate in response-evaluable analysis set.

The study treatments in this study are identical to the ones in Study C16010. Patients will receive ixazomib 4.0 mg on Days 1, 8, and 15 plus lenalidomide (25 mg) on Days 1 through 21 and dexamethasone (40 mg) on Days 1, 8, 15, and 22 of a 28-day cycle. The results of Study C16010 showed that this combination regimen was effective in prolonging PFS and improving response to treatment, resulting in long-term benefit in patients with RRMM. This combination regimen was also well tolerated, with clinically manageable TEAEs.

In Study TB-MC010034, a phase 1 study in Japan, it was shown that ixazomib at a dose of 4.0 mg as a single agent or in combination with LenDex was safe and tolerable in Japanese patients with RRMM.

Based on the above results, the favorable benefit-risk profile of ixazomib at 4.0 mg in combination with LenDex supports the appropriateness of the selection of the doses and schedules of the combination therapy in patients with RRMM in this study.

This study will be continued as a post-marketing clinical study after a marketing approval of ixazomib was obtained in Japan. In the study protocol, the term "study" will be replaced by "post-marketing clinical study" as appropriate. The details of changes in study procedures to be made after shifting to the post-marketing clinical study are found in Appendix 1.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To determine VGPR or better (VGPR + CR) rate in response-evaluable analysis set*
  *Defined as patients who received at least one dose of ixazomib and had measurable disease at baseline, and at least one post baseline response assessment.

5.1.2 Secondary Objectives

- To determine progression-free survival (PFS)
- To determine overall response rate (ORR) (partial response [PR] or better)
- To determine duration of response (DOR)
- To determine time to progression (TTP)
- To determine safety
- To determine overall survival (OS)

5.2 Endpoints

5.2.1 Primary Endpoint

- VGPR or better rate in response-evaluable analysis set

5.2.2 Secondary Endpoints

- PFS, defined as the time from the date of first study drug administration to the date of first documentation of PD or death from any cause, whichever occurs first
- ORR
- DOR, defined as the time from the date of first documentation of response to the date of first documentation of PD
- TTP, defined as the time from the date of first study drug administration to the date of first documentation of PD
- Safety including treatment-emergent adverse events (TEAEs), laboratory parameters, and vital signs
- OS, defined as the time from the date of first study drug administration to the date of death

6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a phase 2, open-label, single arm, multicenter study to evaluate the efficacy and safety of ixazomib plus lenalidomide and dexamethasone in Japanese patients with relapsed and/or refractory multiple myeloma (MM). The patient population will consist of adult men and women who have a confirmed diagnosis of MM, who have received 1 to 3 prior lines of therapy, and who meet other outlined eligibility criteria (see Section 7.0). Approximately 30 patients will be enrolled in the study.

General eligibility criteria may be assessed prior to the formal Screening period if it is part of standard clinical practice. However, per the Schedule of Events, formal screening will occur during the Screening period, which may last for up to 28 days prior to enrollment. A Takeda clinician will confirm patient eligibility prior to enrollment. Determination of disease progression as an entry criterion may be based on patient data obtained during or following the patient's most recent prior antineoplastic therapy.

Patients will receive study drug (ixazomib 4.0 mg) on Days 1, 8, and 15 plus lenalidomide (25 mg) on Days 1 through 21 and dexamethasone (40 mg) on Days 1, 8, 15, and 22 of a 28-day cycle. Patients may continue to receive treatment until progressive disease (PD) or unacceptable toxicity, whichever comes first. Dose modifications may be made based on toxicities. Patients with a low creatinine clearance < 60 mL/min will receive a reduced lenalidomide dose of 10 mg. The lenalidomide dose may be escalated to 15 mg after 2 cycles if the patient is not responding to treatment and is tolerating the treatment. If renal function normalizes (ie, creatinine clearance ≥ 60 mL/min) and the patient continues to tolerate this treatment, lenalidomide may then be escalated to 25 mg.

Patients will be seen at regular treatment cycle intervals while they are participating in the study: four times a treatment cycle for the first 2 cycles, twice a treatment cycle for the 3rd cycle, and then once a treatment cycle for the remainder of their participation in the active treatment and, if applicable, the PFS (every 4 weeks) and OS (every 12 weeks) follow-up phases of the study.

Response will be assessed by investigator according to the IMWG criteria for all patients every 4 weeks until PD. Central laboratory data will be used for serum M-protein, urine M-protein and serum free light chain. All patients will be followed for survival after progression. Patients will be contacted every 12 weeks until death or termination of the study by the sponsor.

Patients will attend an End of Treatment (EOT) visit approximately 30 days after receiving their last dose of study treatment (ixazomib, lenalidomide or dexamethasone) and will continue to be followed for other follow-up assessments specified in the Schedule of Events. Patients discontinuing study treatment prior to PD will continue to be assessed for PD during the PFS follow-up portion of the study.

Analysis is planned to be performed twice during the study. The primary analysis is planned to be performed using the data obtained at approximately 12 months from the enrollment of the last patient. The final analysis is planned to be performed after the final database lock using the data

obtained at approximately 24 months from the enrollment of the last patient. The timing of analysis may be changed or additional analysis may be added upon request of the regulatory authorities. See Section 13.0 for the details.

6.2 Number of Patients

Approximately 30 patients will be enrolled in this study from approximately 20 study sites.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients may remain on treatment until the occurrence of PD or unacceptable toxicity. The maximum treatment period will be 24 months after the last patient is enrolled. Patients who stop treatment for any reason other than PD will continue in PFS follow-up and be seen every 4 weeks until documented PD. After PD, all patients will continue to the OS follow-up phase and be contacted every 12 weeks until death or until the sponsor terminates the study.

Refer to Section 10.3 for adverse event monitoring period after the last dose of the study treatment.

6.3.2 End of Study

The final analysis is planned to be performed using the data obtained at approximately 24 months from the enrollment of the last patient. The study will be closed at 24 months from the enrollment of the last patient, and all the patients will be off study treatment. After that, the patients may be treated with the available drugs at investigator discretion outside of the study. The sponsor will not supply study drug beyond the time period.

6.3.3 Total Study Duration

The duration of the study will be approximately 30 months, including 6 months for the enrollment period, 24 months from the enrollment of the last patient for the treatment and follow-up period.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

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

1. Male or female Japanese patients 20 years of age or older.
2. Multiple myeloma diagnosed according to standard criteria either currently or at the time of initial diagnosis (See Appendix E for the standard criteria)

NOTE: The initial diagnosis must be symptomatic MM, although the relapsed disease does not need to be symptomatic.

3. Patients must have measurable disease defined by at least 1 of the following 3 measurements based on central laboratory data:

Serum M-protein: ≥1 g/dL (≥ 10 g/L).

Urine M-protein: ≥200 mg/24 hours.

Serum free light chain assay: involved free light chain level ≥10 mg/dL (≥ 100 mg/L), provided that the serum free light chain ratio is abnormal.

4. Patients with RRMM who have received 1 to 3 prior therapies.

NOTE: This patient population includes the following 3 categories of patients:

Patients who relapsed from their therapy(s) but were not refractory to any previous therapy.

Patients who were refractory to all lines of previous therapy(s) (ie, patients who have never responded to any therapies received).

Patients who were relapsed from at least 1 line of therapy AND additionally were refractory to at least 1 line of therapy. For the purposes of this study, refractory MM is defined as PD on therapy or PD within 60 days after the last dose of a given therapy.

A line of therapy is defined as 1 or more cycles of a planned treatment program. This may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered 1 line of therapy. [16] Autologous and allogenic transplants are permitted.

5. Patients must meet the following clinical laboratory criteria:

Absolute neutrophil count (ANC) ≥ 1,000/mm^3, hemoglobin ≥ 8 g/dL and platelet count ≥ 75,000/mm^3. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to screening.

Total bilirubin ≤ 1.5 x the upper limit of the normal range (ULN).

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 x ULN.

Calculated creatinine clearance ≥ 30 mL/min.

6. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.
7. Patients who received prior allogenic transplant must have no active graft-versus-host disease (GVHD).
8. Patients who meet the following conditions:

Female patients who:

Are postmenopausal for at least 24 months before the screening visit, OR

Are surgically sterile, OR

Females of childbearing potential must (see Section 8.5 for definition):

1) Have a negative pregnancy test with a sensitivity of at least 25 mIU/mL within 10 to 14 days and again within 24 hours prior to starting Cycle 1 of lenalidomide
2) Agree to practice true abstinence or to begin TWO reliable methods of birth control (1 highly effective method and 1 additional effective method AT THE SAME TIME) for at least 28 days before starting study treatment through 90 days after the last dose of study treatment.
3) Agree to ongoing pregnancy testing
4) Adhere to the guidelines of the RevMate program

Male patients, even if surgically sterilized (ie, status postvasectomy), must:

Agree to avoid sexual intercourse completely 90 days after the last dose of study treatment.

Agree to practice true abstinence or to practice effective barrier contraception during the entire study treatment period and 90 days after the last dose of study treatment if their partner is of childbearing potential, even if they have had a successful vasectomy, AND

Adhere to the guidelines of the RevMate program

9. Thromboembolism prophylaxis is required based on published standard or institutional standard of care.
10. 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.
11. Patient is willing and able to adhere to the study visit schedule and other protocol requirements.

7.2 Exclusion Criteria

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

1. Patients who were refractory to lenalidomide or proteasome inhibitor-based therapy at any line.

NOTE: Refractory disease is defined as PD on treatment or PD within 60 days after the last dose of a given therapy. Patients who progressed the disease after 60 days from the last dose of a given therapy will be considered relapsed and are eligible for inclusion in the study.

