Title: A Phase 2, Open-Label Study of Ixazomib+Daratumumab+Dexamethasone (IDd) in Relapsed and/or Refractory Multiple Myeloma (RRMM)

NCT Number: NCT03439293

Document Date: 30 March 2022

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

PROTOCOL

A Phase 2, Open-Label Study of Ixazomib+Daratumumab+Dexamethasone (IDd) in Relapsed and/or Refractory Multiple Myeloma (RRMM)

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

Study Number: C16047

EudraCT Number: 2017-003977-32

Compound: Ixazomib (NINLARO)

Date: 30 March 2022 **Amendment Number:** 07

Amendment History:

Date	Amendment Number	Amendment Type (for Regional Europe Purposes Only)	Region
30 November 2017	Initial Protocol	Not applicable	Global
15 November 2018	01	Nonsubstantial	France
18 April 2019	02	Substantial	Global
18 April 2019	03	Substantial	France
28 September 2020	04	Substantial	Global
13 October 2020	05	Substantial	France
01 November 2021	06	Substantial (not implemented)	Global
30 March 2022	07	Substantial	Global

Rationale for Amendment 07

This document describes the changes to the protocol incorporating Amendment 07. The primary reason for this amendment is to change the legal entity name of the sponsor to Takeda Development Center Americas, Inc. In addition, a new Schedule of Events has been added for use after the final analysis has been conducted, and the Management of Clinical Events section for ixazomib has been updated to reflect evolving data.

The global Protocol Amendment 06 (dated 01 November 2021) will not be implemented. Thus, the changes described below for the current Protocol Amendment 07 are relative to the most recent protocol version globally implemented, which was Protocol Amendment 04 (dated 28 September 2020).

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

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

Changes in Amendment 07

The purposes of this amendment are to:

1. Change the legal entity name of the sponsor.
2. Add a new Schedule of Events to Appendix A for use after the final analysis has been conducted.
3. Add language on local clinical laboratory evaluations for efficacy and safety after implementation of Amendment 07.
4. Clarify language regarding procedures for reporting product complaints or medication errors.
5. Clarify language about study conduct regarding the coronavirus disease 2019 (COVID-19) pandemic.
6. Update the Management of Clinical Events section for ixazomib to reflect evolving data, including the addition that ixazomib should be discontinued if Stevens-Johnson syndrome (SJS) occurs.
7. Incorporate changes from France-specific Protocol Amendments 01 and 05.
8. Update the terms of the Posttrial Access program.
9. Clarify the daratumumab infusion time period.

1.0 ADMINISTRATIVE

1.1 Contacts

A separate contact information list will be provided to each site. The names and contact information for the medical monitor and responsible medical officer are in the Study Manual.

Serious adverse event and pregnancy reporting information is presented in Section 10.2 and Section 10.5, as is information on reporting product complaints. See the Study Manual for more information.

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] Date

[redacted] Date

[redacted] Date

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, prescribing information, 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/Province)

_____

Location of Facility (Country)

TABLE OF CONTENTS

1.0 ADMINISTRATIVE 3
1.1 Contacts 3
1.2 Approval 4
2.0 STUDY SUMMARY 11
3.0 STUDY REFERENCE INFORMATION 14
3.1 Study-Related Responsibilities 14
3.2 Principal Investigator/Coordinating Investigator 14
3.3 List of Abbreviations 15
3.4 Definition of Terms 17
3.5 Corporate Identification 17
4.0 INTRODUCTION 18
4.1 Background 18
4.2 Ixazomib 18
4.2.1 Approval of Ixazomib+Lenalidomide and Dexamethasone for Patients Previously Treated for MM 19
4.2.2 Other Ixazomib Clinical Development 19
4.3 Daratumumab 20
4.3.1 Approval of Daratumumab for Patients Previously Treated for MM 20
4.4 Rationale for the Proposed Study 21
4.4.1 Rationale for an IDd Regimen 21
4.4.2 Rationale for Dose and Schedule 23
4.4.3 Rationale for Correlative Science/Biomarker Assessments 23
4.4.4 Rationale for PK Assessments 24
5.0 STUDY OBJECTIVES AND ENDPOINTS 24
5.1 Objectives 24
5.1.1 Primary Objective 24
5.1.2 Secondary Objectives 24
5.1.3 Exploratory Objectives 25
5.2 Endpoints 25
5.2.1 Primary Endpoints 25
5.2.2 Secondary Endpoints 25
5.2.3 Exploratory Endpoints 26
6.0 STUDY DESIGN 26
6.1 Overview of Study Design 26

