Clinical Study Protocol

NCT Number: NCT02924272

Title: An Open-Label, Rollover Protocol for Patients Previously Enrolled in Takeda-Sponsored Ixazomib Studies

Study Number: C16027

Document Version and Date: Amendment 3.0, 03 June 2021

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

PROTOCOL

An Open-Label, Rollover Protocol for Patients Previously Enrolled in Takeda-Sponsored Ixazomib Studies

Ixazomib Rollover Study

Sponsor: Takeda Development Center Americas, Inc
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Study Number: C16027

EudraCT Number: 2016-001681-28

Compound: Ixazomib

Date: 03 June 2021 **Amendment Number:** 03

Amendment History:

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
30 June 2016	Initial Protocol	Not applicable	Global
23 March 2017	01	Substantial amendment	Global
08 November 2017	02	Nonsubstantial amendment	Local (Sweden)
03 June 2021	03	Substantial amendment	Global

1.0 ADMINISTRATIVE

1.1 Contacts

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

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

Medical and study drug advice for this protocol is available by contacting the Medical Monitor. Refer to the study manual for contact information.

TDC-sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

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

Contact Type/Role	North America Contact	Europe Contact	Asia Contact
Serious adverse event and pregnancy reporting	See Section 10.2	See Section 10.2	See Section 10.2

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

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

SIGNATURES

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

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

[redacted], MD Date
[redacted], Oncology Clinical Research
[redacted] (or designee)

[redacted] Date
Study Clinical Science Lead (or designee)

[redacted], PhD
[redacted], Statistical and Quantitative Sciences (or designee)

1.3 Protocol Amendment 03 Summary of Changes

Rationale for Amendment 03

This document describes the changes in reference to the protocol incorporating Amendment No. 03. Patients are eligible to enroll in this rollover study if they have previously received and tolerated a defined study regimen in a designated Takeda-sponsored ixazomib clinical study (ie, Studies C16003, C16005, C16006, C16007, C16008, C16010 Global, C16011, C16013, C16014 Global and Korean Continuation, C16017, C16020, C16029, and C16047) and if, in the investigator's opinion, they may benefit from continued therapy with 1 or more of the drugs from the parent protocol. No new anticancer agents can be started or added. Note that for patients whose study therapy in a parent study includes a placebo, the placebo capsule will be discontinued; crossover to ixazomib is not permitted. The primary reason for this amendment is to update the protocol regarding dosing and treatment information from parent protocols.

Additionally, this amendment clarifies other elements of the study design and procedures. Descriptions of how to manage study procedures during the coronavirus disease 2019 (COVID-19) pandemic have been added. Event descriptions were updated to the current program standards for the management of clinical events. Paper-based serious adverse event (SAE) reporting procedures were additionally clarified. The list of acceptable methods of contraception previously added in the Sweden-specific Protocol Amendment 02 has now been added to this global amendment (see Appendix D). See the changes below for a complete list of all changes included in this amendment. Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

For specific descriptions of text changes and where the changes are located, see Appendix E.

Changes in Amendment 03

1. Updated the legal entity of the sponsor.
2. Updated signatories for the study.
3. Clarified that ixazomib and/or combinational study drugs from the designated parent protocols will be provided in this study until other means of accessing treatment are available; no new anticancer agents can be started or added; and for patients whose study therapy in a parent study includes placebo, the placebo capsule will be discontinued and crossover to ixazomib is not permitted.
4. Clarified the study objectives.
5. Clarified the duration of adverse event (AE) follow-up.
6. Updated the background information on other ixazomib clinical trials.
7. Clarified the anticipated number of patients and sites/countries.
8. Clarified the duration of an individual patient's study participation.
9. Clarified the anticipated total study duration.

10. Specified the acceptable methods of contraception to prevent pregnancy.
11. Clarified that systemic treatment with strong cytochrome P-450 (CYP)3A inducers is prohibited for patients receiving ixazomib during the study.
12. Updated the management of ixazomib clinical events to align with the current program standards.
13. Clarified the instructions for management of combination therapy clinical events.
14. Updated the storage, handling, and accountability text to clarify procedures and account for the COVID-19 pandemic.
15. Added language regarding alternative methods for administering study procedures/assessments when it is not possible for the patient to come to the study site due to the COVID-19 pandemic.
16. Clarified that patients previously enrolled in this study who remain on study treatment upon implementation of Amendment 3 may need to be reconsented, according to IRB/IEC standards.
17. Clarified regional exceptions for assessment of carbon dioxide, depending on standard of care.
18. Updated the criteria for withdrawing patients from study.
19. Added language to Procedures for Recording and Reporting Adverse Events and Serious Adverse Events.
20. Revised language regarding the statistical analyses.
21. Clarified language regarding procedures for reporting product complaints or medication errors.
22. Clarified language regarding quality assurance audits and Regulatory Agency inspections.
23. Add information about alternative monitoring approaches, such as remote source data verification, in the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic.
24. Clarify the ixazomib capsule strengths that are available.

INVESTIGATOR AGREEMENT

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

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

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

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Provence)

_____

Location of Facility (Country)

TABLE OF CONTENTS

1.0 ADMINISTRATIVE 2
1.1 Contacts 2
1.2 Approval 3
1.3 Protocol Amendment 03 Summary of Changes 4
2.0 STUDY SUMMARY 11
3.0 STUDY REFERENCE INFORMATION 15
3.1 Study-Related Responsibilities 15
3.2 List of Abbreviations 15
4.0 INTRODUCTION 17
4.1 Background 17
4.1.1 Risk: Benefit Assessment 18
4.2 Rationale for the Proposed Study 19
5.0 STUDY OBJECTIVES AND ENDPOINTS 19
5.1 Objectives 19
5.1.1 Primary Objectives 19
5.2 Endpoints 19
5.2.1 Primary Endpoint 19
6.0 STUDY DESIGN 19
6.1 Overview of Study Design 19
6.2 Number of Patients 21
6.3 Duration of Study 21
6.3.1 Duration of an Individual Patient's Study Participation 21
6.3.2 End of Study/Study Completion Definition and Planned Reporting 22
6.3.3 Timeframe for Primary Endpoint to Support Disclosures 22
6.3.4 Total Study Duration 22
7.0 STUDY POPULATION 22
7.1 Inclusion Criteria 22
7.2 Exclusion Criteria 23
8.0 STUDY DRUG 23
8.1 Study Drug Administration 23
8.2 Reference/Control Therapy 24
8.3 Dose Modification Guidelines 24
8.4 Excluded Concomitant Medications and Procedures 24
8.5 Permitted Concomitant Medications and Procedures 24

8.6 Precautions and Restrictions 24
8.7 Management of Clinical Events 25
8.7.1 Management of Ixazomib Clinical Events 25
8.7.2 Management of Combination Therapy Clinical Events 27
8.8 Blinding and Unblinding 27
8.9 Description of Investigational Agents 27
8.10 Preparation, Reconstitution, and Dispensation 28
8.11 Packaging and Labeling 28
8.12 Storage, Handling, and Accountability 28
8.13 Combination Therapy 29
8.14 Other Protocol-Specified Materials 29
9.0 STUDY CONDUCT 29
9.1 Study Personnel and Organizations 30
9.2 Arrangements for Recruitment of Patients 30
9.3 Treatment Group Assignments 30
9.4 Study Procedures 30
9.4.1 Informed Consent 31
9.4.2 Vital Signs 31
9.4.3 Weight 31
9.4.4 Pregnancy Test 31
9.4.5 Concomitant Medications and Procedures 31
9.4.6 Adverse Events 32
9.4.7 Enrollment 32
9.4.8 Clinical Laboratory Evaluations 32
9.4.9 Disease Assessment 33
9.5 Completion of Study (for Individual Patients) 33
9.6 Withdrawal of Patients From Study 33
9.7 Study Compliance 33
10.0 ADVERSE EVENTS 34
10.1 Definitions 34
10.1.1 Adverse Event Definition 34
10.1.2 Serious Adverse Event Definition 34
10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events 35
10.3 Monitoring of Adverse Events and Period of Observation 36
10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events 37

10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose) 37
10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities 37
11.0 STUDY-SPECIFIC COMMITTEES 38
12.0 DATA HANDLING AND RECORDKEEPING 38
12.1 eCRFs 38
12.2 Record Retention 39
13.0 STATISTICAL METHODS 39
13.1 Statistical and Analytical Plans 39
13.1.1 Analysis Sets 39
13.1.2 Efficacy Analysis 39
13.1.3 Safety Analysis 40
13.2 Interim Analysis and Criteria for Early Termination 40
13.3 Determination of Sample Size 40
14.0 QUALITY CONTROL AND QUALITY ASSURANCE 40
14.1 Study-Site Monitoring Visits 40
14.2 Protocol Deviations 41
14.3 Quality Assurance Audits and Regulatory Agency Inspections 41
15.0 ETHICAL ASPECTS OF THE STUDY 42
15.1 IRB and/or IEC Approval 42
15.2 Subject Information, Informed Consent, and Subject Authorization 43
15.3 Subject Confidentiality 44
15.4 Publication, Disclosure, and Clinical Trial Registration Policy 44
15.4.1 Publication 44
15.4.2 Clinical Trial Registration 45
15.4.3 Clinical Trial Results Disclosure 45
15.5 Insurance and Compensation for Injury 45
16.0 REFERENCES 46

LIST OF IN-TEXT TABLES

Table 6.a Primary Endpoint for Disclosures 22
Table 9.a Clinical Chemistry and Hematology Tests 32

LIST OF APPENDICES

Appendix A Schedule of Events....47
Appendix B Responsibilities of the Investigator....49
Appendix C Investigator Consent to Use of Personal Information....51
Appendix D Acceptable Methods of Contraception....52
Appendix E Detailed Description of Amendments to Text....53

2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc	**Compound:** Ixazomib
Title of Protocol: An Open-Label, Rollover Protocol for Patients Previously Enrolled in Takeda-Sponsored Ixazomib Studies	**EudraCT No.:** 2016-001681-28
Study Number: C16027	**Phase:** 2

Study Design:

This is an open-label, multicenter, rollover study to provide continued access to ixazomib and/or other combinational study drugs from the designated ixazomib parent protocols when the patient has no other means to access study treatment. The study will also evaluate the long-term safety profile of ixazomib.

The patient population will consist of patients who have previously received and tolerated a defined study regimen in a designated Takeda-sponsored ixazomib clinical study, and in the investigator's opinion and approved by the Takeda medical monitor, may benefit from continued therapy with 1 or more of the study drugs from a parent protocol (eg, response to therapy or stable disease without evidence of disease progression).

Patients may be enrolled provided they have not met any of the discontinuation criteria in a parent study. Patients will enter this study on the same dose, schedule of study drug(s), and combination regimen that they were receiving at the time of rollover from the parent study, or according to the required dose modification from a parent study. For those patients who received ixazomib dosing based on body surface area (BSA) per the parent study, the dose may be rounded. The dose may also be rounded for those patients who convert from BSA-based dosing to fixed dosing with approval from the Medical Monitor. No new anticancer agents can be started or added. Note that for patients whose study therapy in a parent study includes a placebo, the placebo capsule will be discontinued; crossover to ixazomib is not permitted.

Following enrollment, patients may receive study treatment until they experience disease progression, clinical deterioration in the investigator's judgment, experience an unacceptable toxicity, withdraw consent, pursue an alternative therapy, meet other study-specified reasons for discontinuation of study drug, or until the patient is transitioned to ixazomib/other therapy through commercial channels.

Patients participating in a designated parent study will enter the rollover study when they have completed the end of treatment (EOT) visit in the parent study and when the rollover study is active at the investigative site. Following their provision of informed consent to continue receiving treatment in the rollover study, patients will be provided with study medication. Patients should enter the study within a maximum of 8 weeks of their last dose of study drug(s) in the parent study or as agreed upon by the Takeda clinician/designee so to minimize any treatment disruption to the patient. Local safety-related laboratory evaluations and vital sign measurements will be performed according to the schedule of events as presented in this rollover study and accordingly will only be recorded in the electronic case report forms (eCRFs) prior to the first dose of ixazomib in the rollover study, at the end of study, and as spontaneously reported by the investigator. Electrocardiogram assessments will only be performed as clinically indicated. During treatment, dosing modification decisions will be made per the parent study. Systemic treatment with strong cytochrome P-450 (CYP)3A inducers is prohibited for patients receiving ixazomib during the study. The procedures prohibited in the patient's parent study are prohibited during this study. Prohibited medications due to co-administration of other agents in the ixazomib regimen are prohibited as per the prescribing information for the co-administered agent(s).

It is recommended that disease assessments are performed per standard of care.

At the time of discontinuation of study drug(s) in this study, an end-of-study (EOS) visit will be scheduled and will occur prior to the initiation of any new therapy, or within 30 days of last dose of study drug administration, whichever is earlier. The reason for treatment discontinuation, an overall investigator assessment of best response obtained during this rollover study, and the investigator assessment of date of progression will be captured in the eCRFs.