Patients who were refractory to thalidomide-based therapy are eligible.

2. Female patients who are breast feeding or pregnant.
3. Failure to have fully recovered (ie, ≤ Grade 1 toxicity) from the effects of prior chemotherapy (except for hair loss) regardless of the interval since last treatment.
4. Major surgery within 14 days before enrollment.
5. Radiotherapy within 14 days before enrollment.
6. Central nervous system involvement.
7. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before enrollment.
8. Rash or pruritus requiring systemic medication within 14 days before enrollment.
9. Diagnosis of Waldenstrom's macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, plasma cell leukemia, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome.
10. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months before enrollment.
11. Systemic treatment with strong CYP3A inducers (rifampicin, carbamazepine, phenytoin), or St. John's wort within 14 days before enrollment.
12. Ongoing or active systemic infection, known human immunodeficiency virus (HIV) positive, known hepatitis B surface antigen seropositive or known hepatitis C virus (HCV)-RNA positive.

NOTE: Patients who have positive hepatitis B core antibody (HBcAb) can be enrolled but must have hepatitis B virus (HBV)-DNA negative. Patients who have positive hepatitis C antibody can be enrolled but must have HCV-RNA negative.

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, peripheral neuropathy 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 gastrointestinal condition that could interfere with the oral absorption or tolerance of treatment.
17. Diagnosed or treated for another malignancy within 2 years before enrollment or previously diagnosed with another malignancy and have any 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.
18. Patients who have participated in the clinical trial of ixazomib, or have been treated with ixazomib.

8.0 STUDY DRUG

8.1 Study Treatment Administration

All protocol-specific criteria for administration of study treatment must be met and documented prior to drug administration. Study treatment will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients should be monitored for toxicity and doses of the appropriate treatment drug or study treatment 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 Schedule of Events. Eligible patients may take study treatment at home as directed.

8.1.1 Ixazomib: Study Drug

Study drug will be supplied as single capsules at 3 different dose strengths, containing 4.0, 3.0, and 2.3 mg of ixazomib. Ixazomib capsules will be provided by the sponsor.

Ixazomib will be given as a single, oral dose of 4.0 mg weekly (Days 1, 8, and 15) for 3 weeks on, followed by 1 week off in a 28-day cycle. Ixazomib should be taken on an empty stomach, at least 1 hour before or no sooner than 2 hours after food. A total of approximately 240 mL of water should be taken with the capsules. Patients should be instructed to swallow ixazomib capsules whole with water and not to break, chew, or open the capsules.

Missed doses can be taken as soon as the patient remembers as long as the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

Patients who take more than the prescribed dose of ixazomib should be instructed to seek emergency medical care if needed and contact study staff immediately.

8.1.2 Lenalidomide: Concomitant Study Therapy

Lenalidomide will be given as a single, daily oral dose of 25 mg for 21 days (Days 1 through 21) in a 28-day cycle. Patients with a low creatinine clearance < 60 mL/min will receive a reduced lenalidomide dose of 10 mg once daily. The lenalidomide dose may be escalated to 15 mg once daily after 2 cycles if the patient is not responding to treatment and is tolerating the treatment. If renal function normalizes (ie, creatinine clearance ≥ 60 mL/min) and the patient continues to tolerate this treatment, lenalidomide may then be escalated to 25 mg once daily.

Administration of lenalidomide will be at approximately the same time each day. Patients should be instructed to swallow lenalidomide capsules whole with or without food and not to break, chew, or open the capsules.

If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

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.

Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

8.1.3 Dexamethasone: Concomitant Study Therapy

Dexamethasone will be given as an oral dose of 40 mg/day weekly on Days 1, 8, 15, and 22 in a 28-day cycle.

Dexamethasone should be taken at approximately the same time preferably with food/milk to avoid stomach irritation. If a dose of dexamethasone was missed, the dose should be taken as soon as the patient remembers it. If enough time has elapsed that it is almost time for the next dose (within 6 hours), the missed dose should be skipped and the next dose is to be taken according to the regular dosing schedule. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

Patients who take more than the prescribed dose of dexamethasone should be instructed to seek emergency medical care if needed and contact study staff immediately.

8.2 Dose Modification Guidelines

Toxicities are to be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 (effective on 14 June 2010) [17]. Each adverse event should be attributed to a specific drug, if possible, so that the dose modifications can be made accordingly. Only 1 dose adjustment per cycle will be performed for a given agent when toxicity is suspected to be related primarily to that agent. Reduction of 1 agent and not the other is appropriate if the toxicity is suspected to be related primarily to 1 of the agents, however, dose reduction of multiple agents may be considered after consultation with Takeda clinician. Guidelines for dose modification within cycles are provided in Sections 8.2.1 through 8.2.5. Prior to beginning the next cycle of treatment, refer to the guidelines in Section 8.2.6. Further clarification can be obtained in consultation with Takeda clinician. If multiple toxicities are noted, the dose adjustments and/or delays should be made according to the most severe toxicity guidelines.

Alternative dose modifications may be recommended in order to maximize exposure of study treatment while protecting patient safety. It is also recommended that the investigator consult with the Takeda clinician before the dose modifications, if possible.

Dose reduction steps for ixazomib, lenalidomide, and dexamethasone are described in Table 8.a, Table 8.b, and Table 8.c, respectively.

Table 8.a Dose Reduction Steps for Ixazomib

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
4.0 mg	3.0 mg	2.3 mg	Discontinue

Table 8.b Dose Reduction Steps for Lenalidomide

Starting Dose[a]	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
25 mg	15 mg	10 mg	5 mg

a Patients with renal dysfunction (creatinine clearance < 60 mL/min) will receive lenalidomide from the starting dose of 10 mg, first dose reduction of 5 mg, and discontinued at the second dose reduction.

Table 8.c Dose Reduction Steps for Dexamethasone

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
40 mg	20 mg	8 mg	Discontinue

8.2.1 Dose Adjustments for Rash: Ixazomib and Lenalidomide

Ixazomib or lenalidomide dose adjustments for rash will be presented as follows:

- Occurrence of Grade 2 rash
  Supportive care and prophylaxis are recommended (see Section 8.6.5).
  - ➢ Occurrence or recurrence of Grade 2 rash manageable by supportive care
    - ✧ Continues ixazomib and lenalidomide at the same dose with supportive care including prophylaxis.
    - ✧ If becomes not manageable, see below.
  - ➢ Occurrence of Grade 2 rash which is not manageable by supportive care
    - ✧ Withhold ixazomib and lenalidomide until rash recovers to ≤ Grade 1. Following recovery within the same cycle (including potential delay for next cycle), resume ixazomib and lenalidomide at the same dose. In recurrence, reduce the drug according to Table 8.d
- Occurrence or recurrence of Grade 3 rash
  - ➢ Supportive care and prophylaxis are recommended. Reduce the drug according to Table 8.d.

In this study, "events manageable by supportive care" means the ones for which symptomatic treatment allows for continued study treatment without dose interruptions or reductions, while "events not manageable by supportive care" means the ones that cannot be managed only by supportive care, and require dose interruptions or reductions.

In severe situations, alternative dose modification may be made as needed. Angioedema and Grade 4 rash have been reported after the use of lenalidomide, and in such case, lenalidomide should be discontinued [18]. Refer to Table 8.h for dose modification of lenalidomide if angioedema, Stevens-Johnson syndrome, or toxic epidermal necrolysis (TEN) is observed.

Table 8.d Dose Reduction Steps for Ixazomib and Lenalidomide for Rash

Reduction	Action on Ixazomib and Lenalidomide	Example of Dose Reduction	
		Dose of Ixazomib	Dose of Lenalidomide[a]
1st reduction	Withhold ixazomib and lenalidomide until rash recovers to ≤ Grade 1. When recovery within the same cycle, resume **ixazomib** at the next **lower** dose and lenalidomide at the same dose.	3.0 mg	25 mg (10 mg)
2nd reduction	Withhold ixazomib and lenalidomide until rash recovers to ≤ Grade 1. When recovery within the same cycle, resume ixazomib at the same dose and **lenalidomide** at the next **lower** dose.	3.0 mg	15 mg (5 mg)
3rd reduction	Withhold ixazomib and lenalidomide until rash recovers to ≤ Grade 1. When recovery within the same cycle, resume **ixazomib** at the next **lower** dose and lenalidomide at the same dose.	2.3 mg	15 mg (5 mg)
4th reduction	Withhold ixazomib and lenalidomide until rash recovers to ≤ Grade 1. When recovery within the same cycle, resume ixazomib at the same dose and **lenalidomide** at the next **lower** dose.	2.3 mg	10 mg (discontinue)

a Dose of lenalidomide in a parenthesis is for patients with renal dysfunction (creatinine clearance < 60 mL/min)

8.2.2 Dose Adjustments for Hematologic Toxicity: Ixazomib and Lenalidomide

A decision regarding which study treatment requires dose reduction will be dependent upon the toxicity, its onset, and time course. Ixazomib or lenalidomide will be adjusted according to each criterion on the occurrence of: thrombocytopenia (refer to Table 8.e), or neutropenia (refer to Table 8.f). When dose reduction is required, the reduction steps for ixazomib and lenalidomide are described in Table 8.a and Table 8.b, respectively.