6.1.1 Study Population 27
6.2 Number of Patients 27
6.3 Duration of Study 27
6.3.1 Duration of an Individual Patient's Study Participation 27
6.3.2 End of Study/Study Completion Definition and Planned Reporting 28
6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures 28
6.3.4 Total Study Duration 28
6.3.5 Posttrial Access 29
7.0 STUDY POPULATION 29
7.1 Inclusion Criteria 29
7.2 Exclusion Criteria 30
8.0 STUDY THERAPY 32
8.1 Overview 32
8.2 Study Treatment Administration 32
8.2.1 Order of Study Treatment Administration 33
8.2.2 Daratumumab 34
8.2.3 Ixazomib 36
8.2.4 Dexamethasone 36
8.3 Dose Modification Guidelines 37
8.3.1 Criteria for Beginning or Delaying a Subsequent Treatment Cycle 37
8.3.2 Ixazomib Treatment Modification 38
8.3.3 Daratumumab Treatment Modification 39
8.3.4 Dexamethasone Treatment Modification 41
8.4 Excluded Concomitant Medications and Procedures 42
8.5 Permitted Concomitant Medications and Procedures 42
8.6 Precautions and Restrictions 43
8.7 Management of Clinical Events 43
8.7.1 Ixazomib 43
8.7.2 Daratumumab 46
8.7.3 Dexamethasone 48
8.8 Blinding and Unblinding 48
8.9 Description of Investigational Agents 48
8.9.1 Ixazomib 48
8.9.2 Daratumumab 49
8.9.3 Dexamethasone 50

8.10 Other Protocol-Specified Materials 50
9.0 STUDY CONDUCT 50
9.1 Study Personnel and Organizations 50
9.2 Arrangements for Recruitment of Patients 50
9.3 Treatment Group Assignments 51
9.4 Study Procedures 51
9.4.1 Assessments During the Treatment Period 51
9.4.2 Assessments During the Follow-Up Periods: PFS and OS 52
9.4.3 Clinical Laboratory Evaluations 53
9.4.4 Disease Assessment 55
9.4.5 Biomarker, Pharmacodynamic, and PK Samples 56
9.4.6 QOL Assessments 58
9.5 PK Measurements 58
9.6 Completion of Study Treatment (for Individual Patients) 59
9.7 Discontinuation of Treatment With Study Drug Treatment and Patient Replacement 59
9.8 Withdrawal of Patients From Study 60
9.9 Study Compliance 60
9.10 Study Closure 60
10.0 ADVERSE EVENTS 61
10.1 Definitions 61
10.1.1 Pretreatment Event Definition 61
10.1.2 AE Definition 61
10.1.3 SAE Definition 61
10.2 Procedures for Recording and Reporting AEs and SAEs 62
10.3 Monitoring of AEs and Period of Observation 64
10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events 64
10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose) 65
10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities 65
11.0 STUDY-SPECIFIC COMMITTEES 65
12.0 DATA HANDLING AND RECORDKEEPING 66
12.1 eCRFs 66
12.2 Record Retention 67
13.0 STATISTICAL METHODS 67
13.1 Statistical and Analytical Plans 67

13.1.1 Analysis Sets....67
13.1.2 Analysis of Demographics and Other Baseline Characteristics....68
13.1.3 Efficacy Analyses....68
13.1.4 PK Analysis....69
13.1.5 MRD Analysis....69
13.1.6 Analyses of Immune Dynamics in Blood and Bone Marrow....69
13.1.7 Analysis of CR+VGPR Rate and PFS in High-Risk Cytogenetic Populations....69
13.1.8 Analysis of Patient-Reported Outcomes....69
13.1.9 Safety Analysis....70
13.2 Interim Analysis and Criteria for Early Termination....71
13.3 Determination of Sample Size....71
14.0 QUALITY CONTROL AND QUALITY ASSURANCE....72
14.1 Study-Site Monitoring Visits....72
14.2 Protocol Deviations....72
14.3 Quality Assurance Audits and Regulatory Agency Inspections....73
15.0 ETHICAL ASPECTS OF THE STUDY....73
15.1 IRB and/or IEC Approval....73
15.2 Subject Information, Informed Consent, and Subject Authorization....74
15.3 Subject Confidentiality....75
15.4 Publication, Disclosure, and Clinical Trial Registration Policy....75
15.4.1 Publication....75
15.4.2 Clinical Trial Registration....76
15.4.3 Clinical Trial Results Disclosure....76
15.5 Insurance and Compensation for Injury....77
16.0 REFERENCES....78

LIST OF IN-TEXT TABLES

Table 6.a Primary and Secondary Endpoints for Disclosures....28
Table 8.a Infusion Rates for Daratumumab IV Administration....35
Table 8.b Dose Reduction Steps for Ixazomib....38
Table 8.c Ixazomib and Daratumumab Dose Modification for Hematologic Toxicities....38
Table 8.d Ixazomib Dose Modification for Nonhematologic Toxicities....39
Table 8.e Daratumumab-Related Toxicity Management....40
Table 9.a Clinical Chemistry and Hematology Tests....53
Table 9.b Primary Specimen Collection Table....58