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events,

Version 5.0, effective date 27 November 2017 [1].

The long-term safety and tolerability of ixazomib will be monitored. The following adverse events (AEs) will be reported from the first dose of study drug for this study through 30 days after administration of the last dose of study drug and recorded in the eCRFs and serious adverse events (SAEs) will also be reported directly to the Sponsor (see Section 10.2). The following AEs that are ongoing at the time of entry into the rollover study will be recorded in the eCRFs as baseline AEs.

- All SAEs.
- All ≥Grade 3 AEs.
- ≥Grade 2 peripheral neuropathy.
- New primary malignancies.
- Any AE resulting in dose modification or discontinuation of any study drug.
- Any other AE that in the opinion of the investigator is a clinically significant event.

The above AEs will be followed until resolution, until the AE becomes chronic or stable, or is determined to be part of the underlying disease process, or until the patient attends the EOS visit and discontinues the study.

The transfer of patients between sites is allowed with the approval of the sponsor's clinician/designee (eg, in the case of site closure, patient moves, etc).

Primary Objective:

- To provide continued access to ixazomib and/or other study drugs from an ixazomib parent study.
- To evaluate the long-term safety profile of ixazomib.

Subject Population: Patients on study drug(s) at the closure of an ixazomib parent study, and who are likely to derive benefit from continued study therapy.

Number of Subjects:	**Number of Sites:**
The estimated number of patients to be enrolled is approximately 250.	The number of countries and sites is not currently specified as this study is open to all countries and sites with qualifying patients from prior company-sponsored ixazomib studies
Dose Level(s):	**Route of Administration:**
Patients will enter this study on the same same dose, schedule of study drug(s), and combination regimen that they were receiving at the time of rollover from the parent study, or according to the required dose modification from a parent study. No new anticancer agents can be started or added. Note that for patients whose study therapy in a parent study includes a placebo, the placebo capsule will be discontinued; crossover to ixazomib is not permitted. For those patients who received ixazomib dosing based on body surface area (BSA) per the parent study, the dose may be rounded. The dose may also be rounded for those patients who convert from BSA-based dosing to fixed dosing with approval from the Medical Monitor.	Oral

Duration of Treatment:	**Period of Evaluation:**
The anticipated duration of treatment in this rollover study will be approximately 5 years. Patients may remain in the rollover study until they are transitioned to ixazomib/other therapy through commercial channels or until any of the other reasons for treatment discontinuation are met, whichever is sooner.	Patients will be followed for 30 days after the last dose of ixazomib/other study drug(s) or the start of subsequent alternative anticancer therapy.
Duration of Study: The estimated time frame for study completion (first patient in to last patient last visit) is approximately 7 years.	

Main Criteria for Inclusion:

Patients previously treated with ixazomib, background therapy, and/or comparator drugs (including placebo) in a Takeda-sponsored ixazomib parent study. Patients will be eligible to enter the rollover study when:

a) The parent study is closed or planned to be closed; and
b) The patient is on ixazomib monotherapy, a combination regimen with ixazomib and other study medication(s), on a placebo combination, or on an alternative arm regimen in a designated ixazomib parent study (ie, Studies C16003, C16005, C16006, C16007, C16008, C16010 Global, C16011, C16013, C16014 Global and Korean Continuation, C16017, C16020, C16029, and C16047); and
c) In the opinion of the investigator and approved by the Takeda medical monitor, the patient may continue to benefit from treatment with ixazomib and/or another study drug/combination regimen (eg, response to therapy or stable disease without evidence of disease progression) and has no alternate means to access the study drug(s) (eg, commercial supply).

Main Criteria for Exclusion:

Patients meeting any of the criteria for treatment discontinuation in the parent study.

Main Criteria for Evaluation and Analyses:

The primary endpoint is safety, as assessed by the incidence of the following AEs:

- All SAEs.
- All ≥Grade 3 AEs.
- ≥Grade 2 peripheral neuropathy.
- New primary malignancies.
- Any AE resulting in dose modification or discontinuation of any study drug.
- Any other AE that in the opinion of the investigator is a clinically significant event.

Statistical Considerations:

The following AEs will be summarized for patients who receive at least 1 dose of ixazomib using the full analysis set:

- All SAEs.
- All ≥Grade 3 AEs.
- ≥Grade 2 peripheral neuropathy.
- New primary malignancies.
- Any AE resulting in dose modification or discontinuation of any study drug.
- Any other AE that in the opinion of the investigator is a clinically significant event.

No formal statistical testing or inferential statistics will be generated.

All AEs will be coded using the Medical Dictionary for Regulatory Activities. Data will be summarized using preferred term and primary system organ class. Local laboratory assessment changes and vital sign changes from study entry to end of study will also be summarized.

Exposure to study drug and study regimen will be tabulated. In addition, reasons for drug discontinuation will be

summarized.

The overall investigator assessment of best response obtained during this rollover study and investigator assessment of date of progression will be listed.

Concomitant medications and procedures related to treatment of AEs from screening through the study period will be classified by generic terms according to the World Health Organization drug dictionary.

Data will be presented by the entire ixazomib Safety population, by population of monotherapy of ixazomib, and by population of ixazomib in combination with other anticancer agents(s), as specified in the SAP. Safety listings will be prepared for patients receiving other study drugs and not ixazomib. Additional safety analyses by subgroups such as drug indication and baseline characteristics may be performed, as specified in the SAP.

Sample Size Justification: There is no statistical hypothesis and no power considerations in this study.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the vendor contact information. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 List of Abbreviations

AE	adverse event
AL amyloidosis	systemic light-chain amyloidosis
ASCT	autologous stem cell transplant
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BUN	blood urea nitrogen
BSA	body surface area
CO_2	carbon dioxide
eCRF	case report form (electronic or paper)
CRO	contract research organization
CYP	cytochrome P-450
ECG	electrocardiogram
EOS	end of study
EOT	end of treatment
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
LDH	lactate dehydrogenase
LenDex	lenalidomide plus dexamethasone
MedDRA	Medical Dictionary for Regulatory Activities
MLN2238	research name for ixazomib, the biologically active boronic acid form of the drug substance

MLN9708	research name for ixazomib citrate, the stable citrate ester of ixazomib
MM	multiple myeloma
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDMM	newly diagnosed multiple myeloma
RRAL amyloidosis	relapsed and/or refractory systemic light-chain amyloidosis
RRMM	relapsed and/or refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
US	United States
USPI	United States Prescribing Information

4.0 INTRODUCTION

4.1 Background

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

Oral ixazomib in combination with lenalidomide and dexamethasone was first approved by the United States (US) Food and Drug Administration (FDA) in November 2015 for the treatment of patients with MM who have received at least 1 prior therapy [3,4]. It has since been approved in over 65 countries globally.

Ixazomib (MLN2238) refers to the biologically active boronic acid form of the drug substance. The drug substance is administered as a stable citrate ester, designated as ixazomib citrate (MLN9708). Under physiological conditions, ixazomib citrate rapidly hydrolyzes to the biologically active boronic acid, ixazomib. Ixazomib is a peptide boronic acid that is structurally different from bortezomib.

Detailed information regarding the nonclinical pharmacology and toxicology of MLN9708 may be found in the ixazomib IB.

Phase 1, phase 1/2, and phase 2 trials have been conducted in MM, relapsed and/or refractory systemic light-chain amyloidosis (RRAL), solid tumors, and lymphoma. In addition, phase 1 studies were conducted in patients with renal impairment who had relapsed and/or refractory multiple myeloma (RRMM) or advanced solid tumors (Study C16015), in patients with hepatic impairment who had advanced solid tumors or hematologic malignancies (Study C16018), and in an absorption, distribution, metabolism, and excretion study in patients with advanced solid tumors or lymphoma (Study C16016). Phase 3 trials in RRMM (C16010), newly diagnosed multiple myeloma (NDMM) (C16014), and RRAL (C16011) have additionally been completed. Phase 3 trials of ixazomib as maintenance therapy following autologous stem cell transplantation (C16019) or in patients who did not receive ASCT (C16021) are ongoing.

Ixazomib had been available as an IV and oral formulation (during the early development of ixazomib); however, only the oral formulation is currently being developed for commercialization. Regardless of the route of administration, in the twice-weekly dosing schedule, ixazomib is given on Days 1, 4, 8, and 11 of a 21-day cycle, and in the weekly dosing schedule, ixazomib is given on Days 1, 8, and 15 of a 28-day cycle. Schedules with longer cycles are being investigated in Study C16006.

The following oncology indications have been studied during the clinical development of ixazomib: RRMM, NDMM, RRAL, advanced solid tumors, advanced lymphoma, and pediatric acute lymphoblastic leukemia. Studies are investigating both single-agent ixazomib and ixazomib in combination with standard treatments.

Further details on these studies are provided in the ixazomib IB.

4.1.1 Risk: Benefit Assessment

4.1.1.1 Risks

The risks (identified and potential) have been assessed in clinical and nonclinical studies and are detailed in the current version of the IB. The emerging safety profile indicates that oral ixazomib is generally well tolerated and, while some potential toxicities may be severe, the predominant toxicities are largely reversible, able to be monitored by routine clinical examination, and manageable by dose reductions, discontinuation, or standard supportive care. It is possible that ixazomib will have toxicities that were not predicted from its evaluation in nonclinical studies or previously observed in ongoing clinical studies. To mitigate the inherent risks in clinical studies of ixazomib, patients are monitored closely for anticipated toxicities. Guidance for the management of adverse events (AEs) and procedures for reducing doses are provided (see Section 8.3 and Section 8.7), and drug dosage can be reduced either by decreasing the dose administered or by interruption of the scheduled treatment. Further information is provided in the IB.

Risks associated with ixazomib therapy have been identified from ongoing clinical studies as well as the registrational trial of ixazomib plus lenalidomide and dexamethasone in the treatment of patients with MM who have received at least 1 prior therapy (see the current IB and the United States Prescribing Information (USPI) for further information). These include blood and lymphatic system disorders (thrombocytopenia, neutropenia and anemia [all reversible]), gastrointestinal toxicities (diarrhea, nausea, vomiting, and constipation), general disorders (fatigue, peripheral edema, and pyrexia), metabolism and nutrition disorders (decreased appetite), nervous system disorders (dizziness, dysgeusia, peripheral neuropathy [generally Grades 1 or 2]), psychiatric disorders (insomnia), skin and subcutaneous tissue disorders (rash [very common], severe dermal events [rare]).

Refer to the current IB for the list of potential risks of ixazomib.

4.1.1.2 Benefits

Ixazomib in combination with lenalidomide and dexamethasone was approved by the US FDA in November 2015 for the treatment of patients with MM who have received at least 1 prior therapy [3,4]. The exploration of other therapeutic areas is ongoing. To date, activity in MM has been seen with single-agent ixazomib and with ixazomib combined with established therapies. In addition, single-agent activity has been observed in relapsed amyloidosis and indolent non-Hodgkin lymphoma. This study will provide continued access to ixazomib and/or other combinational study drugs from the designated ixazomib parent protocols when the patient has no other means to access study treatment. Qualified patients who have been deriving benefit in an ixazomib parent protocol will receive treatment in this study until they are transitioned to ixazomib/other therapy through commercial channels or until any of the other reasons for treatment discontinuation are met, whichever is sooner. Based on approval by the Takeda medical monitor every 24 months, continued access to ixazomib and/or other study drugs will be allowed for patients who in the investigator's opinion are deriving clinical benefit.

4.2 Rationale for the Proposed Study

The primary purpose of this rollover study is to continue to provide ixazomib and/or other combinational study drugs to patients who have previously received and tolerated treatment in an ixazomib parent study, and in the investigator's opinion may benefit from continued therapy with 1 or more of the drugs from the parent protocol (eg, patient demonstrates response to therapy or stable disease without evidence of disease progression). The study will also evaluate the long-term safety profile of ixazomib in those patients who continue to receive ixazomib.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

The primary objectives are:

- To provide continued access to ixazomib and/or other study drugs from an ixazomib parent study.
- To evaluate the long-term safety profile of ixazomib.

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint is safety of ixazomib, as assessed by the incidence of the following AEs:

- All serious adverse events (SAEs).
- All ≥Grade 3 AEs.
- ≥Grade 2 peripheral neuropathy.
- New primary malignancies.
- Any AE resulting in dose modification or discontinuation of any study drug.
- Any other AE that in the opinion of the investigator is a clinically significant event.