Table 8.e Ixazomib and Lenalidomide Dose Adjustment for Thrombocytopenia

Platelet Count	Action on Ixazomib	Action on Lenalidomide	Action
First fall to < 30,000/mm^3	Interrupt treatment	Interrupt treatment	Follow complete blood count (CBC) weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume and **maintain** dose level	Resume at next **lower** dose level	Eg, if lenalidomide dose was 25 mg, reduce to 15 mg
Second fall to < 30,000/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume at next **lower** dose level	Resume and **maintain** dose level	Eg, if ixazomib dose was 4 mg, reduce to 3 mg
Third fall to < 30,000/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume and **maintain** dose level	Resume at next **lower** dose level	Eg, if lenalidomide dose was 15 mg, reduce to 10 mg
Fourth fall to < 30,000/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume at next **lower** dose level	Resume and **maintain** dose level	Eg, if ixazomib dose was 3 mg, reduce to 2.3 mg Do not reduce below 2.3 mg
Fifth fall to < 30,000/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume and **maintain** dose level	Resume at next **lower** dose level	Eg, if lenalidomide dose was 10 mg, reduce to 5 mg Do not reduce below 5 mg

Table 8.f Ixazomib and Lenalidomide Dose Adjustment for Neutropenia

Absolute Neutrophil Count	Action on Ixazomib	Action on Lenalidomide	Action
First fall to < 500/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly; see Section 8.4 for myeloid growth factor recommendations
Return to ≥ 500/mm^3 within the same cycle	Resume and **maintain** dose level	Resume at next **lower** dose level	Eg, if lenalidomide dose was 25 mg, reduce to 15 mg
Second fall to < 500/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly; see Section 8.4 for myeloid growth factor recommendations
Return to ≥ 500/mm^3 within the same cycle	Resume at next **lower** dose level	Resume and **maintain** dose level	Eg, if ixazomib dose was 4 mg, reduce to 3 mg
Third fall to < 500/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly; see Section 8.4 for myeloid growth factor recommendations
Return to ≥ 500/mm^3 within the same cycle	Resume and **maintain** dose level	Resume at next **lower** dose level	Eg, if lenalidomide dose was 15 mg, reduce to 10 mg
Fourth fall to < 500/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly; see Section 8.4 for myeloid growth factor recommendations
Return to ≥ 500/mm^3 within the same cycle	Resume at next **lower** dose level	Resume and **maintain** dose level	Eg, if ixazomib dose was 3 mg, reduce to 2.3 mg Do not reduce below 2.3 mg
Fifth fall to < 500/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly; see Section 8.4 for myeloid growth factor recommendations
Return to ≥ 500/mm^3 within the same cycle	Resume and **maintain** dose level	Resume at next **lower** dose level	Eg, if lenalidomide dose was 10 mg, reduce to 5 mg Do not reduce below 5 mg

8.2.3 Ixazomib Treatment Modification

Dose modification of ixazomib is allowed based on clinical and laboratory findings. Treatment modifications due to ixazomib-related AEs are outlined in Table 8.g. Sequential dose reductions of ixazomib from the starting dose of 4.0 mg once daily are recommended depending on toxicity as indicated in Table 8.a.

Table 8.g Ixazomib Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events

Adverse Event (Severity)	Action on Ixazomib	Further Considerations
Grade 1 peripheral neuropathy	No action	Grade 1 signs & symptoms: asymptomatic, without pain or loss of function, clinical or diagnostic observations only
Grade 1 peripheral neuropathy with pain or Grade 2	Hold ixazomib until resolution to Grade ≤ 1 or baseline After resolution, resume ixazomib and maintain dose level	Grade 2 signs & symptoms: moderate symptoms, limiting instrumental activities of daily living (ADL)
Grade 2 peripheral neuropathy with pain or Grade 3	Hold ixazomib until resolution to Grade ≤ 1 or baseline Reduce ixazomib to next lower dose upon recovery	Grade 3 signs & symptoms: severe symptoms, limiting self care ADL, assistive device indicated
Grade 4 peripheral neuropathy	Discontinue ixazomib	
Grade 3 nonhematologic toxicity judged to be related to ixazomib If does not recover to ≤ Grade 1 or baseline within 4 weeks (including recurrence)	Hold ixazomib until resolution to Grade ≤ 1 or baseline Reduce ixazomib to next lower dose upon return to ≤ Grade 1 or baseline	Symptomatic recommendations noted in Section 8.6 Monitor closely (especially at the time of recurrence), take appropriate medical precautions, and provide appropriate symptomatic care
Grade 4 nonhematologic toxicities judged to be related to ixazomib	Consider permanently discontinuing ixazomib	Exception, in a case where the investigator determines the patient is obtaining a clinical benefit and has discussed this with the Takeda clinician

8.2.4 Lenalidomide Treatment Modification

Dose modification of lenalidomide is allowed based on clinical and laboratory findings. Treatment modifications due to lenalidomide-related AEs are outlined in Table 8.h. Sequential dose reductions of lenalidomide from the starting dose of 25 mg daily (10 mg daily for patients with renal dysfunction) are recommended depending on toxicity as indicated in Table 8.b.

Table 8.h Lenalidomide Treatment Modification (Delays, Reductions, and Discontinuations) Due to Non-Hematologic Adverse Events

Adverse Event (Severity)	Action on Lenalidomide [18]	Further Considerations
Grade 3/4 toxicities judged to be related to lenalidomide	Hold lenalidomide treatment, and restart at the next lower dose level when toxicity has resolved to ≤ Grade 2	Do not reduce below 5 mg daily
Renal dysfunction	Dose reduce per lenalidomide package insert for impaired renal function	Care should be taken in dose selection/modification in the elderly as they are more likely to have decreased renal function. Monitor renal function regularly
≥ Grade 2 thrombosis/embolism	Hold lenalidomide and start anticoagulation therapy; restart at investigator's discretion after adequate anticoagulation; maintain dose level	See Section 8.6.2 for anticoagulation recommendations
Angioedema, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis (TEN)	Permanently discontinue lenalidomide per package insert	
Grade 4 exfoliative or bullous rash	Permanently discontinue lenalidomide per package insert	
Tumor lysis syndrome	Dose modify as per lenalidomide package insert	Monitor closely and take appropriate medical precautions

8.2.5 Dexamethasone Treatment Modification

Dose modification of dexamethasone is allowed based on clinical and laboratory findings. Treatment modifications due to dexamethasone-related AEs are outlined in Table 8.i. Sequential dose reductions of dexamethasone from the starting dose of 40 mg once daily are recommended depending on toxicity as indicated in Table 8.c.

Table 8.i Dexamethasone Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events

Adverse Event (Severity)		Action on Dexamethasone [19]
Gastrointestinal disorder	Dyspepsia, gastric, or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)	Treat with histamine-2 blockers, sucralfate, or omeprazole. If symptoms persist despite these measures, decrease dexamethasone by 1 dose level.
	Dyspepsia, gastric, or duodenal ulcer, gastritis ≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart and decrease 1 dose level of current dose along with concurrent therapy with histamine-2 blockers, sucralfate, or omeprazole. If symptoms persist despite these measures, discontinue dexamethasone and do not resume.
	Acute pancreatitis	Discontinue dexamethasone and do not resume.
Cardiovascular disorder	Edema ≥ Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed and decrease dexamethasone by 1 dose level. If edema persists despite these measures, decrease dose another level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Neurological disorder	Confusion or mood alteration ≥ Grade 3	Hold dexamethasone until symptoms resolve. After the symptoms resolved, restart with 1 dose level reduction. If symptoms persist despite these measures, discontinue dexamethasone and do not resume.
Musculoskeletal disorder	Muscle weakness ≥ Grade 3 (interfering with function ± interfering with activities of daily living)	Decrease dexamethasone dose by 1 dose level. If weakness persists despite these measures, decrease dose by 1 dose level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Metabolic disorder	Hyperglycemia ≥ Grade 3	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite these measures, decrease dexamethasone dose by 1 dose level until levels are satisfactory.

8.2.6 Criteria for Toxicity Recovery Before Beginning the Next Cycle of Treatment

The criteria for toxicity recovery before the patient can begin the next cycle of treatment are as follows:

- ANC ≥ 1,000/mm^3
- platelet count ≥ 75,000/mm^3

- other clinically significant nonhematologic toxicities ≤ Grade 1 or to the patient's baseline condition.

If a patient fails to meet the criteria above for beginning the next cycle of treatment, initiation of the next cycle should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria for retreatment have been met.

If the beginning the next cycle of treatment are delayed more than 2 weeks, resume the study treatment at the next lower dose level (decide which agent will be reduced based on attribution or previous reductions). In the case of the occurrence of rash, see Section 8.2.1 for dose adjustment of ixazomib and lenalidomide. The maximum delay before treatment should be discontinued (except in the case of investigator determined clinical benefit and discussion with the Takeda clinician) will be 3 weeks.

If the patient does not recover completely from the treatment-related toxicity, see Sections 8.2.1 to 8.2.5 for recommended dose reduction.

8.3 Excluded Concomitant Medications and Procedures

The following medications are prohibited during the study:

- Systemic treatment with any of the following drug metabolizing enzyme inducers is not permitted in this study. (Rationale: If there were to be a drug-drug interaction with an inducer, the ixazomib exposure may be decreased.)

Strong CYP3A inducers: rifampin, carbamazepine, phenytoin

- Excluded food products include St. John's wort.

The following procedures are prohibited during the study:

- Any antineoplastic treatment with activity against MM, other than study treatment.
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates PD). Palliative radiotherapy for pain control in a preexisting lesion may be considered after discussion with the Takeda clinician.
- Platelet transfusion to help patients meet eligibility criteria is not allowed within 3 days prior to study drug dosing.