LIST OF IN-TEXT FIGURES

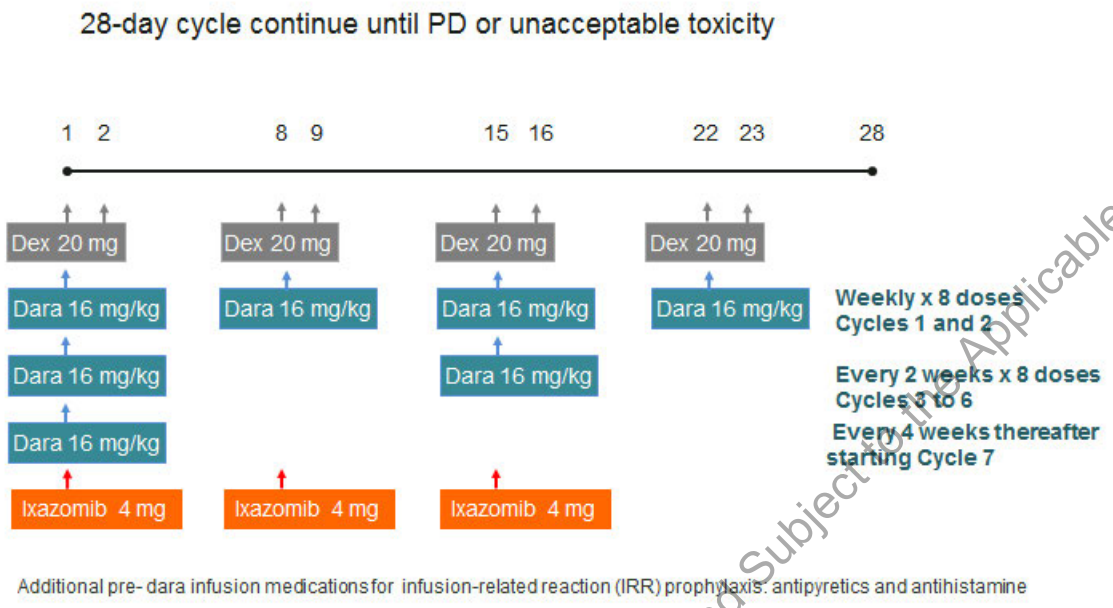
Figure 6.a Study Schema 27
Figure 8.a Study Treatment Administration 33

LIST OF APPENDICES

Appendix A Schedule of Events 83
Appendix B Responsibilities of the Investigator 89
Appendix C Investigator Consent to Use of Personal Information 91
Appendix D Eastern Cooperative Oncology Group Scale for Performance Status 92
Appendix E IMWG Uniform Response Criteria for MM 93
Appendix F EORTC QLQ-C30 (version 3) 94
Appendix G EORTC QLQ-MY20 96
Appendix H Acceptable Methods of Contraception 98
Appendix I Schedule of Events (28-Day Cycle) Previous to Amendment 02 99
Appendix J COVID-19 Trial Communication Letter from Janssen-Cilag International NV 107
Appendix K Amendment 07 Detailed Summary of Changes 109

2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc	**Compound:** Ixazomib (NINLARO)
Title of Protocol: A Phase 2, Open-Label Study of Ixazomib+Daratumumab+Dexamethasone (IDd) in Relapsed and/or Refractory Multiple Myeloma (RRMM)	
Study Number: C16047	**Phase:** 2
Primary Objective: • To evaluate the proportion of patients with a response of very good partial response (VGPR) or better to IDd treatment.	
Secondary Objectives: • To measure progression-free survival (PFS), time to progression (TTP), and overall survival (OS). • To measure overall response rate (ORR), time to response (TTR), and duration of response (DOR). • To collect plasma concentration-time data for ixazomib to contribute to population pharmacokinetic (PK) analyses. • To evaluate the safety/tolerability of IDd administered in a 28-day cycle.	
Subject Population: Adult patients (aged ≥18 years) who have documented evidence of progressive multiple myeloma (MM), as defined by International Myeloma Working Group (IMWG) criteria (see Appendix E) [1-3], on or after their last regimen. All patients must have received between 1 to 3 prior therapies for MM.	
Number of Subjects: Estimated total: 60	**Number of Sites:** Estimated total: 25 sites globally
Study Treatment Dosing: For the purposes of this protocol, study treatment regimen is defined as the combination of ixazomib, daratumumab, and dexamethasone. All cycles are approximately 28 days with treatment given until PD or unacceptable toxicity. (Full details on study treatment administration are in Section 8.2.) See diagram below for details. • Ixazomib will be administered at 4 mg orally on Days 1, 8, and 15 of each 28-day cycle. In Cycle 1 ixazomib will be given after the daratumumab infusion; in subsequent cycles, if there have been no Grade 3 or higher infusion-related reactions (IRRs) in the previous cycle, ixazomib can be given prior to or at approximately the same time as the premedications (see Section 8.2.3). • Daratumumab will be administered intravenously (IV) at 16 mg/kg (note pre- and postinfusion medications of antipyretics and oral antihistamines listed in Section 8.2.2): Daratumumab will be given on the following schedule: – Cycles 1 and 2: Days 1, 8, 15, and 22 (every week; total of 8 doses). – Cycles 3 to 6: Days 1 and 15 (every 2 weeks; total of 8 doses). – Cycles 7 and beyond: Day 1 (every 4 weeks). • Dexamethasone will be given as 20 mg on Day 1, 2, 8, 9, 15, 16, 22, and 23 in each 28-day cycle, to achieve the standard total of 40 mg per week (2 doses of 20 mg per week). This schedule allows for dexamethasone to be given the day of (before) and the day after the daratumumab infusion on daratumumab dosing days. Dexamethasone should be given IV before the first daratumumab dose; but can be given IV or orally thereafter. The dose of dexamethasone may be reduced in some patients (see details in Section 8.2.4).	