6.0 STUDY DESIGN

6.1 Overview of Study Design

This is an open-label, multicenter, rollover study to provide continued access to ixazomib and/or other study drugs from a designated ixazomib parent study (ie, Studies C16003, C16005, C16006, C16007, C16008, C16010 Global, C16011, C16013, C16014 Global and Korean Continuation, C16017, C16020, C16029, and C16047) when the patient has no other means to access study treatment. The study will also evaluate the long-term safety profile of ixazomib in those patients who continue to receive ixazomib. The patient population will consist of patients who have

previously received and tolerated treatment in a Takeda-sponsored clinical study of ixazomib, and in the investigator's opinion and approved by the Takeda medical monitor, may benefit from continued therapy with 1 or more of the drugs from a parent protocol (eg, patient demonstrates response to therapy or stable disease without evidence of disease progression).

Patients may be enrolled provided they have not met any of the discontinuation criteria in their parent study. Patients will enter this study on the same ixazomib dose, schedule of study drug(s), and combination regimen that they were receiving at the time of rollover from the parent study, or according to the required dose modification from a parent study (Section 8.1). For those patients who received ixazomib dosing based on BSA per the parent study, the dose may be rounded. The dose may also be rounded for those patients who convert from BSA-based dosing to fixed dosing with approval from the Medical Monitor. No new anticancer agents can be started or added. Note that for patients whose study therapy in a parent study includes a placebo, the placebo capsule will be discontinued; crossover to ixazomib is not permitted.

Following enrollment, patients may receive study drug(s) until they experience disease progression, clinical deterioration in the investigator's judgment, experience an unacceptable toxicity, withdraw consent, pursue an alternative therapy, meet other study-specified reasons for discontinuation of study drug, or until the patient is transitioned to ixazomib/other therapy through commercial channels.

Patients participating in a designated ixazomib parent study will enter the rollover study at the time-point when they have completed the EOT visit in the parent study and when the rollover study is active at an investigative site. Following their provision of informed consent to receive treatment in the rollover study, patients will be provided with study medication. Patients should enter the study within 8 weeks of their last dose of ixazomib/other study drug(s) in the parent study or as agreed upon by the Takeda clinician/designee so to minimize any treatment disruption to the patient. Local safety-related laboratory evaluations and vital sign measurements will be performed according to the schedule of events as presented in this study and accordingly will only be recorded in the electronic case report forms (eCRF) prior to the first dose of study drug in the rollover study, at the end of study, and as spontaneously reported by the investigator. Electrocardiogram (ECG) assessments will only be performed as clinically indicated. During treatment, dosing modification decisions will be made per the parent study. For patients receiving ixazomib, systemic treatment with strong cytochrome P-450 (CYP)3A inducers (rifabutin, carbamazepine, phenytoin, phenobarbital), or use of St. John's wort) is prohibited during the study. The procedures prohibited in the patient's parent study are prohibited during this study. Prohibited medications due to co-administration of other agents in the ixazomib regimen are prohibited as per the prescribing information for the co-administered agent(s).

It is recommended that disease assessments are performed per standard of care.

At the time of discontinuation of study drug(s) in this study, an end-of-study (EOS) visit will be scheduled and will occur prior to the initiation of any new therapy, or within 30 days of last dose of study drug administration, whichever is earlier. The reason for treatment discontinuation, an overall investigator assessment of best response obtained during this rollover study, and the investigator assessment of date of progression will be captured in the eCRFs.

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0, effective date 27 November 2017 [1].

The long-term safety and tolerability of ixazomib/other study drug(s) will be monitored. The following AEs will be reported from the first dose of study drug in this study through 30 days after administration of the last dose of study drug and recorded in the eCRFs and SAEs will also be reported directly to the Sponsor (see Section 10.2). The following AEs that are ongoing at the time of entry into the rollover study will be recorded in the eCRFs as baseline AEs.

- All SAEs.
- All ≥Grade 3 AEs.
- ≥Grade 2 peripheral neuropathy.
- New primary malignancies.
- Any AE resulting in dose modification or discontinuation of any study drug.
- Any other AE that in the opinion of the investigator is a clinically significant event.

The above AEs will be followed until resolution, until the AE becomes chronic or stable, or is determined to be part of the underlying disease process, or until the patient attends the EOS visit and discontinues the study.

The transfer of patients between sites is allowed with the approval of the sponsor's clinician/designee (eg, in the case of site closure, patient moving, etc).

6.2 Number of Patients

The estimated number of patients to be enrolled is approximately 250. The number of countries and sites is not currently specified as this study is open to all countries and sites with qualifying patients from prior company-sponsored ixazomib studies.

Enrollment is defined as when the patient receives the first dose of study drug in this rollover study.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

The anticipated duration of treatment for an individual patient in this rollover study will be approximately 5 years. Based on approval by the Takeda medical monitor every 24 months, continued access to ixazomib and/or other study drugs will be allowed for patients who in the investigator's opinion are deriving clinical benefit. Patients may remain in the rollover study until they are transitioned to ixazomib/other therapy through commercial channels or until any of the other reasons for treatment discontinuation are met, whichever is sooner.

Patients will be followed for 30 days after the last dose of study drug(s).

Ongoing AEs meeting the criteria in Section 10.2 will be followed until resolution, until the AE becomes chronic or stable or is determined to be part of the underlying disease process, or until the patient attends the EOS visit and discontinues the study.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

Primary Completion/Study Completion

The estimated time frame for study completion (first patient in to last patient last visit) is approximately 7 years.

The final analyses for the primary endpoint and single final clinical study report will be conducted following the end of the study.

6.3.3 Timeframe for Primary Endpoint to Support Disclosures

Please refer to Table 6.a for disclosures information for the primary endpoint.

Table 6.a Primary Endpoint for Disclosures

Endpoint	Maximum Time Frame
Primary: The incidence of the following AEs: • All SAEs. • All ≥Grade 3 AEs. • ≥Grade 2 peripheral neuropathy. • New primary malignancies. • Any AE resulting in dose modification or discontinuation of any study drug. • Any other AE that in the opinion of the investigator is a clinically significant event.	Approximately 5 years of treatment with study drug(s) for an individual patient in this study. Overall, assessment of the primary endpoint will be approximately 7 years after the first patient is enrolled in the study.

AE=adverse event; SAE=serious adverse event.

6.3.4 Total Study Duration

It is anticipated that this study will last for approximately 7 years.

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. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care. Patients should consent and enter the study within a maximum of 8 weeks of their last dose of treatment in the parent study or as agreed by the Takeda clinician/designee.

2. Previously treated with ixazomib, background therapy, and/or comparator drugs (including placebo) in a Takeda-sponsored ixazomib parent study. Patients will be eligible to enter the rollover study when:
   a) The parent study is closed or planned to be closed; and
   b) The patient is on ixazomib monotherapy, a combination regimen with ixazomib and other study medication(s), on a placebo combination, or on an alternative arm regimen in a designated ixazomib parent study (ie, Studies C16003, C16005, C16006, C16007, C16008, C16010 Global, C16011, C16013, C16014 Global and Korean Continuation, C16017, C16020, C16029, and C16047); and
   c) In the opinion of the investigator and approved by the Takeda medical monitor, the patient may continue to benefit from treatment with ixazomib and/or another study drug/combination regimen (eg, response to therapy or stable disease without evidence of disease progression) and has no alternate means to access the study drug(s) (eg, commercial supply).
3. Agree to continue to practice contraceptive methods as outlined in the parent study. See Appendix D for acceptable methods of contraception.

7.2 Exclusion Criteria

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

1. The patient meets any of the criteria for treatment discontinuation in the parent study.
2. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the eligibility period.

8.0 STUDY DRUG

8.1 Study Drug Administration

All study-specific criteria for administration of study drug must be met and documented prior to drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

Ixazomib, as a single agent or in combination with other study drugs, will be administered according to the dose, schedule, and combination regimen the patient was receiving at the time of rollover from the parent study, or according to the required dose modification from a parent study. For those patients who received ixazomib based on BSA dosing per the parent study, the dose may be rounded. The dose may also be rounded for those patients who convert from BSA-based dosing to fixed dosing with approval from the Medical Monitor. No new anticancer agents can be started or added. Note that for patients whose study therapy in a parent study includes a placebo, the placebo capsule will be discontinued; crossover to ixazomib is not permitted.

Patients will be given ixazomib as a single, oral dose on a 21- or 28-day cycle according to the parent protocol. Patients should be instructed to swallow ixazomib capsules whole with water and

to not break, chew, or open the capsules. Ixazomib should be taken on an empty stomach at least 1 hour before or no sooner than 2 hours after a meal. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 oz (240 mL) of water should be taken with the capsules.

Missed doses can be taken as soon as the patient remembers if 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.

8.2 Reference/Control Therapy

Patients whose study treatment in a parent study includes a placebo will discontinue the placebo capsule when they enter this study. Other study medication(s)/alternative arm therapies administered during the parent protocol will be continued according to the dose, schedule, and regimen the patient was receiving at the time of rollover from the parent study, or according to the required dose modification from a parent study.

8.3 Dose Modification Guidelines

Toxicity will be evaluated according to NCI CTCAE, Version 5.0, effective date 27 November 2017 [1].

Dose modifications for the management of AEs will be made according to the parent study.

8.4 Excluded Concomitant Medications and Procedures

The following medications are prohibited during this study:

- For patients receiving ixazomib, systemic treatment with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of St. John's wort.

The procedures prohibited in the patient's parent study are prohibited during this study. Prohibited medications due to co-administration of other agents are prohibited as per the prescribing information for the co-administered agent(s).

8.5 Permitted Concomitant Medications and Procedures

All necessary supportive care consistent with optimal patient care shall be available to patients as needed.

8.6 Precautions and Restrictions

It is not known what effects ixazomib has on human pregnancy or development of the embryo or fetus. Pregnancy prevention measures as per the patient's parent study should continue to be used. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified in the parent study.

8.7 Management of Clinical Events

8.7.1 Management of Ixazomib Clinical Events

Prophylaxis Against Risk of Reactivation of Herpes Infection

Patients may be at an increased risk of infection, including reactivation of herpes zoster and herpes simplex viruses. All patients continuing to receive ixazomib in this rollover study should receive prophylactic antiviral therapy. Patients receiving a non-ixazomib-containing regimen should be guided by the physician's clinical practice.

Nausea or Vomiting

Prophylaxis with standard antiemetics, including serotonin 5-hydroxytryptamine 3 receptor antagonists, is recommended for emesis. Any fluid deficit occurring during treatment should be promptly corrected.

Diarrhea

Diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Any fluid deficit occurring during treatment should be promptly corrected.

Erythematous Rash With or Without Pruritus

Rash may range from limited erythematous areas, macular or small papular bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominantly on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash is most commonly reported within the first 3 cycles of therapy. The rash is often transient and self-limiting and is typically Grade 1 or 2 in severity. If rash occurs, consideration should be given to alternate causes of the rash such as concomitant medications, infections, etc; these other causative agents should be discontinued and alterative agents considered if medically necessary.

Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (eg, prednisone $\leq$ 10 mg per day or equivalent) is permitted.

Management of a Grade 3 rash may require IV antihistamines or corticosteroids. Administration of ixazomib (and other causative agent if given in combination) should be modified and re-initiated at a reduced level from where rash was noted (per parent study). In line with clinical practice, dermatology consult and biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a patient has previously developed a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body or oral or topical antihistamines).

The rare risks of Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), and pemphigus vulgaris have been reported in oncology studies when ixazomib (or placebo) was given with concomitant medications

that are known to cause rash (eg, Bactrim, lenalidomide, aspirin), and/or in the setting of confounding treatment-emergent AEs. These severe, potentially life-threatening or deadly conditions may involve rash with skin peeling and mouth sores and should be clinically managed according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator. Study medications should be discontinued in the event of severe, potentially life-threatening rash. Additional information regarding these reactions can be found in the IB.

Thrombocytopenia

Blood counts should be monitored regularly according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib administration should be modified according to dose modification recommendations in the parent study when thrombocytopenia occurs. Therapy can be reinitiated at a reduced level upon recovery of platelet counts. Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenia purpura and hemolytic uremic syndrome, are rare, serious blood disorders that cause low levels of platelets and red blood cells and result in blood clots in small blood vessels. Symptoms may include fatigue, fever, bruising, nose bleeds, and decreased urination. These disorders, including fatal cases, have been reported in patients receiving ixazomib. If TMA is suspected, consider withdrawal of the suspected causative agent and manage according to standard medical practice.

Neutropenia

Blood counts should be monitored regularly with additional testing, as appropriate, according to standard clinical practice. Neutropenia may be severe but has been manageable. Growth factor support is not required but may be considered according to standard clinical practice. Ixazomib administration should be modified according to dose modification recommendations in the parent study when neutropenia occurs. Therapy can be reinitiated at a reduced level upon recovery of absolute neutrophil count (ANC).

Fluid Deficit

Dehydration should be avoided because ixazomib may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported in patients treated with ixazomib, commonly in the setting of the previously noted gastrointestinal toxicities and dehydration.

Fluid deficit should be promptly corrected before administration of study drug and as needed during treatment to avoid dehydration.