8.4 Permitted Concomitant Medications and Procedures

All necessary supportive care decided by investigator or identified subinvestigator(s) will be available to patients. All blood products, concomitant medications and therapies administered from first dose of study treatment through 30 days after last dose of study treatment or initiation of the subsequent antineoplastic therapies whichever comes first will be recorded in the CRFs.

The following medications and procedures are permitted during the study:

- Myeloid growth factors (eg, granulocyte colony stimulating factor [G-CSF]) are permitted. Their use should follow published guidelines and/or institutional practice; however, alternative usage may be reviewed with the Takeda clinician or study clinician designee.
- Erythropoietin will be allowed in this study, but has an increased risk of deep vein thrombosis when administered with lenalidomide, and has not been approved for the treatment of anemia as a malignant disease in Japan. Therefore, the use of erythropoietin should be minimized as much as possible.
- Patients could be transfused with red blood cells and platelets as clinically indicated.
- When digoxin was co-administered with lenalidomide, the digoxin plasma level was increased [20]. Periodic monitoring of digoxin plasma levels in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication is recommended during administration of lenalidomide.
- Concomitant treatment with bisphosphonates will be permitted.
- Supportive measures consistent with optimal patient care may be given throughout the study.

8.5 Precautions and Restrictions

Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided 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. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Female patients of childbearing potential (FCBP) and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below. FCBP is a female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following chemotherapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has not had menses at any time during the preceding 24 consecutive months).

Any female patients of childbearing potential must either:

- Agree to practice true abstinence for at least 28 days before starting study treatment through 90 days after the last dose of study treatment, OR
- Agree to practice 2 reliable methods of contraception, for at least 28 days before starting study treatment through 90 days after the last dose of study treatment
- The 2 methods of reliable contraception must include 1 highly effective method and 1 additional effective (barrier) method. The following are examples of highly effective and additional effective methods of contraception:

  Highly effective methods:

Intrauterine device (IUD)

Hormonal (birth control pills, injections, implants)

Tubal ligation

Partner's vasectomy

Additional effective methods:

Condom

Diaphragm

Cervical Cap

- Must also adhere to RevMate program

Male patients, even if surgically sterilized (ie, status postvasectomy), must:

- Agree to practice true abstinence during the entire study treatment period and through 90 days after the last dose of study treatment, OR
- Agree to use effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study treatment if their partner is of childbearing potential, even if they have had a successful vasectomy, AND
- Must also adhere to RevMate program

8.6 Management of Clinical Events

8.6.1 Prophylaxis Against Risk of Reactivation of Herpes Infection

Patients may be at an increased risk of opportunistic infection including reactivation of herpes zoster and herpes simplex viruses. Antiviral therapy such as acyclovir or valacyclovir should be considered.

8.6.2 Thromboembolism Prophylaxis

While on lenalidomide, patients should be on routine thromboprophylaxis [21]. Prophylactic therapy per published standard or institutional standard of care is required for all patients to prevent thromboembolic complications that may occur with lenalidomide-based regimens in combination with dexamethasone.

8.6.3 Nausea and/or Vomiting

Standard anti-emetics including 5-hydroxytryptamine 3 serotonin receptor (5-HT3) 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 treatment and during treatment.

8.6.4 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.

8.6.5 Erythematous Rash With or Without Pruritus

Rash has been reported with both lenalidomide and ixazomib. The lenalidomide-induced rash is characterized as generalized, maculopapular, morbilliform, urticarial, papular, often with pruritus. Serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme have been reported [18][22][23]. Lenalidomide interruption or discontinuation should be considered as described in the package insert and Section 8.2.

Rash with ixazomib 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, in the clinical studies of ixazomib (single dose or combination with other cancer therapies), 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. 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, intravenous (IV), or oral steroid (eg, prednisone ≤ 10 mg per day or equivalent) is permitted. Management of a Grade 3 rash may require IV antihistamines or corticosteroids. Administration of ixazomib (and/or other causative agent if given in combination) should be modified per protocol and reinitiated at a reduced level from where rash was noted (also per protocol).

In line with clinical practice, dermatology consult and biopsy of Grade 3 or higher rash or any SAE involving rash is recommended at the discretion of the investigator. 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. Additional information regarding these reactions can be found in the IB.

8.6.6 Thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib or lenalidomide administration should be modified as per dose modification recommendations in the protocol when thrombocytopenia occurs (see Table 8.e). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura, a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. Thrombotic thrombocytopenic purpura should be managed symptomatically according to standard medical practice.

8.6.7 Neutropenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable. Growth factor support is not required but may be considered according to standard clinical practice. Ixazomib or lenalidomide administration should be modified as noted as per dose modification recommendations in the protocol when neutropenia occurs (see Table 8.f). Therapy can be reinitiated at a reduced level upon recovery of absolute neutrophil counts.

8.6.8 Fluid Deficit

Dehydration should be avoided since lenalidomide is substantially excreted by kidney, and ixazomib may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported in patients treated with ixazomib, commonly in the setting of the previously noted gastrointestinal toxicities and dehydration. Fluid replacement should be performed before initiation of study treatment as needed during treatment to avoid dehydration.

8.6.9 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 replacement should be performed 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.

8.6.10 Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome (PRES), which ultimately resolved, has been reported with ixazomib. 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.

8.6.11 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 transverse myelitis cannot be excluded. Transverse myelitis should be managed according to standard medical practice.

8.6.12 Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML), which may be fatal, has occurred in less than 1% of oncology patients receiving ixazomib in combination with other cancer therapies. It is not known whether ixazomib causes PML; however, the possibility that ixazomib may have contributed to PML cannot be excluded. In the event of occurrence of PML, ixazomib should be discontinued and supportive care provided as needed.

8.6.13 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study patient, at a dose above that which is assigned to that individual patient according to the study protocol. If overdose occurs, consider close observation for hemodynamics and supportive care under hospitalization in study site. Gastric lavage and administration of charcoal may be considered, but it should be kept in mind that ixazomib absorption is rapid, with an overall median Tmax of 1 hour. Ixazomib is not readily dialyzable. Latest information can be found in the IB.

8.7 Blinding and Unblinding

This is an open-label study.

8.8 Description of Investigational Agents

The ixazomib drug products are provided in the 3 different dose strengths as shown in Table 8.j, and are differentiated by both capsule size and color.

Table 8.j Ixazomib Capsules

Dose Strength	Capsule Size	Capsule Color
4.0 mg	Size 3	Ivory
3.0 mg	Size 4	Light grey
2.3 mg	Size 4	Flesh

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

8.9 Packaging and Labeling

The ixazomib capsules will be provided by Takeda. The study drug labels will fulfill all requirements specified by governing regulations. The formulation consists of 4.0-, 3.0-, and 2.3-mg capsules for oral administration.

The capsules are individually packaged using cold form foil-foil blisters that are in a child resistant carton. There are 3 capsules in each wallet/carton.

8.10 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 in a refrigerator at 2°C to 8°C (36°F to 46°F). 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 sponsor. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

Study drug dispensed to the patient should remain in the blister packaging and carton and refrigerated as noted above until the point of use. Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients should be given only 1 cycle of study drug at a time, unless agreed upon by Takeda clinician. Patients should be instructed to store the medication refrigerated (36°F to 46°F, 2°C to 8°C) for the duration of each cycle. Patients should be instructed to return their empty cartons to the investigative site, rather than discarding them. Reconciliation will occur accordingly when the patient returns for their next cycle of study drug. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

Because ixazomib is an anticancer agent, 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. Ixazomib 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 contract. 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 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.

Refer to the Pharmacy Manual for additional instructions.

8.10.1 Concomitant Study Therapy

8.10.1.1 Lenalidomide

Lenalidomide will be supplied by the study site through the RevMate program.

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

8.10.1.2 Dexamethasone

Dexamethasone will be supplied by the study site.

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

8.11 Other Protocol-Specified Materials

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

9.0 STUDY CONDUCT

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

9.1 Study Personnel and Organizations

The contact information for the Takeda clinician, the central laboratory, any additional clinical laboratories or vendors participating on the study as well as the list of investigators can be found in the protocol annex.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice, or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB).

9.3 Study Enrollments

After written informed consent has been obtained, the patient will be assigned an subject identification code.

Patient eligibility will be confirmed by a Takeda clinician before enrollment by the investigator into the study. Re-enrollment of the same patient will not be permitted. If a patient discontinues from the study, that subject identification code will not be reused.

The date of enrollment is defined as the date when the Registration Center faxes the "registration confirmation sheet" to the investigator.

9.3.1 Enrollment Procedures

After the completion of subject screening for each subject, the investigator enrolls the subject according to the following procedures:

The investigator ensures that a subject meets all the eligibility criteria and faxes a "subject registration sheet" to the Registration Center after confirming the necessary information is completed. The contact information on the Registration Center can be found in the protocol annex. The "subject registration sheet" may be the source data of the investigator's judgment for the each eligibility criteria.

The Registration Center, specifically the Takeda clinician, confirms that a subject meets the all inclusion criteria and does not meet any of the exclusion criteria, and then the Registration Center identifies the subject as an enrolled subject and faxes a "registration confirmation sheet" to the investigator. If a subject is considered ineligible by the Registration Center, the center will not identify the subject as an enrolled subject. A "registration confirmation sheet" describing the "reason for ineligibility" will be faxed to the investigator.