Abbreviations: Dara,daratumumab; Dex, dexamethasone; PD, progressive disease.

Duration of Treatment:	**Period of Evaluation:**
All patients will receive study therapy until they experience progressive disease (PD), have an unacceptable toxicity, or withdraw consent, or when the study has completed or until the sponsor terminates the study.	The study will be considered complete approximately 1 year after 50% of patients have died or experienced PD. The estimated timeframe is approximately 4 years after the first patient in (FPI).

Main Inclusion Criteria:

- Adult patients (aged ≥18 years) who have been diagnosed with MM according to IMWG criteria
- All patients must have measurable disease by at least 1 of the following measurements:
  - Serum M-protein ≥1 g/dL (≥10 g/L).
  - Urine M-protein ≥200 mg/24 hours.
- All patients must have documented evidence of PD on or after their last regimen as defined by IMWG criteria. All patients must have received between 1 to 3 prior therapies for MM.
- All patients must have achieved a response (partial response [PR] or better) to at least 1 prior therapy.
- All patients must have an Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2.
- All patients must have adequate hematologic, hepatic, and renal function.

*Full details in Section 7.0.

Main Criteria for Exclusion:

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

- Patients have undergone prior allogenic bone marrow transplantation.
- Patients have received prior ixazomib at any time or daratumumab or other anti-CD38 therapies except as part of initial therapy if this was stopped to move on to stem cell transplant (SCT) and the patient did not progress on anti-CD38 treatment.
- Patients are refractory to bortezomib or carfilzomib at the last exposure before this study (defined as patient having PD while receiving bortezomib or carfilzomib therapy or within 60 days after ending bortezomib therapy).
- Patients planning to undergo a SCT prior to PD on this study (ie, these patients should not be enrolled in order to reduce disease burden prior to transplant).
- Patients with Grade 2 or higher residual toxicities from prior therapy (including Grade 2 or higher peripheral neuropathy or any grade neuropathy with pain; excluding alopecia).
- Patient has any concurrent medical condition or disease that is likely to interfere with study procedures, results, or assessment of safety or toxicity or that in the opinion of the investigator would constitute a hazard for participating in this study.

*Full details in Section 7.0.

Endpoints and Assessments:

The primary endpoint is response of VGPR or better as assessed by the investigator. Additionally, efficacy will be assessed by PFS, TTP, ORR, TTR, DOR, and OS. Patients will be assessed for disease response by the investigator according to the IMWG criteria.

Safety assessments will be evaluated through the incidence and severity of adverse events (AEs) and changes in clinical hematology and chemistry laboratory test results.

Statistical Considerations:

This phase 2 study is designed to evaluate the safety and efficacy of IDd. The total sample size will be approximately 60 patients.

Two interim analyses and a final analysis will be conducted. The primary endpoint and all response-related endpoints will be analyzed for the response-evaluable population; other endpoints and assessments (PFS, TTP, OS, safety) will be analyzed for the safety population. The definition of the response-evaluable population is patients who receive at least 1 dose of ixazomib, have measurable disease at baseline or screening, and have at least 1 postbaseline response assessment.

The first interim analysis will be conducted 6 months after the last patient is enrolled. The second interim analysis will be conducted after 50% of the PFS events have occurred. The final analysis will be conducted 1 year after 50% of the PFS events have occurred. No other formal statistical analyses are planned.

Sample Size Justification:

The sample size is calculated using binomial exact test for single proportion based on the rate of VGPR or better of the IDd treatment regimen. Statistical assumption was based on observed CR+VGPR rates in clinical studies with ixazomib [4], bortezomib [5], and daratumumab [6].