Hypotension

Symptomatic hypotension and orthostatic hypotension with or without syncope have been reported with ixazomib. Blood pressure should be closely monitored as per standard of care while the patient is on study treatment, and fluid deficit should be corrected as needed, especially in the setting of concomitant symptoms such as nausea, vomiting, diarrhea, or decreased appetite. Patients taking medications or diuretics to manage their blood pressure (for either hypotension or hypertension) should be managed according to standard clinical practice, including considerations

for dose adjustments of their concomitant medications during the course of the trial. Fluid deficit should be corrected before administration of study drug and as needed during treatment to avoid dehydration.

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome, which ultimately resolved, has been reported with ixazomib. This condition is usually transient and reversible. It is characterized by headache, seizures, and visual loss, and abrupt increase in blood pressure. Diagnosis may be confirmed by magnetic resonance imaging or computed tomography. If the syndrome is diagnosed or suspected, symptom-directed treatment should be maintained until the condition is reversed by control of hypertension or other instigating factors.

Transverse Myelitis

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

Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. Overdose has been reported in patients taking ixazomib. Symptoms of overdose are generally consistent with the known risks of ixazomib. Reports of accidental overdose have been associated with serious adverse events, such as nausea, lung infections including aspiration pneumonia, multiple organ failure, and death. If overdose occurs, consider close observation including hospitalization for hemodynamic support. Gastric lavage may be considered if instituted within 1 hour of ingestion of ixazomib overdose.

AEs associated with an overdose will be documented on AE eCRF according to Section 10.0, Adverse Events. SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2, Collection and Reporting of SAEs.

8.7.2 Management of Combination Therapy Clinical Events

For each medication(s) used as combination therapy with or without ixazomib, please refer to the prescribing information and details in the parent protocol for the applicable management of clinical events.

8.8 Blinding and Unblinding

This is an open-label study.

8.9 Description of Investigational Agents

The ixazomib capsule formulation consists of the drug substance (ixazomib citrate), microcrystalline cellulose, talc, and magnesium stearate. There are 7 capsule strengths: 0.2, 0.5,

2.0, 2.3, 3.0, 4.0, and 5.5 mg. Each strength is differentiated by a unique capsule size and color. Dosage strength is stated as ixazomib. Ixazomib capsules are individually packaged in blisters.

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

8.10 Preparation, Reconstitution, and Dispensation

The 0.2, 0.5, and 2.0 mg ixazomib capsules (B1 formulation) are supplied in 1×4 blister strips that are individually perforated. The strips are placed in cartons containing 6 strips (24 total capsules) of the same strength.

The 2.3, 3.0, 4.0, and 5.5 mg ixazomib capsules (B2 formulation) are individually packaged using cold form foil-foil blisters that are in a child-resistant carton. There are 3 capsules (of exact strength) in each carton.

8.11 Packaging and Labeling

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

8.12 Storage, Handling, and Accountability

On receipt at the investigative site, ixazomib should remain in the blister pack and carton provided until use or dispensation. The container should be stored as directed by the label on the packaging. All excursions should immediately be brought to the sponsor's attention for assessment and authorization for continued use. Ensure that the drug is used before the retest expiry date provided by Takeda. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

Ixazomib dispensed to the patient for take-home dosing should remain in the blister packaging and carton and stored as directed by the label on the packaging as noted previously until the point of use. Patients who are receiving take-home medication should be given a supply of study drug as per the parent study schedule or for up to 3 cycles at the discretion of the investigator. (Note: Patients in France are only permitted to receive 1 cycle of medication at a time). In case of the COVID-19 pandemic preventing a patient from attending the study site, sites may use alternative strategies to deliver study drug to patients (eg, via courier or site staff), per local standard practice and regulations and with prior approval from the investigator and the sponsor's project clinician/designee. Comprehensive instructions should be provided to the patient to ensure compliance with, and understanding of, dosing procedures and to avoid the potential for incorrect self-administration or overdose of medication.

Patients should be instructed to store the medication as directed by the label on the packaging. Patients should be instructed to return their empty or partially used cartons to the investigative site at their next visit, rather than discarding them, as permitted by site policy. Reconciliation will occur accordingly when the patient returns at their next visit for take-home medication. In case of the COVID-19 pandemic preventing a patient from attending the study site, drug packs and dosing

diaries should be returned at the next available on-site clinic visit. Any excursions in temperature should be reported and dealt with on a case-by-case basis.

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

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

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

Please refer to the Pharmacy Manual for this study for additional instructions.

8.13 Combination Therapy

Patients who entered the study receiving a combination therapy with ixazomib or with other study medications will continue to receive the combination regimen.

The medication(s) used in combination with ixazomib or the control arm treatments may be site-sourced from commercial supply with commercial packaging and labeling when arrangements have been made and agreed to by Takeda and the clinical site and when regulations allow for clinical site sourcing, appropriate labeling, and compliance with local and regional regulations. The medication(s) may be provided by the sponsor if the site is unable to obtain these drugs from commercial sources.

Additional details are provided in the package insert (PI) /summary of product characteristics (SmPC) for the applicable medication(s) used in the parent study.

8.14 Other Protocol-Specified Materials

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

9.0 STUDY CONDUCT

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

9.1 Study Personnel and Organizations

The contact information for the Medical Monitor for this study, and any additional clinical laboratories, the coordinating investigator for each member state/country, and other vendors as necessary, such as the interactive voice response system (IVRS)/interactive web response system (IWRS) provider, and the contract research organization (CRO) team may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

9.2 Arrangements for Recruitment of Patients

Patients will only be considered for this study if they were enrolled in 1 of the parent studies. The transfer of patients between sites is allowed with the approval of the sponsor's clinician/designee (eg, in the case of site closure, patient moving, etc). No additional recruitment activity is needed.

9.3 Treatment Group Assignments

Patients will enter this study on the same dose, schedule of study drug(s), and combination regimen that they were receiving at the time of rollover from the parent study (Section 8.1), or according to the required dose modification from a parent study. For those patients who received ixazomib based on BSA dosing per the parent study, the dose may be rounded. The dose may also be rounded for those patients who convert from BSA-based dosing to fixed dosing with approval from the Medical Monitor. No new anticancer agents can be started or added. Note that for patients whose study therapy in a parent study includes a placebo, the placebo capsule will be discontinued; crossover to ixazomib is not permitted.

9.4 Study Procedures

In acknowledgement of hospital, local, state or national government restrictions, or other site-related factors caused by the COVID-19 pandemic that may prevent investigators from conducting the study according to the Schedule of Events at the clinical study site, investigators may continue patients in the study despite departure from the Schedule of Events. Investigators are expected to evaluate the impact to the safety of the study participants and site personnel for patients to continue. In evaluating such requests, the investigator/study site staff will give the highest priority to the safety and welfare of the patients. Patients must be willing and able to continue taking study medication and remain compliant with the protocol. For patients that are impacted by the COVID-19 pandemic, any procedures not conducted per the study protocol will be documented in the eCRF.

Alternative methods should be considered for performing the assessments by other means than the patient presenting to the clinic (eg, remote assessment, having lab assessment performed at a facility closer to the patient's home, etc.) If a patient misses an in-person study visit, the investigator/study team staff will speak directly with the patient by telephone or other medium (eg, a computer-based video communication) during each visit window to assess subject safety and overall clinical status. During this contact with the patient, the study site physician or other qualified site staff should at minimum conduct AE collection and an assessment of clinical symptoms. Other study assessments may be collected remotely as is feasible and may involve

audio or video recording. Assessments/procedures that cannot be completed during the protocol-specified window because a site visit is done remotely (eg, hematology, clinical chemistry, concomitant medications/procedures) are waived.

Refer to the Schedule of Events (Appendix A) for timing of assessments. Procedures performed at the end of treatment (EOT)/EOS in the patient's parent study and collected in the eCRFs within 28 days of the study entry/Day 1 visit do not need to be repeated.

Additional details are provided as necessary in the sections that follow.

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.

Patients previously enrolled in this study who remain on study treatment upon implementation of Amendment 3 may need to be reconsented, according to IRB/IEC standards. Reconsenting should be done in person, where possible. Remote reconsenting is permitted as long as the process adheres to site, IRB/IEC, and GCP standards and local regulations.

9.4.2 Vital Signs

Vital sign measurements include measurements of diastolic and systolic blood pressure and heart rate.

9.4.3 Weight

Weight will be measured at the Study Entry/ Day 1 visit and at the EOS visit.

9.4.4 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at the Study Entry/ Day 1 visit before the first dose of study drug and at the EOS visit. The serum pregnancy test may be completed within 28 days of the Study Entry/Day 1 Visit. The results must be available and negative before the study drug regimen is administered. Pregnancy tests may also be repeated during the study if requested by an independent ethics committee (IEC)/institutional review board (IRB) or if required by local regulations or the prescribing information for any medication(s) used as combination therapy with ixazomib.

Pregnancy prevention measures as per the parent study should continue to be used.

9.4.5 Concomitant Medications and Procedures

Only concomitant medications and therapeutic procedures related to the treatment of AEs that are reported in the study eCRFs (see Section 10.2) will be recorded in the eCRFs as specified in the Schedule of Events Appendix A. See Section 8.4 and Section 8.5 for a list of medications and therapies that are prohibited and/or allowed during the study.

9.4.6 Adverse Events

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

SAEs, ≥Grade 3 AEs, ≥Grade 2 peripheral neuropathy, new primary malignancies, any AE resulting in dose modification or discontinuation of any study drug, or any other AE that in the opinion of the investigator is a clinically significant event will be recorded in the eCRFs and SAEs will also be reported directly to the sponsor (see Section 10.2). The AEs meeting the definitions above that are ongoing at the time of entry into the rollover study will be recorded in the eCRFs as baseline AEs.

9.4.7 Enrollment

A patient is considered to be enrolled in the study when he/she has received the first dose of study drug in this rollover study.

Procedures for completion of the enrollment information are described in the Study Manual.

9.4.8 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Local laboratory normal ranges will be entered in the eCRFs.

9.4.8.1 Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the clinical chemistry and hematological parameters shown in Table 9.a will be obtained and recorded in the eCRFs as specified in the Schedule of Events Appendix A.

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	Serum Chemistry	
Hematocrit	Albumin	Chloride
Hemoglobin	Alkaline phosphatase (ALP)	Gamma glutamyl transferase (GGT)
Leukocytes with differential	Alanine aminotransferase (ALT)	Glucose
Neutrophils ANC	Aspartate aminotransferase (AST)	Lactate dehydrogenase (LDH)
Platelet (count)	Bilirubin (total)	Magnesium
	Blood urea nitrogen (BUN)	Phosphate
	Calcium	Potassium
	Carbon dioxide (CO_2)[a]	Sodium
	Creatinine	Urate

[a]If CO_2 is not done as a part of standard care in the participant's region, then this test does not need to be performed.

9.4.9 Disease Assessment

It is recommended that disease assessments are performed per standard of care. An overall investigator assessment of best response obtained during this rollover study and the investigator assessment of date of progression will be recorded in the eCRF at the EOS visit.

9.5 Completion of Study (for Individual Patients)

Patients will be considered to have completed the study if they are discontinued from study treatment for any reason.

9.6 Withdrawal of Patients From Study

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

- Progressive disease (as defined in the patient's parent study).
- Pregnancy.
- Transition to commercial supply of study drug(s).
- Study terminated by sponsor.
- Withdrawal by subject.
- Lost to follow-up.
- Death.

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

- Adverse event.
- Protocol deviation.
- Clinical deterioration, in the investigator's opinion.
- Investigator's decision.
- 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.

9.7 Study Compliance

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

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Event Definition

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

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

10.1.2 Serious Adverse Event Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 5.0, effective date 27 November 2017 [1]. Clarification should be made

between an SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

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

The following 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).

- All SAEs (see Section 10.1.2).
- All ≥Grade 3 AEs (see Section 10.1.2).
- ≥Grade 2 peripheral neuropathy.
- New primary malignancies.
- Any AE resulting in dose modification or discontinuation of any study drug.
- Any other AE that in the opinion of the investigator is a clinically significant event.

Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE, but should only be recorded in eCRF if meeting any of the above criteria. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Takeda, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

The paper SAE forms must be submitted via fax (see fax numbers below) within 24 hours of awareness. In case of fax, site personnel must confirm successful transmission of all pages and include an e-mail address on the fax cover sheet so that an acknowledgment of receipt can be returned via e-mail within 1 business day. E-mail submission of paper SAE forms with a PDF attachment should only be used in the case where fax is not possible within 24 hours of receiving

the event. In case of e-mail, site personnel must confirm successful transmission by awaiting an acknowledgment of the receipt via e-mail within 1 business day. If SAEs are reported via fax or by e-mail, the EDC application must be updated as soon as possible with the appropriate information.