The investigator must retain the "subject registration sheet", the "registration confirmation sheet", and the "reason for ineligibility" as the source documents appropriately in the study sites.

9.4 Study Procedures

Patients will be evaluated at scheduled visits during Screening, Treatment, End of Treatment (EOT), and Follow-Up. Refer to the Schedule of Events for the timing of assessments (Appendix A). Tests and procedures should be performed on schedule, but occasional changes are allowable (± 2 days) for holidays and other administrative reasons. If the study schedule is shifted, assessments must be shifted to ensure that collection of assessments is completed before dosing. If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the permission of the Takeda clinician.

Additional details are provided as necessary in the following sections.

9.4.1 Informed Consent

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

9.4.2 Patient Demographics

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

9.4.3 Medical History

During the Screening period, a complete medical history will be compiled for each patient, including diagnosis (refer to Appendix E) and current staging (refer to Appendix G) of MM. The history should include a review of all current medications, prior radiation or antineoplastic therapy, and the patient's current smoking status.

9.4.4 Physical Examination

A complete physical examination and symptom-directed physical exam will be conducted at the time points specified in the Schedule of Events.

9.4.5 Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed using the ECOG performance scale (refer to Appendix D) at the time points specified in the Schedule of Events.

9.4.6 Height and Weight

Height will only be assessed at the Screening visit. Weight will be measured at the time points specified in the Schedule of Events.

9.4.7 Vital Signs

Measurement of vital signs, including temperature, blood pressure, heart rate, and respiratory rate will be done at the time points specified in the Schedule of Events.

9.4.8 Pregnancy Test

Two pregnancy tests with sensitivity of at least 25 mIU/mL will be performed for all women of childbearing potential prior to initiation of study treatment. The first pregnancy test must be performed within 10 to 14 days prior to the start of study treatment and the second pregnancy test must be performed within 24 hours prior to the start of study treatment of Cycle 1. The results must be available and negative before the first dose of study treatment is administered.

FCBP is a female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal (amenorrhea following chemotherapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has not had menses at any time during the preceding 24 consecutive months).

FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on treatment (including breaks in therapy), at discontinuation of study treatment, and at Day 28 after the last dose of study treatment. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on study (including breaks in therapy), at discontinuation of study treatment, and at Days 14 and 28 after the last dose of study treatment. All patients must be counseled about pregnancy precautions, risks of fetal exposure, and other risks in accordance with RevMate program.

9.4.9 Skeletal Survey

A complete skeletal survey, using roentgenography, will be performed at Screening (within 8 weeks prior to enrollment) and annually in all patients. If at any time the investigator 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.

At the discretion of the investigator, CT scan, a positron emission tomography (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.

Radiographs will be analyzed locally and reports maintained with the patient source record for review.

9.4.10 Skeletal-Related Events

Selected skeletal-related events, defined as new fractures (excluding vertebral compression or rib fractures), irradiation of or surgery on bone, or spinal cord compression, will be captured from the start of the study treatment through death or study termination by the sponsor at the time points listed in the Schedule of Events.

9.4.11 Serum Free Light Chain Assay

A blood sample for serum free light chain assay will be obtained at the time points specified in the Schedule of Events.

9.4.12 Immunofixation of Serum and Urine

Serum and urine samples for the analysis of immunofixation of immunoglobulins will be obtained at the time points specified in the Schedule of Events.

9.4.13 Bone Marrow Evaluation

Central Laboratory Evaluation

Cytogenetics

The sample of the bone marrow aspirate obtained at Screening (within 28 days before the first dose of study treatment) will be used for evaluation of cytogenetics that will cover a panel of high-risk abnormalities including the following: del(13), +1q21, t(4;14), t(14;16), and del(17). This sample will be submitted to the central laboratory (See a separately created manual). The first or second pull of the bone marrow aspirate is the preferred specimen to be sent to the central laboratory for this analysis.

Local Laboratory Evaluations

Disease Assessment

A bone marrow aspirate will be obtained at Screening for disease assessment and at any time bone marrow aspirate sample is obtained to assess CR or to investigate suspected PD. This evaluation will be performed locally.

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

Cytogenetics

An additional bone marrow aspirate or bone marrow sample may also be submitted for cytogenetics to be analyzed locally, according to local standards, if the site has capability to perform analysis and there is sufficient sample available. The central laboratory cytogenetic results will be utilized for study analysis, whereas local laboratory cytogenetic results (where available) will only be utilized in instances when central laboratory results are not available.

9.4.14 Response Assessment

Patients will be assessed by investigator for disease response according to the IMWG criteria, version 2011 (refer to Appendix H)[16]. Central laboratory data will be used for serum M-protein, urine M-protein and serum free light chain.

Response assessments should occur every cycle until PD. The Takeda clinician will confirm the investigator assessment of PD prior to the investigator taking the patient off treatment.

Response and relapse categories are as follows:

Table 9.a Response Assessment

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

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

Note that in order to determine a response of sCR, bone marrow, immunohistochemistry, or immunofluorescence for kappa/lambda ratio, as well as serum free light chain assay, should be performed for all patients suspected to be in CR to meet this response category's requirements.

Patients with measurable disease in either SPEP or UPEP or both will be assessed for response only based on these 2 tests and not by the free light chain assay. Free light chain response criteria are only applicable to patients without measurable disease in the serum or urine, and to fulfill the requirements of the category of sCR.

9.4.15 Concomitant Medications and Procedures

Concomitant medications and therapy will be recorded from the first dose of study treatment through 30 days after last dose of study treatment or initiation of the subsequent antineoplastic therapies whichever comes first. If an AE is still on follow-up, the concomitant medications and therapy will be recorded during the follow-up period. See Section 8.3 for a list of prohibited concomitant medications and therapies and Section 8.4 for a list of allowed concomitant medications and therapies.

9.4.16 Adverse Events

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

9.4.17 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed by the central laboratory. Central laboratory results should be used for confirmation of patient eligibility. 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 within 3 days

before Day 1 dosing and within 24 hours before Days 8, 15 and 22 dosing, where required. Local laboratory evaluations may be done more frequently at the investigator's discretion, ie, for acute management of adverse events.

In the instance when local laboratory results are used and central laboratory results are subsequently available, a retrospective review will be completed by the Takeda clinician to determine any significant difference between those results. In the event of a significant difference, the Takeda clinician will consider regarding recommended actions for the site/patient.

Blood samples for analysis of the following hematology and chemistry will be obtained as specified in the Schedule of Events. Blood samples will be collected before the study treatment administration.

Table 9.b Hematology and Chemistry Tests

Hematology	**Chemistry**	
Hemoglobin	blood urea nitrogen (BUN)	Glucose
Hematocrit	Creatinine	Sodium
Platelet Count	Total bilirubin	Potassium
WBC Count with Differential	Uric Acid	Chloride
	lactate dehydrogenase (LDH)	carbon dioxide (CO_2)
	Alkaline phosphatase	Magnesium
	AST	Calcium
	ALT	Phosphate
	Albumin	Thyroid Stimulating Hormone (TSH)

9.4.18 Radiographic Disease Assessment

For patients with documented extramedullary disease, other assessments and scans such as a CT, PET-CT or MRI scan may be required to better delineate the lesion sites and measurements of extramedullary disease. Follow-up scans should be performed at Screening (within 8 weeks prior to enrollment), every other cycle during treatment, and every 8 weeks during the PFS follow-up period, until disease progression.

All follow-up scans should use the same imaging modality used at Screening.

Radiographs will be analyzed locally and the reports will be maintained as the patient source record for review.

9.4.19 β2-Microglobulin

A blood sample for central laboratory evaluation will be collected at Screening for serum β2 microglobulin testing.

9.4.20 Quantification of M-Protein

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

9.5 Completion of Study Treatment for Individual Patients

Patients will be considered to have completed study treatment if they receive the study treatment until PD or until discontinuation for unacceptable toxicity, withdrawal of consent, or death. Takeda clinician will review the source data documenting PD prior to the investigator taking the patient off treatment or stopping disease assessments due to PD. Patients will attend an EOT visit approximately 30 days after receiving their last dose of the study treatment and will continue to be followed for other follow-up assessments specified in the Schedule of Events. Refer to the Schedule of Events for EOT visit assessments.

9.6 Completion of Study for Individual Patients

Patients will be considered to have completed the study if they are followed until death or until the sponsor terminates the study.

9.7 Discontinuation of Treatment With Study Treatment

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

- Adverse event
- Protocol deviation
- Study terminated by sponsor
- Withdrawal by patient
- Lost to follow-up
- PD
- Other

Prior to the investigator taking the patient off treatment, the investigator is required to submit the rationale to the Takeda clinician for review.

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

9.8 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
- Death
- 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.

9.9 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or subinvestigator(s). The investigational product administrator will maintain records of study drug receipt and dispensing.

9.10 Posttreatment Follow-up Assessments (Progression-Free Survival and Overall Survival)

Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up should occur every 4 weeks until the occurrence of PD, and radiographic disease assessments are to be performed every 8 weeks. All subsequent antineoplastic therapies will be recorded, regardless if they are initiated before or after PD. Patients who start an alternative antineoplastic therapy prior to PD will continue to be followed for PD.

Patients who stop treatment due to PD will continue to have OS visits/assessments. During the OS follow-up, assessments can be made over the phone and do not require a clinic visit. Data may be collected by methods that include but are not limited to telephone, e-mail, and mail. The OS follow-up should be conducted every 12 weeks after documented PD until death or termination of the study by the sponsor. All subsequent antineoplastic therapies will be recorded during the OS follow-up period.