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor or designee will perform all study-related activities with the exception of those identified in the Clinical Study Supplier List or equivalent. 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 Principal Investigator/Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AE	adverse event
ADCC	antibody-dependent cell mediated cytotoxicity
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BMA	bone marrow aspirate
CDC	complement-dependent cytotoxicity
CFR	Code of Federal Regulations
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CR	complete response
CRO	contract research organization
CT	computed tomography
DOR	duration of response
DSMB	Drug Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30
EORTC QLQ-MY20	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Multiple Myeloma module
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
G-CSF	granulocyte colony-stimulating factor
FPI	first patient in
GCP	Good Clinical Practice
HR	hazard ratio
IB	investigator's brochure
ICH	International Conference on Harmonisation
ICF	informed consent form
IDd	ixazomib+daratumumab+dexamethasone
IEC	independent ethics committee
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IRB	institutional review board
IRR	infusion-related reaction

IV	intravenous(ly)
LenDex	lenalidomide+dexamethasone
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MRD	minimal residual disease
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDMM	newly diagnosed multiple myeloma
NGF	next-generation flow cytometry
NGS	next-generation sequencing
NSAIDs	nonsteroidal anti-inflammatory drugs
ORR	overall response rate
OS	overall survival
PD	progressive disease, progression of disease, disease progression
PET	positron emission tomography
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PR	partial response
PTA	posttrial access
QOL	quality of life
RBC	red blood cell
RRAL	relapsed and/or refractory systemic light-chain amyloidosis
RRMM	relapsed and/or refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
SCT	stem cell transplant
SJS	Stevens-Johnson syndrome
SPEP	serum protein electrophoresis
SUSARs	suspected unexpected serious adverse reactions
TEAEs	treatment-emergent adverse events
TEN	toxic epidermal necrolysis
TMA	thrombotic microangiopathy
TTP	time to progression
TTR	time to response
ULN	upper limit of normal range
UPEP	urine protein electrophoresis
US	United States
Vd	bortezomib+dexamethasone
VGPR	very good partial response

WBC	white blood cell
WHO	World Health Organization

3.4 Definition of Terms

prior therapy	two or more cycles of therapy given as a treatment plan for MM (eg, a single-agent or combination therapy or a sequence of planned treatments, such as induction therapy followed by ASCT and then consolidation and/or maintenance therapy) [7]. Typically each prior therapy is separated by PD.

3.5 Corporate Identification

TDC Europe	Takeda Development Centre Europe Ltd
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

Multiple myeloma (MM) is a genetically complex disease that is characterized by an abnormal clonal plasma cell infiltration that accumulates in the bone marrow [8]. Clinical complications include anemia, renal insufficiency, bone destruction, hypercalcemia, recurrent infections, cytopenias, bone pain/fractures and hyperviscosity syndrome [9]. Prognosis in myeloma is related to both patient factors and tumor variables at the time of diagnosis. Patient-related factors include age, performance status, and renal function; tumor factors include disease stage, as well as light chain and IgA disease [10-13].

Treatment of relapsed and/or refractory MM (RRMM) continues to present a therapeutic challenge. Although the prognosis for MM has improved over the past 2 decades because of the introduction of new and more effective therapies, it is still a fatal disease in nearly all cases. Despite the current therapeutic options, RRMM is characterized by frequent relapses; thus there is a need to sequence available therapy through multiple relapses. Such strategies involve consideration for the characteristics of prior therapy, including both depth and duration of response, tolerability of therapy, as well as combining different agents in an attempt to achieve long-term disease control [14]. As per the International Myeloma Working Group (IMWG) [3], different therapeutic approaches may be utilized according to the benefit/risk of each regimen and the patient's age, disease status, and quality of life (QOL).

Treatment of patients with MM continues to evolve. Proteasome inhibitors (PIs) form a backbone of current treatment strategies starting with the first-in-class PI, VELCADE (bortezomib) [15]. VELCADE is approved globally for patients with MM and is frequently used as a part of a patient's initial therapy. Ixazomib was designed to build upon the attributes of VELCADE and improve the safety profile while also providing an option for oral administration. Ixazomib is now approved (under the brand name NINLARO®) in combination with lenalidomide+dexamethasone (LenDex) for the treatment of patients with MM who have received at least 1 prior therapy [16,17]. Monoclonal antibodies (mAbs) are a recent addition to MM therapies [18]. Daratumumab is an anti-CD38 mAb that has demonstrated substantial activity and good tolerability as monotherapy, as well as in combination with current standard treatments in RRMM. Daratumumab was the first anti-CD38 mAb approved (under the brand name DARZALEX®) for patients with RRMM [19,20]. Thus, this current study aims to examine the efficacy and safety of the ixazomib+daratumumab+dexamethasone (IDd) treatment regimen in a patient population comparable to that which was evaluated in pivotal trials with ixazomib and daratumumab.

4.2 Ixazomib

Ixazomib, an oral inhibitor of the 20S proteasome, is under development for the treatment of 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 Development Center Americas, Inc's first-in-class PI [21].

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 ixazomib can be found in the ixazomib Investigator's Brochure (IB) as well as in the NINLARO prescribing information.