SAE Reporting Contact Information

Cognizant

US and Canada

Toll-Free Fax #: 1-800-963-6290

E-mail: takedaoncocases@cognizant.com

All Other Countries (Rest of World)

Fax #: 1-202-315-3560

E-mail: takedaoncocases@cognizant.com

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

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug administration.

Severity (toxicity grade) for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE, Version 5.0, effective date 27 November 2017 [1]. The criteria are provided in the Study Manual.

Relationship of the event to study drug 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 drug?"

10.3 Monitoring of Adverse Events and Period of Observation

AEs meeting the criteria in Section 10.2 must be reported to the sponsor as follows:

- AEs will be reported from the first dose of study drug for this study through 30 days after administration of the last dose of study drug and recorded in the eCRFs. AEs meeting the criteria in Section 10.2 that are ongoing at the time of entry into the rollover study will be recorded in the eCRFs as baseline AEs.
- AEs meeting the criteria in Section 10.2 will be followed until resolution, until the AE becomes chronic or stable, or is determined to be part of the underlying disease process, or until the patient attends the EOS visit and discontinues the study.

- SAEs
  - Related and unrelated treatment-emergent SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

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

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

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

A product complaint is 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 to: ctmcomplaint@takeda.com.

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

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this to Cognizant (refer to Section 10.2).

10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events

and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

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 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 signs an informed consent form.

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

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

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

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

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

12.2 Record Retention

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

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

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.

13.1.1 Analysis Sets

The full analysis set (FAS) will included all enrolled patients who receive at least 1 dose of study medication and will be used for the safety analyses.

13.1.2 Efficacy Analysis

No efficacy analyses are planned for this study as there is no statistical hypothesis testing.

The overall investigator assessment of best response obtained during this rollover study and investigator assessment of date of progression will be listed.

13.1.3 Safety Analysis

The following AEs will be summarized with descriptive statistics for all patients who receive at least 1 dose of ixazomib using the FAS:

- All SAEs.
- All ≥Grade 3 AEs.
- ≥Grade 2 peripheral neuropathy.
- New primary malignancies.
- Any AE resulting in dose modification or discontinuation of any study drug.
- Any other AE that in the opinion of the investigator is a clinically significant event.

No formal statistical testing or inferential statistics will be generated.

All AEs will be coded using the current MedDRA version at the time of the analysis. Data will be summarized using preferred term and primary system organ class. Local laboratory assessment changes and vital sign changes from study entry to end of study will also be summarized.

Exposure to study drug and study regimen will be tabulated. In addition, reasons for drug discontinuation will be summarized.

Concomitant medications and procedures related to treatment of AEs from screening through the end of study will be classified by generic terms according to the WHO drug dictionary.

Data will be presented by the entire ixazomib safety population, by population of monotherapy of ixazomib, and by population of ixazomib in combination with other anticancer agents(s) as specified in the SAP. Safety listings will be prepared for patients receiving other study drugs and not ixazomib. Additional safety analyses by subgroups such as drug indication and baseline characteristics may be performed as specified in the SAP.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

There is no statistical hypothesis and no power considerations in this study. The number of patients will be determined as discussed in Section 6.2.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

The study site will be monitored remotely by the CRO periodically during the study to ensure that all aspects of the protocol are followed. Monitoring will include electronic data collection, which has a set of automatic data checks with data queries for programmed data collection. There will be

monitoring of study site by telephone and email to ensure that the drug supplies have been provided to the site and patients and that protocol instructions are well understood and applied.

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

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches such as remote source data verification (SDV) or telephone contact may be used to ensure data quality and integrity and maintain patient safety. Alternative monitoring approaches should be used only where allowed by the local Health Authority and permitted by the IRB/IEC.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form or equivalent form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

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. The investigator agrees to provide access to records, facilities, and personnel for conduct of any inspection or audit. If a quality assurance audit is requested, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and

Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the 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 or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives drug/notification no protocol activities, including screening may occur.

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

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

15.2 Subject Information, Informed Consent, and Subject Authorization

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

Patients previously enrolled in this study who remain on study treatment upon implementation of Amendment 3 may need to be reconsented, according to IRB/IEC standards. Reconsenting should be done in person, where possible. Remote reconsenting is permitted as long as the process adheres to site, IRB/IEC, and GCP standards and local regulations.

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

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

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

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

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

15.3 Subject Confidentiality

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

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

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

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

any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

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

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

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

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.

Data Sharing

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which may be unrelated to the study drug or the patient's disease. The data provided to external researchers will not include information that identifies patients personally.

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

1. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. November 2017.
2. VELCADE (bortezomib) for Injection, October [package insert]. Cambridge, MA: Millennium Pharmaceuticals, Inc., October 2012.
3. NINLARO® (ixazomib) capsules, for oral use [prescribing information]. Cambridge, MA: Takeda Pharmaceutical Company Limited.
4. Moreau P, Masszi T, Grzasko N, Bahlis NJ, Hansson M, Pour L, et al. Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. New England Journal of Medicine 2016;374(17):1621-34.

Appendix A Schedule of Events

Schedule Of Events (a)			
Tests and Observations	**Study Entry/ Day 1 Visit (a)**	**On Study Visits (b)**	**EOS (c)**
Informed Consent/ Reconsent (d)	X		
Inclusion/exclusion criteria	X		
Disease assessment (e)	X		X (f)
Vital signs (g)	X		X
Weight	X		X
Concomitant medications and procedures (h)	Record from first dose of study drug in this study through 30 days after the last dose of study drug		
Adverse event reporting (i)	Record from first dose of study drug in this study through 30 days after the last dose of study drug		
	Record **SAEs** from first dose of study drug in this study through 30 days after the last dose of study drug		
Samples/Laboratory Assessments			
Hematology (j)	X		X
Clinical chemistry (j)	X		X
Serum Pregnancy (β-hCG) (k)	X		X
Study drug(s) administration (l)	Continue regimen established in parent study		

Procedures performed at EOT/EOS in the patient's parent study and collected in the eCRFs within 28 days of the Study Entry/Day 1 visit do not need to be repeated.

Tests and procedures should be done on schedule, but visit windows of ±2 days are allowed (except as otherwise specified) occasionally for holidays, vacations, and other administrative reasons. If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled assessment within this time frame, the patient may continue in the study only with written permission from the Medical Monitor.

AE=adverse event; β-hCG=beta human chorionic gonadotropin; EOS=end of study; EOT=end of treatment; IEC=independent ethics committee; IRB=institutional review board; SAE=serious adverse event.

(a) Patients ending ixazomib treatment in the parent study and who are eligible and wish to rollover into this study should have their EOT/EOS procedures coincident with or as soon as possible after stopping therapy. The Study Entry/Day 1 visit for this rollover study should similarly be coincident with or as soon as possible after the EOT/EOS visit in the parent study. In order to avoid a hiatus in ixazomib therapy, the Study Entry/Day 1 visit will be no more than 8 weeks after the last visit in the parent study.

(b) The frequency of study visits is to occur as per the patient's parent study (eg, 21- or 28-day cycles). If more than 1 cycle of study drug is dispensed to a patient at a time, the frequency of study visits can occur at the discretion of the investigator. Unscheduled visits can occur at the investigator's discretion.

(c) The EOS visit will be conducted 30 (+10) days after the last dose of ixazomib.

(d) Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care. Patients previously enrolled in this study who remain on study treatment upon implementation of Amendment 3 may need to be reconsented, according to IRB/IEC standards. Reconsenting should be done in person, where possible. Remote reconsenting is permitted as long as the process adheres to site, sponsor, IRB/EC, regulatory, and GCP standards and local regulations.

(e) It is recommended that disease assessments are performed per standard of care.

(f) At EOS, record an overall investigator assessment of best response obtained during this rollover study and investigator assessment of date of progression.
(g) Vital sign measurements, which include measurements of diastolic and systolic blood pressure and heart rate, will be obtained at Study Entry/Day 1, EOS, and as medically needed at the discretion of investigator.
(h) Only concomitant medications and therapeutic procedures related to the treatment of AEs that are collected in the study (see Section 10.2), will be recorded in the eCRFs.
(i) This will included collection of the following:

- All SAEs.
- All ≥Grade 3 AEs.
- ≥Grade 2 peripheral neuropathy.
- New primary malignancies.
- Any AE resulting in dose modification or discontinuation of study drug.
- Any other AE that in the opinion of the investigator is a clinically significant event (see Section 10.2).

(j) For all patients, hematology and chemistry laboratory evaluations will be obtained at the Study Entry/Day 1 visit and at the EOS visit. Laboratory evaluations may be done within 4 weeks of the Study Entry/Day 1 visit. Unscheduled hematology and chemistry laboratory assessments may be performed if clinically indicated. Laboratory samples will be processed locally.
(k) A serum β-hCG pregnancy test will be performed only for women of childbearing potential. The serum pregnancy test may be completed within 28 days of the Study Entry /Day 1 visit. See Section 9.4.4 for additional details. Pregnancy tests may also be repeated during the study if required by an IEC/IRB or if required by local regulations.
(l) Study drug(s) will be administered at the dose, schedule of study drug(s), and combination regimen that they were receiving at the time of rollover from the parent study, or according to the required dose modification from a parent study. For those patients who received ixazomib dosing based on body surface area (BSA) per the parent study, the dose may be rounded. The dose may also be rounded for those patients who convert from BSA-based dosing to fixed dosing with approval from the Medical Monitor. No new anticancer agents can be started or added. Note that for patients whose study therapy in a parent study includes a placebo, the placebo capsule will be discontinued; crossover to ixazomib is not permitted. Patients will continue to receive study treatment until disease progression, occurrence of an unacceptable toxicity, and/or other criteria as detailed in Section 9.6). Ixazomib and/or other study drug(s) will be dispensed at each on-study visit (up to a 3-cycle supply to the patient [eg, 21- or 28-day cycles] at the discretion of the investigator. Note: patients in France are only permitted to receive 1 cycle of medication at a time). The study center staff will check the patient's supply of remaining ixazomib tablets at each on-study visit to ensure proper compliance with dosing.

Appendix B Responsibilities of the Investigator

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

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

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

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Investigator Consent to Use of Personal Information

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 and IECs.

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 Acceptable Methods of Contraception

The following information is based on (and in line with) the informed consent form for ixazomib.

Female patients: Unless the patient cannot have children because of surgery or other medical reasons (had an effective tubal ligation, had the ovaries or the uterus removed, or is postmenopausal), the patient must use 2 effective methods of birth control from the time of signing the informed consent form through the entire study drug treatment period (including interruptions in treatment) and for 90 days after completing study drug treatment. It is strongly recommended that at least 1 of these 2 methods be highly effective (see examples below).

Highly Effective Methods	Other Effective Methods (Barrier Methods)
Intrauterine devices	Latex or nonlatex condom with or without a spermicidal agent
Hormonal (birth control pills/oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants)	Diaphragm with spermicide; cervical cap with a spermicide; sponge with a spermicide
If one of the highly effective methods cannot be used, using 2 effective methods at the same time is recommended.	

The patient must use birth control methods as directed above, unless the patient completely avoids having heterosexual intercourse.

Male patients: We do not know if using ixazomib will affect sperm. Therefore, because of potential risk, the patient should not get a partner pregnant during the study drug treatment period (including interruptions in treatment). Even if the patient is surgically sterilized (ie, had a vasectomy), the patient must agree to use an appropriate method of barrier contraception (latex or nonlatex condom with or without a spermicidal agent) during the entire study drug treatment period and for 90 days after completing study drug treatment, or the patient should completely avoid having heterosexual intercourse.

Highly Effective Methods	Other Effective Methods (Barrier Methods)
Vasectomy	Latex or nonlatex condom with or without a spermicidal agent
	Diaphragm with spermicide; cervical cap with spermicide; sponge with spermicide
If one of the highly effective methods cannot be used, using 2 effective methods at the same time is recommended.	

All patients (male or female): If the patient or a partner becomes pregnant during this study, the patient must tell the study doctor immediately. The doctor will advise the patient of the possible risks to the unborn child and discuss options for managing the pregnancy with the patient. For female patients who become pregnant while on this study, the study drug will be stopped immediately, and the pregnancy will be followed until conclusion.

Appendix E Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment No. 03 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Updated the legal entity of the sponsor.

The primary change occurs on the cover page, in the Sponsor row:

Initial wording:	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited 40 Landsdowne Street Cambridge, MA USA 02139 Telephone: +1 (617) 679-7000 Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium," "Sponsor," or "Takeda".
Amended or new wording:	~~Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited~~ **Takeda Development Center Americas, Inc** ~~40 Landsdowne Street~~**95 Hayden Avenue** ~~Cambridge~~**Lexington**, MA ~~USA~~ 02139**421 USA** Telephone: +1 (617) 679-7000 ~~Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium," "Sponsor," or "Takeda".~~

Rationale for Change:

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

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
- Section 3.2 List of Abbreviations
- Section 3.3 Corporate Identification [removed]
- Section 4.1 Background
- Section 6.1 Overview of Study Design
- Section 6.3.1 Duration of an Individual Patient's Study Participation
- Section 7.1 Inclusion Criteria
- Section 8.11 Packaging and Labeling
- Section 8.12 Storage, Handling, and Accountability
- Section 8.13 Combination Therapy.