Information for new primary malignancy should be collected during the study, including the PFS and OS follow-up periods.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

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

10.1.2 Adverse Event Definition

An adverse event (AE) means any untoward medical occurrence in a patient or subject who received a pharmaceutical product (or a study drug); the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or 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 not considered a clinically significant change from baseline by the investigator.

10.1.3 Serious Adverse Event Definition

A serious adverse event (SAE) means any untoward medical occurrence at any dose that:

- 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 existing hospitalization** (see Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity.** (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect.**
- Is a **medically important event.** This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the

development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [17]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1,000/mm^3 to less than 2,000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

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

Regardless of causality, SAEs and serious PTEs (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Emergency Reception Center for Safety Information (contact information provided below). This should be done by e-mailing or faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created and designated by Takeda, or the equivalent form specified by each study site shall be used. If the first SAE report was filed, the original SAE Form should be submitted to Takeda later. If applicable, copies of relevant records also need to be submitted to Takeda when they became available. The investigator should give the detailed information about the SAE to Takeda in a timely manner after he/she sent the first report. The details of subsequent SAE information should be reported according to the above-stated reporting procedures. Follow-up information on the SAE or serious PTE may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information (the Emergency Reception Center for Safety Information)

Bell Medical Solutions, Inc.

PPD

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 severity (toxicity grade) of the event and the relationship of the event to study treatment administration. For serious PTEs, the investigator must determine both the severity (toxicity grade) of the event and the causality of the event in relation to study procedures.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [17].

The relationship between the event and study treatment administration (ie, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: "Is there a reasonable possibility that the AE is associated with the study treatment (any of ixazomib, lenalidomide, or dexamethasone) ?"

10.3 Monitoring of Adverse Events and Period of Observation

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

- AEs will be reported during the period from the first dose of study treatment through 30 days after administration of the last dose of study treatment, or the start of subsequent antineoplastic therapy, whichever occurs first, and recorded in the eCRFs. Even after this period, skeletal-related events (refer to Section 9.4.10 for details) and new primary malignancies must be reported during the period from the first dose of study treatment through death or termination of the study by the sponsor.
- All AEs should be followed until resolution or until become a chronic condition. This will not necessarily be done, however, if the investigator considers it is clinically appropriate to discontinue the follow-up or if the subject is lost to follow-up.
- SAEs

Serious PTEs will be reported to the Emergency Reception Center for Safety Information from the time of the signing of the informed consent form up to the first dose of study treatment, and will not be recorded in the eCRF.

Related and unrelated treatment-emergent SAEs will be reported to the Emergency Reception Center for Safety Information during the period from the first dose of study treatment through 30 days after administration of the last dose of study treatment, or the start of subsequent antineoplastic therapy, whichever occurs first, and recorded in the eCRF. After this period, only related SAEs must be reported to the Emergency Reception Center for Safety Information. The information on new primary malignancy, even though it was obtained after this period, must be provided to the Emergency Reception Center for Safety Information during the period from the first dose of study treatment through death or termination of the study by the sponsor, regardless of whether the malignancy is related to the study treatment.

All serious PTEs and 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).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a female patient becomes pregnant or suspects that she is pregnant while participating in this study or within 90 days after the last dose of study treatment, she must inform the investigator immediately and permanently discontinue study treatment. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Emergency Reception Center for Safety Information (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study or within 90 days after the last dose of study treatment, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Emergency Reception Center for Safety Information (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10.5 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 this to "Dohmen Life Sciences" addresses provided below.

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 and underdoses constitute medication errors, doses missed inadvertently by a patient do not. All medication error (including overdose) should be recorded on eCRF by the principal investigator or subinvestigator. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the phone numbers or e-mail addresses provided below.

Product complaints in Japan can be reported to study monitor (CRA) as well as "Dohmen Life Sciences".

Call Center	Phone Number	E-mail	Fax	Business Hours
Dohmen Life Science Services	PPD PPD	PPD	PPD	PPD PPD

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 the Emergency Reception Center for Safety Information (refer to Section 10.2).

10.6 Safety Reporting to Investigators, IRBs and Regulatory Authorities

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

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 eCRFs

Completed eCRFs are required for each subject who receives study drug. The sponsor or its designee will allow the study sites to have access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, CRO partners, and regulatory authorities. eCRFs should be prepared in English.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. These corrections of eCRFs are recorded as audit trails that capture the information before and after correction, correctors' names, correction dates and reasons for each correction.

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

The sponsor or its designee must review eCRFs for accuracy and completeness when visiting the study site. The sponsor or its designee will be permitted to review subjects' medical and hospital records pertinent to the study to ensure the accuracy of eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator and the head of the study site agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, source worksheets, all original signed and dated informed consent forms, electronic copies of eCRFs, including the audit trails, and detailed records of drug disposition. The investigator and the head of the study site must retain the essential documents until the following date of 1) or 2), whichever occurs later. However, if the sponsor requests a longer time period for retention, the head of the study site should discuss how long and how to retain those documents with the sponsor.

1) The day when a marketing approval of the study drug was obtained (or the day 3 years after the notification of early termination of the study).
2) The day 3 years after the date of early termination or completion of the study.

In addition, the investigator and the head of the study site should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

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

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A data review will be conducted prior to database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

Analysis is planned to be performed twice during the study. The primary analysis is planned to be performed using the data obtained at approximately 12 months from the enrollment of the last patient. The final analysis is planned to be performed after the final database lock using the data obtained at approximately 24 months from the enrollment of the last patient. The timing of analysis may be changed or additional analysis may be added upon request of the regulatory authorities.

13.1.1 Analysis Sets

In this study, the following three analysis sets ("full analysis set (FAS)", "response-evaluable analysis set" and "safety analysis set") are defined. The definition of each analysis set is as follows:

- FAS: All subjects who received at least one dose of the study drug during the treatment period.
- Response-evaluable analysis set: All FAS subjects with measurable disease at baseline, and at least one post baseline response assessment.
- Safety analysis set: All subjects who received at least one dose of the study drug during the treatment period.

The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data, consulting a medical expert as needed. If necessary, the SAP will be supplemented with handling rules that were not specified in the planning stage before finalization.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

The key demographics and other baseline characteristics will be summarized.

13.1.3 Efficacy Analysis

(1) Primary endpoint and the analytical methods

[Primary endpoint]

VGPR or better (CR + VGPR) rate in response-evaluable analysis set

[Primary analysis]

The VGPR or better (CR + VGPR) rate and the 2-sided 95% confidence interval (CI) will be provided in the response-evaluable analysis set.

[Sensitivity analysis]

The VGPR or better (CR + VGPR) rate and the 2-sided 95% CI will be provided in FAS. Non-evaluable subjects in FAS will be included in the analysis as not VGPR or CR.

(2) Secondary endpoints and their analytical methods

[Secondary endpoints]

- PFS
- ORR
- DOR
- TTP
- OS

[Analytical Method]

For the PFS, the Kaplan-Meier survival curve [and the 25th, 50th (median), and 75th percentiles, if estimable] will be calculated with their 2-sided 95% CIs in FAS. PFS is defined as the time from the date of first study drug administration to the date of first documentation of PD or death from any cause, whichever occurs first.

The overall response rate and the 2-sided 95% CI will be calculated for the response-evaluable analysis set and FAS. Non-evaluable subjects in FAS will be included in the analysis as non-responders.

For the DOR, the Kaplan-Meier survival curve [and the 25th, 50th (median), and 75th percentiles, if estimable] will be calculated with their 2-sided 95% CIs for the subjects who responded to the study treatment among the FAS. DOR is defined as the time from the date of first documentation of response to the date of first documentation of PD.

For the TTP, the Kaplan-Meier survival curve [and the 25th, 50th (median), and 75th percentiles, if estimable] will be calculated with their 2-sided 95% CIs in FAS. TTP is defined as the time from the date of first study drug administration to the date of first documentation of PD.

For the OS, the Kaplan-Meier survival curve [and the 25th, 50th (median), and 75th percentiles, if estimable] will be calculated with their 2-sided 95% CIs in FAS. OS is defined as the time from the date of first study drug administration to the date of death.

(1) Data conversion and handling of missing data

Details will be provided in the SAP.

(2) Significance level and confidence coefficient

Confidence coefficient: 95% (2-sided)

13.1.4 Safety Analysis

The following analyses will be performed using the safety analysis set.

(1) Treatment-emergent Adverse Events

Treatment-emergent adverse event (TEAE) is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug.

The frequency of TEAEs listed below will be calculated. All TEAEs will be coded using the MedDRA, and tabulated by the System Organ Class and Preferred Terms.

- All TEAEs
- Drug-related TEAEs
- Grade 3 or higher TEAEs
- Grade 3 or higher drug-related TEAEs
- All TEAEs by grade
- Drug-related TEAEs by grade
- TEAEs leading to any study drug discontinuation
- Serious TEAEs
- All TEAEs over time

(2) Laboratory values, vital signs

For continuous variables, the observed values and the changes from baseline will be summarized for each visit using descriptive statistics. Case plots will also be presented for the observed values.

For categorical variables, shift tables showing the number of patients in each category at baseline and each post-baseline visit will be provided.

13.2 Interim Analysis and Criteria for Early Termination

The primary analysis is planned to be performed using the data obtained at approximately 12 months from the enrollment of last patient. The continuation or discontinuation of the study will not be determined by this analysis. However, the timing of analysis may be changed or additional analysis may be added upon request of the regulatory authorities.