4.2.1 Approval of Ixazomib+Lenalidomide and Dexamethasone for Patients Previously Treated for MM

Ixazomib was approved (under the brand name NINLARO) in combination with LenDex for the treatment of patients with MM who have received at least 1 prior therapy by the United States (US) Food and Drug Administration (FDA) in November 2015 [4,17]. Ixazomib is now approved in over 45 countries including Canada, the European Union (EU), and Japan with further applications for marketing authorization currently under review globally.

The efficacy of ixazomib+LenDex was evaluated in a global, randomized, double-blind, placebo-controlled, phase 3 study (C16010) in patients with RRMM who had received at least 1 prior therapy [4]. The primary endpoint of progression-free survival (PFS) was met at the primary analysis, with a statistically significant and clinically meaningful PFS benefit for patients receiving ixazomib+LenDex versus placebo+LenDex (hazard ratio [HR]=0.742, p=0.012; median PFS 20.6 vs 14.7 months). The PFS benefit in the ixazomib regimen was supported by improvements versus the placebo regimen in other efficacy data, such as response rates, duration of response (DOR), and time to progression (TTP). After a median follow-up of approximately 23 months, the median overall survival (OS) had not been reached in either regimen. The rates of serious adverse events (SAEs) and rates of on-study deaths were similar in the 2 regimens (47% with ixazomib, 49% with placebo; 4% and 6%, respectively); ≥Grade 3 adverse events (AEs) occurred in 74% and 69% of the patients, respectively, largely driven by increased thrombocytopenia in the ixazomib+LenDex regimen. The most common adverse reactions (≥20%) are diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, and back pain. Overall, the addition of ixazomib to LenDex did not add substantial toxicity [17].

The PFS benefit and safety profile seen in global Study C16010 was corroborated in the China Continuation study, a double-blind, placebo-controlled study of similar design with the same inclusion criteria, stratification factors, and stringency of execution. As a regional expansion study, all patients were enrolled in China. In addition to the PFS benefit, an OS benefit in favor of the ixazomib+LenDex group was observed at the final analysis [22].

4.2.2 Other Ixazomib Clinical Development

Ixazomib has been tested as an intravenous (IV) and an oral formulation (during the early development of ixazomib); however, only the oral formulation is currently being developed for commercialization. The approved dosing schedule is a weekly dosing schedule, where ixazomib is given on Days 1, 8, and 15 of a 28-day cycle. Clinical development has focused on MM (newly

diagnosed MM [NDMM] and RRMM) and relapsed and/or refractory systemic light-chain amyloidosis (RRAL), with additional studies in the nononcology setting including but not limited to lupus nephritis and graft-versus-host disease.

The safety profile indicates that ixazomib administration can lead to AEs that are generally manageable with appropriate monitoring for early recognition of adverse effects, dose modification, and supportive care. The most common treatment-emergent AEs (TEAEs) include nausea, vomiting, diarrhea, rash, and thrombocytopenia. Additionally, the AEs in the studies where ixazomib is given in combination with standard agents are consistent with the safety profile of the individual agents in the combination regimen (eg, myelosuppression is common in regimens containing melphalan, and rash is common in regimens containing lenalidomide). While some of these potential toxicities may be severe, they can be managed by clinical monitoring for early recognition of adverse effects and standard medical intervention (as found in the ixazomib IB). Across the program, ixazomib appears to show signs of antitumor activity as evidenced by at least 50% reduction in disease burden in some patients, including patients that have been heavily pretreated as well as those with NDMM, and prolonging stabilization of the underlying disease in other patients across all ongoing studies. High quality responses, including achievement of minimal residual disease (MRD) negativity, has also been reported [23-25]. Although additional data are needed to establish the clinical benefit of this drug across additional indications, the emerging data support the continued development of ixazomib (see the ixazomib IB). Late-stage ixazomib development is ongoing in patients with NDMM, RRMM, and RRAL (Studies C16014 [NCT01850524], C16019 [NCT02181413], C16021 [NCT02312258], C16029 [NCT03170882], and C16011 [NCT01659658]).

4.3 Daratumumab

Daratumumab is a human IgG1 anti-CD38 mAb that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. CD38 is highly and uniformly expressed on all MM cells. In binding to CD38, daratumumab inhibits the growth of CD38-expressing tumor cells by inducing apoptosis directly through Fc mediated cross-linking as well as by immune-mediated tumor cell lysis through complement-dependent cytotoxicity (CDC), antibody-dependent cell mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis. For additional information regarding the pharmacokinetics (PK), pharmacodynamics, (pre)clinical experience, and safety profile of daratumumab, refer to the prescribing information [19,20].