Change 2: Updated signatories for the study.

The primary change occurs in Section 1.2 Approval:

Description of change:	• Removed [redacted] and [redacted] as signatories. • Added [redacted] and [redacted] as signatories.

Rationale for Change:

To reflect the current Takeda personnel responsible for approving the protocol.

Change 3: Clarified that ixazomib and/or combinational study drugs from the designated parent protocols will be provided in this study until other means of accessing treatment are available; no new anticancer agents can be started or added; and for patients whose study therapy in a parent study includes placebo, the placebo capsule will be discontinued and crossover to ixazomib is not permitted.

The primary change occurs in Section 6.1 Overview of Study Design:

Initial wording:	This is an open-label, multicenter, rollover study to provide continued access to ixazomib and evaluation of the long-term safety profile of ixazomib. The patient population will consist of patients who have previously received and tolerated ixazomib in a Millennium-sponsored clinical study, and in the investigator's opinion and confirmed by the Millennium medical monitor, may benefit from continued ixazomib therapy (eg, patient demonstrates response to therapy or stable disease without evidence of disease progression). Patients may be enrolled provided they have not met any of the discontinuation criteria in the parent study. Patients will enter this study on the same ixazomib dose and

	schedule that they were receiving in the parent study (Section 8.1). For those patients who received ixazomib dosing based on BSA per the parent study, the dose may be rounded. The dose may also be rounded for those patients who convert from BSA-based dosing to fixed dosing with approval from the Medical Monitor. Patients who enter this study receiving a combination therapy with ixazomib and another medication(s) will continue to receive the combination regimen (which will be sourced locally) until there is a need to selectively discontinue the other medication(s) (eg, due to cumulative toxicity, product expiry, or other factors that limit availability from local sources). In that situation, the patient will continue to receive ixazomib without the discontinued agent(s), if, in the opinion of the investigator and with sponsor approval, it is likely that the patient will continue to derive benefit from single agent ixazomib; no new anticancer agents can be started or added. Patients receiving a combination of ixazomib and another medication(s) will be discontinued from this study when ixazomib therapy is discontinued. Following enrollment, patients may receive ixazomib until they experience disease progression, clinical deterioration in the investigator's judgment, experience an unacceptable toxicity, withdraw consent, pursue an alternative therapy, meet other study-specified reasons for discontinuation of study drug, or until ixazomib is available to the patient through commercial channels, including reimbursement for the patient's indication. Patients participating in eligible ixazomib parent studies will enter the rollover study at the time-point when the rollover study is active at an investigative site. Following their provision of informed consent to continue in the rollover study, patients will be provided with study medication. Patients should enter the study within 8 weeks of their last dose of ixazomib in the parent study or as agreed upon by the Millennium clinician/designee.
Amended or new wording:	This is an open-label, multicenter, rollover study to provide continued access to ixazomib and**/or other study drugs from a designated ixazomib parent study (ie, Studies C16003, C16005, C16006, C16007, C16008, C16010 Global, C16011, C16013, C16014 Global and Korean Continuation, C16017, C16020, C16029, and C16047) when the patient has no other means to access study treatment. The study will also** evaluati~~on~~**e** ~~of~~ the long-term safety profile of ixazomib **in those patients who continue to receive ixazomib**. The patient population will consist of patients who have previously received and tolerated ~~ixazomib~~**treatment** in a ~~Millennium~~**Takeda**-sponsored clinical study **of ixazomib**, and in the investigator's opinion and ~~confirmed~~**approved** by the ~~Millennium~~**Takeda** medical monitor, may benefit from continued ~~ixazomib~~ therapy **with 1 or more of the drugs from a parent protocol** (eg, patient demonstrates response to therapy or stable disease without evidence of disease progression). Patients may be enrolled provided they have not met any of the discontinuation criteria in ~~the~~**their** parent study. Patients will enter this study on the same ixazomib dose ~~and~~**,**

schedule **of study drug(s), and combination regimen** that they were receiving ~~in~~**at the time of rollover from** the parent **study, or according to the required dose modification from a parent** study (Section 8.1). For those patients who received ixazomib dosing based on BSA per the parent study, the dose may be rounded. The dose may also be rounded for those patients who convert from BSA-based dosing to fixed dosing with approval from the Medical Monitor. ~~Patients who enter this study receiving a combination therapy with ixazomib and another medication(s) will continue to receive the combination regimen (which will be sourced locally) until there is a need to selectively discontinue the other medication(s) (eg, due to cumulative toxicity, product expiry, or other factors that limit availability from local sources). In that situation, the patient will continue to receive ixazomib without the discontinued agent(s), if, in the opinion of the investigator and with sponsor approval, it is likely that the patient will continue to derive benefit from single agent ixazomib; no~~**No** new anticancer agents can be started or added. ~~Patients receiving a combination of ixazomib and another medication(s)~~**Note that for patients whose study therapy in a parent study includes a placebo, the placebo capsule** will be discontinued ~~from this study when~~**; crossover to** ixazomib ~~therapy is discontinued~~**is not permitted**.

Following enrollment, patients may receive ~~ixazomib~~**study drug(s)** until they experience disease progression, clinical deterioration in the investigator's judgment, experience an unacceptable toxicity, withdraw consent, pursue an alternative therapy, meet other study-specified reasons for discontinuation of study drug, or until ~~ixazomib is available to~~ the patient **is transitioned to ixazomib/other therapy** through commercial channels~~, including reimbursement for the patient's indication.~~

Patients participating in ~~eligible~~**a designated** ixazomib parent ~~studies~~**study** will enter the rollover study at the time-point when **they have completed the EOT visit in the parent study and when** the rollover study is active at an investigative site. Following their provision of informed consent to ~~continue~~**receive treatment** in the rollover study, patients will be provided with study medication. Patients should enter the study within 8 weeks of their last dose of ixazomib**/other study drug(s)** in the parent study or as agreed upon by the ~~Millennium~~**Takeda** clinician/designee **so to minimize any treatment disruption to the patient**.

Rationale for Change:

To clarify the study drug administration and supply language to make provision for future patients enrolling from designated ixazomib parent protocols.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
- Section 4.1.1.2 Benefits.
- Section 4.2 Rationale for the Proposed Study.
- Section 7.1 Inclusion Criteria, Criterion 2.
- Section 8.1 Study Drug Administration.
- Section 8.13 Combination Therapy.
- Section 9.3 Treatment Group Assignments.
- Appendix A Schedule of Events, footnote "l".

Change 4: Clarified the study objectives.

The primary change occurs in Section 5.1.1 Primary Objectives:

Initial wording:	The primary objective is: • To provide continued access of ixazomib and to evaluate the long-term safety profile of ixazomib.
Amended or new wording:	The primary objective**s** ~~is~~**are**: • **To provide continued access to ixazomib and/or other study drugs from an ixazomib parent study.** • To ~~provide continued access of ixazomib and to~~ evaluate the long-term safety profile of ixazomib.

Rationale for Change:

To clarify that the study objectives in light of continued access to other study drugs from an ixazomib parent study.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
- Section 5.2.1 Primary Endpoint

Change 5: Clarified the duration of adverse event (AE) follow-up.

The primary change occurs in Section 6.3.1 Duration of an Individual Patient's Study Participation:

Initial wording:	Patients will be followed for 30 days after the last dose of study drug(s) or the start of subsequent alternative anticancer therapy. Ongoing AEs meeting the criteria in Section 10.2 will be followed until resolution, until the AE becomes chronic or stable, or is determined to be part of the underlying disease process, or until the patient starts alternative therapy.
Amended or new wording:	Patients will be followed for 30 days after the last dose of study drug(s) ~~or the start of subsequent alternative anticancer therapy~~. Ongoing AEs meeting the criteria in Section 10.2 will be followed until resolution, until the AE becomes chronic or stable~~,~~ or is determined to be part of the underlying disease process, or until the patient ~~starts alternative therapy~~**attends the EOS visit and discontinues the study**.

Rationale for Change:

To clarify that AEs will be followed until the patient attends an EOS visit and discontinues the study; this will occur prior to a patient starting alternative therapy.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
- Section 6.1 Overview of Study Design.
- Section 10.3 Monitoring of Adverse Events and Period of Observation.

Change 6: Updated the background information on other ixazomib clinical trials.

The primary change occurs in Section 4.1 Background:

Initial wording:	Ixazomib is an investigational, oral, inhibitor of the 20S proteasome that is under development for the treatment of multiple myeloma (MM), plasma cell dyscrasias, amyloidosis, lymphoma, nonhematologic malignancies, and lupus nephritis. Inhibition of the 20S proteasome has been validated as a therapeutic target for the treatment of malignancies using VELCADE® (bortezomib) for Injection, Millennium Pharmaceuticals, Inc.'s first-in-class proteasome inhibitor [2]. Oral ixazomib in combination with lenalidomide and dexamethasone was approved by the United States (US) Food and Drug Administration (FDA) in November 2015 for the treatment of patients with MM who have received at least 1 prior therapy [3,4]. … Phase 1, phase 1/2, and phase 2 trials are ongoing in MM, relapsed and/or refractory

systemic light-chain amyloidosis (RRAL), solid tumors, and lymphoma. In addition, a phase 1 study is ongoing in patients with renal impairment who have relapsed and/or refractory multiple myeloma (RRMM) or advanced solid tumors (Study C16015). Phase 1 studies have been completed in patients with hepatic impairment who have advanced solid tumors or hematologic malignancies (Study C16018) and in an absorption, distribution, metabolism, and excretion study in patients with advanced solid tumors or lymphoma (Study C16016). Phase 3 trials in RRMM, newly diagnosed multiple myeloma (NDMM), and RRAL are underway. As of 27 March 2016, data are available from 929 patients known to have received at least 1 dose of either the intravenous (IV) or oral ixazomib formulations across the clinical development program; 2417 patients have been enrolled in 5 phase 3 clinical trials:

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

Ixazomib is available as an IV and oral formulation (during the early development of ixazomib); however, only the oral formulation is currently being developed for commercialization. Regardless of the route of administration, in the twice-weekly dosing schedule, ixazomib is given on Days 1, 4, 8, and 11 of a 21-day cycle, and in the weekly dosing schedule, ixazomib is given on Days 1, 8, and 15 of a 28-day cycle. Schedules with longer cycles are being investigated in Study C16006.

The following oncology indications are being studied during the clinical development of ixazomib: RRMM, NDMM, RRAL, advanced solid tumors, and advanced lymphoma. Studies are investigating both single-agent ixazomib and ixazomib in combination with standard treatments. However, other therapeutic areas are also being explored.

Amended or new wording:

Ixazomib is an investigational, oral, inhibitor of the 20S proteasome that ~~is under development~~**has been studied** for the treatment of multiple myeloma (MM), plasma cell dyscrasias, amyloidosis, lymphoma, nonhematologic malignancies, and lupus nephritis. Inhibition of the 20S proteasome has been validated as a therapeutic target

for the treatment of malignancies using VELCADE® (bortezomib) for Injection, ~~Millennium~~**Takeda** Pharmaceuticals, Inc.'s first-in-class proteasome inhibitor [2].

Oral ixazomib in combination with lenalidomide and dexamethasone was **first** approved by the United States (US) Food and Drug Administration (FDA) in November 2015 for the treatment of patients with MM who have received at least 1 prior therapy [3,4]. **It has since been approved in over 65 countries globally.**

…

Phase 1, phase 1/2, and phase 2 trials ~~are ongoing~~**have been conducted** in MM, relapsed and/or refractory systemic light-chain amyloidosis (RRAL), solid tumors, and lymphoma. In addition, ~~a~~ phase 1 ~~study is ongoing~~**studies were conducted** in patients with renal impairment who ~~have~~**had** relapsed and/or refractory multiple myeloma (RRMM) or advanced solid tumors (Study C16015)~~. Phase 1 studies have been completed~~**,** in patients with hepatic impairment who ~~have~~**had** advanced solid tumors or hematologic malignancies (Study C16018)**,** and in an absorption, distribution, metabolism, and excretion study in patients with advanced solid tumors or lymphoma (Study C16016). Phase 3 trials in RRMM **(C16010)**, newly diagnosed multiple myeloma (NDMM) **(C16014)**, and RRAL ~~are underway. As of 27 March 2016, data are available from 929 patients known to have received at least 1 dose of either the intravenous (IV) or oral ixazomib formulations across the clinical development program; 2417 patients have been enrolled in 5 phase 3 clinical trials:~~

~~—~~**(C16011) have additionally been completed. Phase 3 trials of ixazomib**

~~Double-blind, placebo-controlled Study C16010 and Study C16010 China continuation study (CCS) of ixazomib versus placebo in combination with lenalidomide + dexamethasone (LenDex) in patients with RRMM.~~

~~— Double-blind, placebo-controlled Study C16014 and Study C16014 extension in South Korea (KES) of ixazomib versus placebo in combination with LenDex in patients with NDMM.~~

~~Double-blind, placebo-controlled Study C16019 of ixazomib versus placebo~~ as maintenance ~~in patients with NDMM who have undergone~~ **maintenance** ~~therapy~~ **following** autologous stem cell transplantation (~~ASCT) before entering the study~~**C16019) or in patients who did not receive ASCT (C16021) are ongoing**.