13.3 Determination of Sample Size

Assuming the expected VGPR or better rate is [CCI]% and the threshold rate is [CCI]% based on the results of Study C16010, a sample size of [CCI] would be necessary to provide a point estimate of VGPR or better rate higher than the threshold rate with [CCI]% probability. Assuming a drop-out ratio of [CC]%, the target number of patients has been set to 30. The expected response rate and the threshold assumptions are based on VGPR or better rate in ixazomib + LenDex arm and placebo + LenDex arm in Study C16010 (intent-to-treat population, primary analysis).

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

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

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including the Investigator's Binder, study medication, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator or subinvestigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible and an approval from IRB should be obtained.

The investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB Approval

IRBs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before signing a contract for the clinical study). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives notification, no protocol activities including assignment of patients may occur.

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

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

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date that informed consent is

given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The principal investigator is responsible for the preparation, content, and IRB approval of the informed consent form. The informed consent form must be approved by both the IRB and the sponsor prior to use.

The informed consent form must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject determines he or she will participate in the study, then the informed consent form must be signed and dated by the subject, at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form at the time of consent and prior to subject entering into the study.

Once signed, the original informed consent form will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form shall be given to the subject.

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

15.3 Subject Confidentiality

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

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

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

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

The investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

15.4.2 Clinical Trial Registration

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

15.4.3 Clinical Trial Results Disclosure

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

15.5 Insurance and Compensation for Injury

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

16.0 REFERENCES

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Appendix A Schedule of Events

SCHEDULE OF EVENTS

Study Procedures	Screening	Treatment Period											End of Treatment[a]	Follow-up	
		28-Day Cycles												PFS	OS
Cycle		C1				C2				C3		C4 and beyond		Every 4 weeks	Every 12 weeks
Days	-28 to -1	1	7	14	21	1	7	14	21	1	14	1			
Window		± 2 days[b]											+1 wk	± 1 wk	± 1 wk
Informed Consent	X														
Inclusion/Exclusion Criteria[c]	X														
Demographics	X														
Medical History	X														
Physical Exam	X												X		
Symptom-Directed Physical Exam	X					X				X		X		X	
ECOG performance status	X					X				X		X	X	X	
Vital Signs	X	X				X				X		X	X	X	
Height (cm) & Weight (kg)	X[d]	X[d]				X[d]				X[d]		X[d]	X[d]		
Pregnancy Test[e]	X	X	X	X	X	X				X		X	X		
Hematology Laboratory[f]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry Laboratory[f]	X	X				X				X		X	X		
Thyroid testing	X											X[g]	X		
Skeletal Survey[h]	X											X		X	
Radiographic Disease Assessment[i]	X					X						X	X	X	
β2-microglobulin	X														

Study Procedures	**Screening**	**Treatment Period**											**End of Treatment[a]**	**Follow-up**	
		28-Day Cycles												**PFS**	**OS**
Cycle		**C1**				**C2**				**C3**		**C4 and beyond**		**Every 4 weeks**	**Every 12 weeks**
Days	**-28 to -1**	**1**	**7**	**14**	**21**	**1**	**7**	**14**	**21**	**1**	**14**	**1**			
Window		**± 2 days[b]**											**+1 wk**	**± 1 wk**	**± 1 wk**
M-protein Measurements (SPEP)	X	X[j]				X				X		X	X	X	
M-protein Measurements (UPEP [24hr Urine collection])	X	X[j]				X				X		X	X	X	
Serum Free Light Chain Assay	X	X[j]				X				X		X	X	X	
Immunofixation - serum and urine	X	X[j]				X				X		X	X	X	
Bone Marrow Aspiration															
- Disease Assessment	X[k]					X[k]				X[k]		X[k]	X[k]	X[k]	
- Cytogenetic assessment	X[l]														
Adverse Event Reporting[m]		Recorded from the first dose of study treatment through 30 days after last dose of study treatment, or the start of subsequent antineoplastic therapy, whichever occurs first													
	Serious adverse events and serious pretreatment events will be collected from signing of the informed consent through 30 days after administration of the last dose of study treatment, or the start of subsequent antineoplastic therapy, whichever occurs first														
Concomitant Medications/Procedures[n]		Recorded from the first dose of study treatment through 30 days after administration of the last dose of study treatment, or the start of subsequent antineoplastic therapy, whichever occurs first													
Skeletal-related Events		Continuous from the start of study treatment administration until death or termination of the study by the sponsor													
New Primary Malignancy Assessment		Continuous from the start of study treatment administration until death or termination of the study by the sponsor													
Survival															X

Study Procedures	**Screening**	**Treatment Period**											**End of Treatment[a]**	**Follow-up**	
		28-Day Cycles												**PFS**	**OS**
Cycle		**C1**				**C2**				**C3**		**C4 and beyond**		**Every 4 weeks**	**Every 12 weeks**
Days	**-28 to -1**	**1**	**7**	**14**	**21**	**1**	**7**	**14**	**21**	**1**	**14**	**1**			
Window		**± 2 days[b]**											**+1 wk**	**± 1 wk**	**± 1 wk**
Study Treatment Administration															
Ixazomib		Days 1, 8 and 15 of each cycle													
Lenalidomide		Daily Days 1 through 21 of each cycle													
Dexamethasone		Days 1, 8, 15 and 22 of each cycle													

a Review by Takeda clinician required prior to discontinuing patient from treatment.

b Tests and procedures should be performed on schedule, but occasional changes may be allowed (± 2 days) for holidays and other administrative reasons. If the study schedule is shifted, assessments must be shifted to ensure that collection of assessments is completed prior to dosing. If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the permission of the Takeda clinician.

c Confirmation of patient eligibility by Takeda clinician is required prior to enrollment.

d Height assessed at screening only.

e Pregnancy tests (Refer to Section 9.4.8):

- Screening: Female patients of childbearing potential (FCBP) must have 2 negative pregnancy tests prior to starting study treatment. The first pregnancy test must be performed within 10 to 14 days prior to the start of study treatment and the second pregnancy test must be performed within 24 hours prior to the start of study treatment of Cycle 1.
- On-Treatment: Pregnancy tests for FCBP to be collected weekly for the first 28 days and then every 28 days while on treatment. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on treatment.
- End of Treatment: Pregnancy tests for FCBP to be collected at treatment discontinuation and at Day 28 following therapy. If menstrual cycles are irregular, the pregnancy testing must occur at drug discontinuation and at Days 14 and 28 following drug discontinuation.

f Clinical laboratory evaluations will be performed by the central laboratory. Central laboratory results should be used for confirmation of patient eligibility. 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 within 3 days before Day 1 dosing of each cycle and within 24 hours before Days 8, 15 and 22 dosing, where required. Local laboratory evaluations may be done more frequently at the investigators discretion, ie, for acute management of adverse events. (Refer to Section 9.4.17)

g Thyroid testing required every 4 cycles on treatment.

h Skeletal survey will be performed at screening (within 8 weeks prior to enrollment) and, at a minimum, annually for all patients. More frequent assessments can be done at the discretion of the investigator (ie, for symptoms or signs that indicate increased or new bone lesions). (Refer to Section 9.4.9)

i Patients with documented extramedullary disease must have radiographic disease assessments (CT/PET-CT/MRI) performed at screening (within 8 weeks prior to enrollment), every other cycle during treatment, and every 8 weeks during the PFS follow-up period, until disease progression. (Refer to Section 9.4.18)
j If the screening test was performed more than 14 days prior to the first dose, the test will be repeated at baseline.
k The bone marrow disease assessment will be made at baseline. This assessment will be made again only if resolution of serum and urine M-protein consistent with CR is suspected or to investigate suspected PD by principal investigator /subinvestigator, if applicable. (Refer to Section 9.4.13)
l Bone marrow aspirate (first or second pull preferred) for cytogenetics are required to be sent to the central laboratory at baseline. Of note, cytogenetics may also be done locally if the site has the capability to perform analysis and sufficient specimen is available. Assessment of the following: +1q21, translocations t(4;14) and t(14;16), del(17), del(13). (Refer to Section 9.4.13)
m All AEs should be followed until they either resolve or become a chronic condition. This will not necessarily be done, however, if the investigator considers it is clinically appropriate to discontinue the follow-up or if the subject is lost to follow-up. (Refer to Section 10.3)
n If an AE is still on follow-up, the concomitant medications and therapy will be recorded during the follow-up period.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities.

1. Conduct the appropriate study in accordance with the protocol and GCP considering the rights, safety and wellbeing of human subjects.
2. When a part of the important activities related to the study are delegated to the sub-investigator or the study collaborator, prepare the lists of activities to be delegated and responsible personnel, submit the lists to the head of the study in advance to get them accepted.
3. Prepare a written informed consent form and other written information, and update as appropriate.
4. Confirm the contents of the clinical study agreement.
5. Provide necessary information on the protocol, medications and responsibilities of individual personnel to the investigator and study collaborator, and provide guidance and supervision.
6. Screen subjects who meet the requirements of the protocol, provide the explanation of the study in writing and obtain the written consent.
7. Assume responsibility for all the medical judgement related to the study.
8. Ensure in collaboration with the head of the study that sufficient medical care on all clinically significant adverse events related to the study are provided to subjects throughout and beyond the period when subjects participate in the study.
9. If a subject consults other medical institution or other department, notify the physician of the medical institution or department of the subject's participation in the study upon obtaining the consent of the subject, as well as the end and termination of the study in writing, and document such records.
10. In case of urgent report of a SAE, immediately notify the head of the study and the sponsor in writing.
11. Prepare correct and complete (e)CRFs, and submit them to the sponsor with electronic signature.
12. Check and confirm the contents of (e)CRFs prepared by the sub-investigator or transcribed from the source data by the study collaborator, and submit them to the sponsor with electronic signature.
13. Discuss any proposal from the sponsor including update of the protocol.
14. Notify the director of the site of the end of the study in writing.