4.3.1 Approval of Daratumumab for Patients Previously Treated for MM

Daratumumab received "breakthrough therapy" designation for RRMM by the US FDA in May 2013 [26]. In November 2015, the FDA granted accelerated approval for daratumumab in monotherapy to treat patients with MM who have received at least 3 prior treatments including a PI and an immunomodulatory drug (IMiD) or who are double-refractory to a PI and an IMiD. In May 2016 the European Medicines Agency (EMA) approved daratumumab monotherapy in Europe to treat patients with MM whose prior therapy included a PI and an IMiD and who have demonstrated PD on the last therapy. In 2017, both the FDA and the EMA approved daratumumab in combination with LenDex or bortezomib+dexamethasone (Vd) for the treatment of patients with

MM after at least 1 prior therapy. Daratumumab is also approved by the FDA in combination with pomalidomide and dexamethasone for the treatment of patients with MM who have received at least 2 prior therapies including lenalidomide and a PI. The approved dose and schedule when given in a 4-week treatment cycle is daratumumab 16 mg/kg IV every week for 8 doses, then every 2 weeks for 8 doses, then every 4 weeks onwards [19,20].

In heavily pretreated patients with RRMM, single-agent daratumumab was associated with an overall response rate (ORR) of 31.1% based on the results of 2 open-label single-arm studies [20,27,28]. The efficacy of daratumumab in combination with standard MM regimens was evaluated in 2 global, randomized, phase 3 studies (POLLUX: LenDex±daratumumab and CASTOR: Vd±daratumumab) in patients with RRMM who had received at least 1 prior therapy. In both studies the primary endpoint was met. Of particular relevance to this study, the rate of PFS was significantly higher in the daratumumab group (daratumumab+Vd) than in the control group (Vd) as reported in the CASTOR study; the 12-month rate of PFS was 60.7% in the daratumumab group versus 26.9% in the control group. After a median follow-up period of approximately 7 months, the median PFS was not reached in the daratumumab+Vd group compared with 7.2 months in the Vd group (HR: 0.39; P<0.001) [15]. The most frequently reported adverse reactions (incidence ≥20%) in clinical trials were infusion reactions, neutropenia, thrombocytopenia, fatigue, nausea, diarrhea, constipation, vomiting, muscle spasms, arthralgia, back pain, pyrexia, chills, dizziness, insomnia, cough, dyspnea, peripheral edema, peripheral sensory neuropathy, and upper respiratory tract infection [20]. Daratumumab use is associated with special considerations, namely infusion-related reactions (IRRs) but also blood typing interference and interference with complete response (CR) assessment. With daratumumab, IRRs have been reported in about half of patients receiving daratumumab: 95% of these were seen at the first dose. Typically the IRRs involve the upper respiratory tract and include rhinitis, cough, wheeze, bronchospasm, laryngospasm, and chest pain. More rarely they include rash, fever, and nausea [20,29]. For IRRs of any grade/severity, the daratumumab infusion should be immediately interrupted and medical management instituted as needed. Management of infusion reactions may further require reduction in the rate of infusion. Permanently discontinue daratumumab therapy for life-threatening (Grade 4) reactions. For further guidance see the DARZALEX prescribing information [20] as well as Section 8.3.3 of this protocol. The clinical development of daratumumab is currently ongoing (ir.genmab.com/releasedetail.cfm?releaseid=1026834, GenMab company announcement, accessed 19 September 2017).

4.4 Rationale for the Proposed Study

4.4.1 Rationale for an IDd Regimen

Although the prognosis for MM has improved over the past 2 decades because of the introduction of new and more effective therapies, it is still a fatal disease in nearly all cases and new treatment options are needed.

Preclinical work has demonstrated that the antimyeloma activity of daratumumab can be potentiated by combination with a PI (eg, bortezomib) and IMiD (eg, lenalidomide), even in patients refractory to a PI and IMiD. PIs may enhance the therapeutic activity of daratumumab by

enhancing the susceptibility of myeloma cells to natural killer cell-mediated killing, a key mechanism of antibody-mediated lysis of MM cells [30-33].

Ixazomib and daratumumab have both been investigated in patients with RRMM, including the population to be enrolled in this study. Ixazomib is an oral PI approved (under the brand name NINLARO) for use in combination with LenDex in patients with MM who have received at least 1 prior therapy [16,17]. Daratumumab is a human IgG1κ mAb against CD38. Daratumumab is approved (under the brand name DARZALEX) for patients with MM who have received at least 1 prior therapy (in combination with either Vd or LenDex; US and EU), in addition to approvals in patients who have been more heavily pretreated [19,20].