~~— Double-blind, placebo-controlled Study C16021 of ixazomib versus placebo as maintenance in patients with NDMM who have not undergone ASCT.~~

~~— Open-label Study C16011 of ixazomib and dexamethasone versus physician's choice of a dexamethasone-containing regimen in patients with RRAL.~~

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

cycle, and in the weekly dosing schedule, ixazomib is given on Days 1, 8, and 15 of a 28-day cycle. Schedules with longer cycles are being investigated in Study C16006.

The following oncology indications ~~are being~~**have been** studied during the clinical development of ixazomib: RRMM, NDMM, RRAL, advanced solid tumors, ~~and~~ advanced lymphoma**, and pediatric acute lymphoblastic leukemia**. Studies are investigating both single-agent ixazomib and ixazomib in combination with standard treatments. ~~However, other therapeutic areas are also being explored.~~

Rationale for Change:

To update the current status of the ixazomib development program.

Change 7: Clarified the anticipated number of patients and sites/countries.

The primary change occurs in Section 6.2 Number of Patients:

Initial wording:	The maximum number of patients to be enrolled is estimated to be 250. The number of countries and sites cannot be determined as this study is open to all countries and sites with qualifying patients from prior company-sponsored ixazomib studies.
Amended or new wording:	The ~~maximum~~**estimated** number of patients to be enrolled is ~~estimated to be~~**approximately** 250. The number of countries and sites ~~cannot be determined~~**is not currently specified** as this study is open to all countries and sites with qualifying patients from prior company-sponsored ixazomib studies.

Rationale for Change:

To provide clarification.

Section 2.0 STUDY SUMMARY also contains this change.

Change 8: Clarified the duration of an individual patient's study participation.

The primary change occurs in Section 6.3.1 Duration of an Individual Patient's Study Participation:

Initial wording:	The anticipated duration of treatment in this rollover study will be up to 5 years. Patients will be followed for 30 days after the last dose of ixazomib or the start of subsequent alternative anticancer therapy.

Amended or new wording:	The anticipated duration of treatment **for an individual patient** in this rollover study will be ~~up to 5 years.~~**approximately 5 years. Based on approval by the Takeda medical monitor every 24 months, continued access to ixazomib and/or other study drugs will be allowed for patients who in the investigator's opinion are deriving clinical benefit. Patients may remain in the rollover study until they are transitioned to ixazomib/other therapy through commercial channels or until any of the other reasons for treatment discontinuation are met, whichever is sooner.** Patients will be followed for 30 days after the last dose of ~~ixazomib~~**study drug(s)** or the start of subsequent alternative anticancer therapy**, whichever occurs earlier**.

Rationale for Change:

To provide clarification.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 6.3.3 Timeframe for Primary Endpoint to Support Disclosures.

Change 9: Clarified the anticipated total study duration.

The primary change occurs in Section 6.3.2 End of Study/Study Completion Definition and Planned Reporting:

Added text: The estimated time frame for study completion (first patient in to last patient last visit) is **approximately** 7 years.

Rationale for Change:

To add flexibility to the anticipated total study duration.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 6.3.3 Timeframe for Primary Endpoint to Support Disclosures.
- Section 6.3.4 Total Study Duration.

Change 10: Specified the acceptable methods of contraception to prevent pregnancy.

The primary change occurs in Section 7.1 Inclusion Criteria and Appendix D:

Description of change:	Added Appendix D to describe acceptable methods of contraception. Added a referenced to Appendix D in Section 7.1, Inclusion Criterion 3.

Rationale for Change:

To incorporate the acceptable methods of contraception appendix (first added to Sweden-specific Protocol Amendment 02) into the Global protocol.

Change 11: Clarified that systemic treatment with strong cytochrome P-450 (CYP)3A inducers is prohibited for patients receiving ixazomib during the study.

The primary change occurs in Section 8.4 Excluded Concomitant Medications and Procedures:

Initial wording:	• Systemic treatment with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of St. John's wort.
Amended or new wording:	• **For patients receiving ixazomib, s**~~S~~ystemic treatment with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of St. John's wort.

Rationale for Change:

To add clarity to this protocol.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 6.1 Overview of Study Design.

Change 12: Updated the management of ixazomib clinical events to align with the current program standards.

The primary change occurs in Section 8.7.1 Management of Ixazomib Clinical Events:

Initial wording:

Prophylaxis Against Risk of Reactivation of Herpes Infection

Patients may be at an increased risk of infection, including reactivation of herpes zoster and herpes simplex viruses. Antiviral therapy, such as acyclovir, valacyclovir, or other antivirals, may be initiated as clinically indicated.

Nausea or Vomiting

Standard anti-emetics, including serotonin 5-hydroxytryptamine 3 receptor antagonists, are recommended for emesis if it occurs; prophylactic anti-emetics may also be considered at the physician's discretion. Fluid deficit should be corrected during treatment.

Diarrhea

Diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected during treatment.

Erythematous Rash With or Without Pruritus

Rash may range from limited erythematous areas, macular or small papular bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominantly on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash is most commonly reported within the first 3 cycles of therapy. The rash is often transient and self-limiting and is typically Grade 1 or 2 in severity. If rash occurs, consideration should be given to alternate causes of the rash such as concomitant medications, infections, etc.

Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (eg, prednisone ≤ 10 mg per day or equivalent is permitted. Management of a Grade 3 rash may require IV antihistamines or corticosteroids. Administration of ixazomib (and other causative agent if given in combination) should be modified and re-initiated at a reduced level from where rash was noted (per parent study).

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

The rare risks of Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), and pemphigus vulgaris have been reported in oncology studies when ixazomib (or placebo) was given with concomitant medications that are known to cause rash (eg, Bactrim, lenalidomide, aspirin), and/or in the setting of confounding treatment-emergent AEs. These severe, potentially life-threatening or deadly conditions may involve rash with skin peeling and mouth sores and should be clinically managed according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator. Additional information regarding these reactions can be found in the IB.

Thrombocytopenia

Blood counts should be monitored regularly according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib administration should be modified according to dose modification recommendations in the parent study when thrombocytopenia occurs. 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.

…

Fluid Deficit

Dehydration should be avoided because ixazomib may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported in patients treated with ixazomib, commonly in the setting of the previously noted gastrointestinal toxicities and dehydration.

Fluid deficit should be corrected before administration of study drug and as needed during treatment to avoid dehydration.

…

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome, which ultimately resolved, has been reported with ixazomib. This condition is characterized by headache, seizures, and visual loss, and abrupt increase in blood pressure. Diagnosis may be confirmed by magnetic resonance imaging or computed tomography. If the syndrome is diagnosed or suspected, symptom-directed treatment should be maintained until the condition is reversed by control of hypertension or other instigating factors.

Transverse Myelitis

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

Overdose

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

…

Amended or new wording:

Prophylaxis Against Risk of Reactivation of Herpes Infection

Patients may be at an increased risk of infection, including reactivation of herpes zoster and herpes simplex viruses. **All patients continuing to receive ixazomib in this rollover study should receive prophylactic** ~~A~~**a**ntiviral therapy~~, such as acyclovir, valacyclovir, or other antivirals, may be initiated as~~**. Patients receiving a non-ixazomib-containing regimen should be guided by the physician's** clinical~~ly~~

~~indicated~~**practice**.

Nausea or Vomiting

Prophylaxis with ~~S~~standard anti-emetics, including serotonin 5-hydroxytryptamine 3 receptor antagonists, ~~are~~**is** recommended for emesis~~ if it occurs; prophylactic anti-emetics may also be considered at the physician's discretion.~~**. Any** ~~F~~fluid deficit ~~should be corrected~~**occurring** during treatment **should be promptly corrected**.

Diarrhea

Diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. **Any** ~~F~~fluid deficit ~~should be corrected~~**occurring** during treatment **should be promptly corrected**.

Erythematous Rash With or Without Pruritus

Rash may range from limited erythematous areas, macular or small papular bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominantly on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash is most commonly reported within the first 3 cycles of therapy. The rash is often transient and self-limiting and is typically Grade 1 or 2 in severity. If rash occurs, consideration should be given to alternate causes of the rash such as concomitant medications, infections, etc**; these other causative agents should be discontinued and alterative agents considered if medically necessary**.

Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (eg, prednisone ≤ 10 mg per day or equivalent**)** is permitted.

Management of a Grade 3 rash may require IV antihistamines or corticosteroids. Administration of ixazomib (and other causative agent if given in combination) should be modified and re-initiated at a reduced level from where rash was noted (per parent study). In line with clinical practice, dermatology consult and biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a patient has previously developed a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body or oral or topical antihistamines).

The rare risks of Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), and pemphigus vulgaris have been reported in oncology studies when ixazomib (or placebo) was given with concomitant medications that are known to cause rash (eg, Bactrim, lenalidomide, aspirin), and/or in the setting of confounding treatment-emergent AEs. These severe, potentially life-threatening or deadly

conditions may involve rash with skin peeling and mouth sores and should be clinically managed according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator. **Study medications should be discontinued in the event of severe, potentially life-threatening rash.** Additional information regarding these reactions can be found in the IB.

Thrombocytopenia

Blood counts should be monitored regularly according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib administration should be modified according to dose modification recommendations in the parent study when thrombocytopenia occurs. Therapy can be reinitiated at a reduced level upon recovery of platelet counts. ~~A rare risk is~~**Thrombotic microangiopathy (TMA), including** thrombotic thrombocytopeni~~c~~**a** purpura~~, a~~ **and hemolytic uremic syndrome, are** rare**, serious** blood disorder**s** ~~where~~**that cause low levels of platelets and red blood cells and result in** blood clots ~~form~~ in small blood vessels ~~throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. Thrombotic thrombocytopenic purpura should be managed symptomatically~~**. Symptoms may include fatigue, fever, bruising, nose bleeds, and decreased urination. These disorders, including fatal cases, have been reported in patients receiving ixazomib. If TMA is suspected, consider withdrawal of the suspected causative agent and manage** according to standard medical practice.

…

Fluid Deficit

Dehydration should be avoided because ixazomib may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported in patients treated with ixazomib, commonly in the setting of the previously noted gastrointestinal toxicities and dehydration.

Fluid deficit should be **promptly** corrected before administration of study drug and as needed during treatment to avoid dehydration.

…

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome, which ultimately resolved, has been reported with ixazomib. This condition is **usually transient and reversible. It is** characterized by headache, seizures, and visual loss, and abrupt increase in blood pressure. Diagnosis may be confirmed by magnetic resonance imaging or computed tomography. If the syndrome is diagnosed or suspected, symptom-directed treatment should be maintained until the condition is reversed by control of hypertension or other instigating factors.

Transverse Myelitis

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

Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. **Overdose has been reported in patients taking ixazomib. Symptoms of overdose are generally consistent with the known risks of ixazomib. Reports of accidental overdose have been associated with serious adverse events, such as nausea, lung infections including aspiration pneumonia, multiple organ failure, and death.** If overdose occurs, consider close observation including hospitalization for hemodynamic support. Gastric lavage may be considered if instituted within 1 hour of ingestion of ixazomib overdose.

…

Rationale for Change:

To add information currently available around clinical events.

Change 13: Clarified the instructions for management of combination therapy clinical events.

The primary change occurs in Section 8.7.2 Management of Combination Therapy Clinical Events:

Initial wording:	For each medication(s) used as combination therapy with ixazomib please refer to the prescribing information for the applicable medication used in combination with ixazomib for the management of the clinical events.
Amended or new wording:	For each medication(s) used as combination therapy with **or without** ixazomib**,** please refer to the prescribing information **and details in the parent protocol** for the applicable ~~medication used in combination with ixazomib for the~~ management of ~~the~~ clinical events.

Rationale for Change:

To add clarification to this protocol.

Change 14: Updated the storage, handling, and accountability text to clarify procedures and account for the COVID-19 pandemic.