Appendix C Investigator Consent to Use of Personal Information

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

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

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

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

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

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

Appendix D 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. American Journal of Clinical Oncology 1982;5(6):649-55.

Appendix E 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 (non-secretory 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.

Appendix F Cockcroft-Gault Equation

For males:

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

For females:

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

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

Appendix G International Staging System Staging Criteria and Durie-Salmon 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: Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Bladé J et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23(15):3412-20.

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.

Durie-Salmon Criteria

Stage	Criteria
I	All of the following: • Hemoglobin value > 10 g/dL • Serum calcium value normal or ≤ 12 mg/dL • Bone x-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only • Low M component production rate ○ IgG value < 5 g/dL; IgA value < 3 g/dL ○ Bence Jones protein < 4 g/24 h
II	Neither stage I nor stage III
III	1 or more of the following: • Hemoglobin value < 8.5 g/dL • Serum calcium value > 12 mg/dL • Advanced lytic bone lesions (scale 3) • High M component production rate ○ IgG value > 7 g/dL; IgA value > 5 g/dL ○ Bence Jones protein > 12 g/24 h

Durie-Salmon sub classifications (either A or B)
A: Relatively normal renal function (serum creatinine value < 2.0 mg/dL)
B: Abnormal renal function (serum creatinine value ≥ 2.0 mg/dL)

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.

Appendix H Response Criteria

Patients will be assessed for disease response according to the IMWG criteria below, versions 2011.

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.

For VGPR: Disappearance of any soft tissue plasmacytomas present at baseline and no new plasmacytomas.

Source: 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.

Appendix I Changes in Procedures in Study Protocol after Shifting to the Post-marketing Clinical Study

After a marketing approval of ixazomib was obtained in Japan, this study will be continued as a post-marketing clinical study in compliance with the GCP and the Good Post-marketing Study Practice. The changes in procedures in the study protocol after shifting to the post-marketing clinical study are described below.

Entire Protocol

In the protocol, the term "study" will be replaced by "post-marketing clinical study".

8.0 Study Drug

Even after a marketing approval of ixazomib was obtained, ixazomib capsules should be supplied by the sponsor as a drug used in this post-marketing clinical study, and handling procedures should not be changed.

10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

The following actions will be added in Section 10.2.

If any non-serious adverse events were observed after a marketing approval of ixazomib was obtained, the principal investigator/subinvestigator should report them to the sponsor. The investigator or subinvestigator should submit the report to the sponsor upon request within a period of time designated by the sponsor.

10.6 Safety Reporting to Investigators, IRBs and Regulatory Authorities

The Section 10.6 will be changed as follows (underlined text was added).

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to the regulatory authorities, investigators, IRBs or the head of each study site. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. All <u>SUSARs and known SAEs will be</u>

submitted to the regulatory authorities as an expedited report within the reporting deadlines specified in applicable regulatory requirements.

(The rest is omitted)

12.2 Record Retention

The section 12.2 will be changed as follows (Underlined texts were added).

(First part omitted)

The investigator and the head of the study site must retain the essential documents until the following date of 1) or 2), whichever occurs later. After a marketing approval of ixazomib was obtained, the duration of record retention shall expire on the day when a re-examination of ixazomib is completed, instead of the following dates of 1) and 2). However, if the sponsor requests a longer time period for retention, the head of the study site should discuss how long and how to retain those documents with the sponsor.

1) The day when a marketing approval of the study drug was obtained (or the day 3 years after the notification of early termination of the study).

2) The day 3 years after the date of early termination or completion of the study.

In addition, the investigator and the head of the study site should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

(The rest omitted)

Appendix J Detailed Description of Amendments to Text

The following is described based on the contents of Amendment 01.

Page 1, Cover Page (Amendment History)

Existing Text

(No Text)

Added Text

Note: This study will be continued as a post-marketing clinical study after a marketing approval of ixazomib was obtained in Japan. In the protocol, the term "study" will be replaced by "post-marketing clinical study" as appropriate, and the protocol is continuously used.

Rationale for Amendment

Actions taken after a marketing approval of ixazomib was obtained will be described.

Page 9, Section 2.0

Existing Text

(No Text)

Added Text

Note: This study will be continued as a post-marketing clinical study after a marketing approval of ixazomib was obtained in Japan. In the protocol, the term "study" will be replaced by "post-marketing clinical study" as appropriate, and the protocol is continuously used.

Rationale for Amendment

Actions taken after a marketing approval of ixazomib was obtained will be described.

Page 14, Section 4.2

Existing Text

(No Text)

Added Text

This study will be continued as a post-marketing clinical study after a marketing approval of ixazomib was obtained in Japan. In the study protocol, the term "study" will be replaced by "post-marketing clinical study" as appropriate. The details of changes in study procedures to be made after shifting to the post-marketing clinical study are found in Appendix 1.

Rationale for Amendment

Actions taken after a marketing approval of ixazomib was obtained will be described.

Page 20, Section 7.2

Existing Text

12. Ongoing or active systemic infection, known human immunodeficiency virus (HIV)-RNA positive, known hepatitis B surface antigen seropositive or known hepatitis C virus (HCV)-RNA positive.

Revised Text

12. Ongoing or active systemic infection, known human immunodeficiency virus (HIV)- positive, known hepatitis B surface antigen seropositive or known hepatitis C virus (HCV)-RNA positive.

Rationale for Amendment

To correct typographical errors in the text.

Page 32, Section 8.5

Existing Text

(No Text)

Added Text

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

Rationale for Amendment

To ensure the subjects' safety.

Page 48, Section 10.2

Existing Text

Regardless of causality, SAEs and serious PTEs (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Emergency Reception Center for Safety Information (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event.

(snip)

SAE Reporting Contact Information (the Emergency Reception Center for Safety Information)

Bell Medical Solutions, Inc.

PPD

Revised Text

Regardless of causality, SAEs and serious PTEs (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Emergency Reception Center for Safety Information (contact information provided below). This should be done by **e-mailing or** faxing the SAE Form within 24 hours after becoming aware of the event.

(snip)

SAE Reporting Contact Information (the Emergency Reception Center for Safety Information)

Bell Medical Solutions, Inc.

PPD

Rationale for Amendment

Reporting by e-mail has become available.

Page 49, Section 10.3

Existing Text

- Related and unrelated treatment-emergent SAEs will be reported to the Emergency Reception Center for Safety Information during the period from the first dose of study treatment through 30 days after administration of the last dose of study treatment, or the start of subsequent antineoplastic therapy, whichever occurs first, and recorded in the

eCRF. After this period, only related SAEs must be reported to the Emergency Reception Center for Safety Information.

Revised Text

– Related and unrelated treatment-emergent SAEs will be reported to the Emergency Reception Center for Safety Information during the period from the first dose of study treatment through 30 days after administration of the last dose of study treatment, or the start of subsequent antineoplastic therapy, whichever occurs first, and recorded in the eCRF. After this period, only related SAEs must be reported to the Emergency Reception Center for Safety Information. **However, even after this period, the information on new primary malignancy must be reported to the Emergency Reception Center for Safety Information during the period from the first dose of study treatment through death or termination of the study by the sponsor, regardless of whether the malignancy is related to the study treatment**

Rationale for Amendment

To clarify the reporting of information on new primary malignancy.

Page 50, Section 10.5

Existing Text

Whereas overdoses constitute medication errors, doses missed inadvertently by a patient do not.

Revised Text

Whereas overdoses **and underdoses** constitute medication errors, doses missed inadvertently by a patient do not.

Rationale for Amendment

To follow the Study Protocol Template.

Page 64, Appendix A

Existing Text

Study Procedure	Screening	Treatment Period											End of Treatment	(Omitted)
		28-day Cycle												
Cycle		C1				C2				C3		C4 and beyond		
Days	-28 to -1	1	7	14	21	1	7	14	21	1	14	1		
Window		±2 days[b]											+1 week	
(Omitted)														
Height (cm) & Body Weight (kg)	○[d]												○[d]	

Revised Text

Study Procedures	Screening	Treatment Period											End of Treatment [a]	(Omitted)
		28-day Cycle												
Cycle		C1				C2				C3		C4 and beyond		
Days	-28 to -1	1	7	14	21	1	7	14	21	1	14	1		
Window		±2 days[b]											+1 week	
(Omitted)														
Height (cm) & Body Weight (kg)	○[d]	○[d]				○[d]				○[d]		○[d]	○[d]	

Rationale for Amendment

To correct typographical errors in the text

Page 67, Appendix A, Footnote k

Existing Text

Only to be repeated if resolution of serum and urine M-protein consistent with CR is suspected or to investigate suspected PD by principal investigator /subinvestigator, if applicable. (Refer to Section 9.4.13)

Revised Text

The disease assessment will be made at baseline. This assessment will be made again only if resolution of serum and urine M-protein consistent with CR is suspected or to investigate suspected PD by principal investigator /subinvestigator, if applicable. (Refer to Section 9.4.13)

Rationale for Amendment

To clarify the text.

Page 76, Appendix I

The changes in procedures to be made after shifting to the post-marketing clinical study are described. (The replacements and changes are not detailed here.)