The primary change occurs in Section 8.12 Storage, Handling, and Accountability:

Initial wording:	On receipt at the investigative site, ixazomib should remain in the blister and carton provided until use or dispensation. The container should be stored as directed by the label on the packaging. All excursions should be brought to the sponsor's attention for assessment and authorization for continued use. Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life. Ixazomib dispensed to the patient for take-home dosing should remain in the blister packaging and carton and stored as directed by the label on the packaging as noted previously until the point of use. Patients who are receiving take-home medication should be given a supply of study drug as per the parent study schedule or for up to 3 cycles at the discretion of the investigator. Comprehensive instructions should be provided to the patient to ensure compliance with dosing procedures and to avoid the potential for incorrect self-administration or overdose of medication. Patients should be instructed to store the medication as directed by the label on the packaging. Patients should be instructed to return their empty or partially used cartons to the investigative site at their next visit, rather than discarding them, as permitted by site policy. Reconciliation will occur accordingly when the patient returns at their next visit for take-home medication. Any excursions in temperature should be reported and dealt with on a case-by-case basis.
Amended or new wording:	On receipt at the investigative site, ixazomib should remain in the blister **pack** and carton provided until use or dispensation. The container should be stored as directed by the label on the packaging. All excursions should **immediately** be brought to the sponsor's attention for assessment and authorization for continued use. Ensure that the drug is used before the retest expiry date provided by ~~Millennium~~**Takeda**. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life. Ixazomib dispensed to the patient for take-home dosing should remain in the blister packaging and carton and stored as directed by the label on the packaging as noted previously until the point of use. Patients who are receiving take-home medication should be given a supply of study drug as per the parent study schedule or for up to 3 cycles at the discretion of the investigator. **(Note: Patients in France are only permitted to receive 1 cycle of medication at a time). In case of the COVID-19 pandemic preventing a patient from attending the study site, sites may use alternative strategies to deliver study drug to patients (eg, via courier or site staff), per local standard practice and regulations and with prior approval from the investigator and the sponsor's project clinician/designee.** Comprehensive instructions should be provided to the patient to ensure compliance with**, and understanding of,** dosing procedures and to avoid the potential for incorrect self-administration or overdose of medication. Patients should be instructed to store the medication as directed by the label on the packaging. Patients should be instructed to return their empty or partially used cartons

to the investigative site at their next visit, rather than discarding them, as permitted by site policy. Reconciliation will occur accordingly when the patient returns at their next visit for take-home medication. **In case of the COVID-19 pandemic preventing a patient from attending the study site, drug packs and dosing diaries should be returned at the next available on-site clinic visit.** Any excursions in temperature should be reported and dealt with on a case-by-case basis.

Rationale for Change:

To add clarification to this protocol.

Change 15: Added language regarding alternative methods for administering study procedures/assessments when it is not possible for the patient to come to the study site due to the COVID-19 pandemic.

The primary change occurs in Section 9.4 Study Procedures:

Added text: **In acknowledgement of hospital, local, state or national government restrictions, or other site-related factors caused by the COVID-19 pandemic that may prevent investigators from conducting the study according to the Schedule of Events at the clinical study site, investigators may continue patients in the study despite departure from the Schedule of Events. Investigators are expected to evaluate the impact to the safety of the study participants and site personnel for patients to continue. In evaluating such requests, the investigator/study site staff will give the highest priority to the safety and welfare of the patients. Patients must be willing and able to continue taking study medication and remain compliant with the protocol. For patients that are impacted by the COVID-19 pandemic, any procedures not conducted per the study protocol will be documented in the eCRF.**

Alternative methods should be considered for performing the assessments by other means than the patient presenting to the clinic (eg, remote assessment, having lab assessment performed at a facility closer to the patient's home, etc.) If a patient misses an in-person study visit, the investigator/study team staff will speak directly with the patient by telephone or other medium (eg, a computer-based video communication) during each visit window to assess subject safety and overall clinical status. During this contact with the patient, the study site physician or other qualified site staff should at minimum conduct AE collection and an assessment of clinical symptoms. Other study assessments may be collected remotely as is feasible and may involve audio or video recording. Assessments/procedures that cannot be completed during the protocol-specified window because a site visit is done remotely (eg, hematology, clinical chemistry, concomitant medications/procedures) are waived.

Rationale for Change:

To account for the COVID-19 pandemic affecting study conduct.

Change 16: Clarified that patients previously enrolled in this study who remain on study treatment upon implementation of Amendment 3 may need to be reconsented, according to IRB/IEC standards.

The primary change occurs in Section 9.4.1 Informed Consent:

Added text: **Patients previously enrolled in this study who remain on study treatment upon implementation of Amendment 3 may need to be reconsented, according to IRB/IEC standards. Reconsenting should be done in person, where possible. Remote reconsenting is permitted as long as the process adheres to site, IRB/IEC, and GCP standards and local regulations.**

Rationale for Change:

To clarify that patients previously enrolled and still on treatment in this rollover study may need to reconsent.

The following sections also contain this change:

- Section 15.2 Subject Information, Informed Consent, and Subject Authorization.
- Appendix A Schedule of Events, footnote "d".

Change 17: Clarified regional exceptions for assessment of carbon dioxide, depending on standard of care.

The primary change occurs in Section 9.4.8.1 Clinical Chemistry, Hematology, and Urinalysis:

Description of change: Footnote added to "Carbon Dioxide" in Table 9.a Clinical Chemistry and Hematology Tests.

Added text: [a] **If CO_2 is not done as a part of standard care in the participant's region, then this test does not need to be performed.**

Rationale for Change:

To clarify assessments in this protocol.

Change 18: Updated the criteria for withdrawing patients from study.

The primary change occurs in Section 9.6 Withdrawal of Patients From Study:

Initial wording: A patient will be withdrawn from the study for any of the following reasons:

- Study terminated by sponsor.
- Withdrawal by subject.

	• Lost to follow-up. • Death. A patient may also be withdrawn from the study for any of the following reasons: • Adverse event. • Protocol deviation. • Progressive disease (as defined in the patient's parent study). • Clinical deterioration, in the investigator's opinion. • Pregnancy. • Other.
Amended or new wording:	A patient will be withdrawn from the study for any of the following reasons: • **Progressive disease (as defined in the patient's parent study).** • **Pregnancy.** • **Transition to commercial supply of study drug(s).** • Study terminated by sponsor. • Withdrawal by subject. • Lost to follow-up. • Death. A patient may also be withdrawn from the study for any of the following reasons: • Adverse event. • Protocol deviation. • ~~Progressive disease (as defined in the patient's parent study).~~ • Clinical deterioration, in the investigator's opinion. • ~~Pregnancy~~**Investigator's decision**. • Other.
Rationale for Change: To clarify the withdrawal criteria in this protocol.	

Change 19: Added language to Procedures for Recording and Reporting Adverse Events and Serious Adverse Events.

The primary change occurs in Section 10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events:

Added text: **The paper SAE forms must be submitted via fax (see fax numbers below) within 24 hours of awareness. In case of fax, site personnel must confirm successful transmission of all pages and include an e-mail address on the fax cover sheet so that an acknowledgment of receipt can be returned via e-mail within 1 business day. E-mail submission of paper SAE forms with a PDF attachment should only be used in the case where fax is not possible within 24 hours of receiving the event. In case of e-mail, site personnel must confirm successful transmission by awaiting an acknowledgment of the receipt via e-mail within 1 business day. If SAEs are reported via fax or by e-mail, the EDC application must be updated as soon as possible with the appropriate information.**

Rationale for Change:

To assist in timely submission of SAE reports.

Change 20: Revised language regarding the statistical analyses.

The primary change occurs in Section 13.1.3 Safety Analysis:

Initial wording:

The following AEs will be summarized using the FAS:

- All SAEs.
- All ≥Grade 3 AEs.
- ≥Grade 2 peripheral neuropathy.
- New primary malignancies.
- Any AE resulting in dose modification or discontinuation of any study drug.
- Any other AE that in the opinion of the investigator is a clinically significant event.

No statistical testing or inferential statistics will be generated.

All AEs will be coded using MedDRA. Data will be summarized using preferred term and primary system organ class. Local laboratory assessment changes and vital sign changes from study entry to end of study will also be summarized.

Exposure to study drug and study regimen will be tabulated. In addition, reasons for drug discontinuation will be summarized.

Concomitant medications and procedures related to treatment of AEs from screening through the end of study will be classified by generic terms according to the WHO

drug dictionary.

Data will be presented by the entire safety population, by population of monotherapy of ixazomib and by population of ixazomib in combination with other anticancer agents(s) as specified in the SAP. Additional safety analyses by subgroups such as drug indication and baseline characteristics may be performed as specified in the SAP.

Amended or new wording:

The following AEs will be summarized **with descriptive statistics for all patients who receive at least 1 dose of ixazomib** using the FAS:

- All SAEs.
- All ≥Grade 3 AEs.
- ≥Grade 2 peripheral neuropathy.
- New primary malignancies.
- Any AE resulting in dose modification or discontinuation of any study drug.
- Any other AE that in the opinion of the investigator is a clinically significant event.

No **formal** statistical testing or inferential statistics will be generated.

All AEs will be coded using **the current** MedDRA **version at the time of the analysis**. Data will be summarized using preferred term and primary system organ class. Local laboratory assessment changes and vital sign changes from study entry to end of study will also be summarized.

Exposure to study drug and study regimen will be tabulated. In addition, reasons for drug discontinuation will be summarized.

Concomitant medications and procedures related to treatment of AEs from screening through the end of study will be classified by generic terms according to the WHO drug dictionary.

Data will be presented by the entire **ixazomib** safety population, by population of monotherapy of ixazomib**,** and by population of ixazomib in combination with other anticancer agents(s) as specified in the SAP. **Safety listings will be prepared for patients receiving other study drugs and not ixazomib.** Additional safety analyses by subgroups such as drug indication and baseline characteristics may be performed as specified in the SAP.

Rationale for Change:

To clarify the statistical analyses for this study.

Section 2.0 STUDY SUMMARY also contains this change.

Change 21: Clarified language regarding procedures for reporting product complaints or

medication errors.

The change occurs in Section 10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose):

Initial wording:	A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or e-mail 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. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the phone numbers or e-mail address provided below. [Table of contact information] Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE Form should be completed and sent to Cognizant (refer to Section 10.2).
Amended or new wording:	A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report ~~this via the phone numbers or e-mail addresses provided below~~**to: ctmcomplaint@takeda.com**. **Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE Form should be completed and sent to Cognizant (refer to Section 10.2).** A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this ~~via the phone numbers or e-mail address provided below~~**to Cognizant (refer to Section 10.2)**. [Deleted table of contact information] ~~Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE Form should be completed and sent to Cognizant (refer to Section 10.2).~~

Rationale for Change:

To clarify procedures in this protocol.

Change 22: Clarified language regarding quality assurance audits and Regulatory Agency inspections.

The change occurs in Section 14.3 Quality Assurance Audits and Regulatory Agency Inspections:

Initial wording:	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.
Amended or new wording:	The study site also may be subject to quality assurance audits by the sponsor or designees. ~~In this circumstance~~**The investigator agrees to provide access to records, facilities, and personnel for conduct of any inspection or audit. If a quality assurance audit is requested**, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit.

Rationale for Change:

To clarify procedures in this protocol.

Change 23: Add information about alternative monitoring approaches, such as remote source data verification, in the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic.

The change occurs in Section 14.1 Study-Site Monitoring Visits:

Added text: **In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches such as remote source data verification (SDV) or telephone contact may be used to ensure data quality and integrity and maintain patient safety. Alternative monitoring approaches should be used only where allowed by the local Health Authority and permitted by the IRB/IEC.**

Rationale for Change:

To clarify remote source data verification procedures to account for the COVID-19 pandemic.

Change 24: Clarify the ixazomib capsule strengths that are available.

The primary change occurs in Section 8.9 Description of Investigational Agents:

Initial wording:	The ixazomib capsule formulation consists of the drug substance (ixazomib citrate), microcrystalline cellulose, talc, and magnesium stearate. There are 6 capsule strengths: 0.2, 0.5, 2.0, 2.3, 3.0, and 4.0 mg. Each strength is differentiated by a unique capsule size and color. Dosage strength is stated as ixazomib. Ixazomib capsules are individually packaged in blisters. For additional details, please see the ixazomib IB and Pharmacy Manual.
Amended or new	The ixazomib capsule formulation consists of the drug substance (ixazomib citrate), microcrystalline cellulose, talc, and magnesium stearate. There are ~~6~~ **7** capsule

wording:	strengths: 0.2, 0.5, 2.0, 2.3, 3.0, ~~and~~ 4.0**, and 5.5** mg. Each strength is differentiated by a unique capsule size and color. Dosage strength is stated as ixazomib. Ixazomib capsules are individually packaged in blisters. For additional details, please see the ixazomib IB and Pharmacy Manual.

Section 8.10 Preparation, Reconstitution, and Dispensation also contains this change.

Rationale for Change:

To clarify that capsule strength 5.5 mg is available.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	07-Jun-2021 20:53 UTC
[redacted]	Clinical Science Approval	07-Jun-2021 21:07 UTC
[redacted]	Clinical Science Approval	08-Jun-2021 14:00 UTC