The rationale to investigate the potential of the IDd regimen is multifactorial:

- Bortezomib and lenalidomide have important antimyeloma activity in NDMM; however, not all patients respond. Even for patients who do respond, the natural course of MM is still characterized by multiple relapses which in many patients eventually are hampered by the development of drug resistance [34]. Therefore, there is an ongoing need to expand the active treatment options, prolong therapy with considerations to limiting toxicities, and improve patients' QOL, as well as provide treatments for patients who have developed drug resistance.
- Despite the positive impact of bortezomib for the treatment of MM, its use in clinical practice is limited by significant side effects, constraining administration schedules, and the development of drug resistance [34]. Bortezomib has a high incidence of peripheral neuropathy and requires injectable administration (either IV or subcutaneous administration). The concern regarding peripheral neuropathy results in limited treatment duration (approved duration 8 cycles) and potential premature treatment termination. Ixazomib is the only approved oral PI and has a more benign side effect profile compared to other PIs, including bortezomib, allowing for prolonged treatment until progression. Therefore, it is possible that ixazomib in combination with daratumumab and dexamethasone could provide patients with a treatment option that is a safer and more convenient regimen, potentially resulting in longer treatment duration and tumor control.
- Daratumumab has emerged as a very active and safe agent in MM, and therefore the IDd regimen could provide a PI combination that is lenalidomide sparing. This could be of particular relevance in patients treated with a lenalidomide-based combination regimen, namely since the recent approval of lenalidomide for NDMM and as maintenance therapy [35,36]. The increased exposure to lenalidomide in earlier lines of treatment necessitates options for PI-based therapy for patients who have relapsed while receiving, or who are refractory to, lenalidomide.
- New approaches are needed for patients with RRMM. Combining agents of different classes that have nonoverlapping and synergistic mechanisms of action can be a successful strategy to improve clinical outcomes for patients with MM [30]. As noted, ixazomib and daratumumab have different and nonoverlapping mechanisms of action. Ixazomib, as with the first-in-class PI bortezomib, may enhance the therapeutic effect of daratumumab by sensitizing tumor cells for antibody-mediated lysis [33].

- Triplet regimens are recommended for patients with RRMM, given the regimens' contribution to improvements in PFS [14,37,38]. The IDd regimen could offer patients an active triplet regimen with the extended treatment duration of PI therapy (ixazomib) that is non–lenalidomide-containing, as many patients discontinue lenalidomide therapy and are refractory to lenalidomide-based regimens as frontline therapy.

This phase 2 design will allow the assessment of efficacy and safety of the IDd regimen, given until progression, within the context of other available treatment options in RRMM. The primary endpoint will be the rate of very good partial response (VGPR) or better. Based on safety results from studies of both agents when given in combination regimens, it is expected that the safety profile will be consistent with that of the individual agents in the combination regimen (eg, IRR is common with daratumumab and rash is common with ixazomib) [16,17,19,20]. While some of the potential toxicities with either agent may be severe, they can be managed by clinical monitoring for early recognition of adverse effects and standard medical intervention. An internal interim safety review will be conducted early in the proposed trial given ixazomib and daratumumab have not been combined previously (see Section 13.2 for more details).

4.4.2 Rationale for Dose and Schedule

The dose and schedule for both ixazomib and daratumumab are the ones approved for patients with RRMM. Ixazomib will be given at 4 mg by mouth weekly on Days 1, 8, and 15 in a 28-day cycle. With a 28-day cycle (4-week treatment cycle), daratumumab will be given at a dose of 16 mg/kg IV every week for 8 doses, then every 2 weeks for 8 doses, then every 4 weeks onwards. Dexamethasone is part of the anti-MM background regimen, but in this combination consideration needs to be made for the management of daratumumab- induced IRR. Therefore, dexamethasone will be given weekly in split doses, ie, 20 mg the day before and after each daratumumab IV infusion. For patient consistency and aid in compliance, the same dexamethasone schedule (2 sequential days) will be followed even on non-daratumumab infusion weeks [20].

[redacted]

4.4.4 Rationale for PK Assessments

In order to characterize the PK of ixazomib in combination with daratumumab and dexamethasone, an adequate number of sparse PK samples will be collected in Cycles 1 to 5 of the study. The PK data collected in this study will contribute to population PK analyses for ixazomib and may also be used for exposure-response analyses.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To evaluate the proportion of patients with a response of VGPR or better to IDd treatment.

5.1.2 Secondary Objectives

The secondary objectives are:

- To measure PFS, TTP, and OS.
- To measure ORR, time to response (TTR), and DOR.
- To collect plasma concentration-time data for ixazomib to contribute to population PK analyses.
- To evaluate the safety/tolerability of IDd administered in a 28-day cycle.

5.1.3 Exploratory Objectives

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoint is the rate of VGPR or better, as evaluated by the investigator according to IMWG criteria, in patients that are response-evaluable (see Appendix E) [1-3].

5.2.2 Secondary Endpoints

The secondary endpoints are:

- PFS, defined as the time from the date of first dose of any study drug treatment to the date of first documentation of progressive disease (PD)-based IMWG criteria as evaluated by investigator, or death due to any cause, whichever occurs first [1-3].
- TTP, defined as the time from the date of first dose of any study drug treatment to the date of first documented evidence of PD.
- OS, measured as the time from the date of first dose of any study drug treatment to the date of death.
- ORR (defined as CR, VGPR, plus partial response [PR]; per IMWG criteria) during or after the study treatment, but before subsequent therapy or PD.
- TTR, defined as the time from the date of first dose of any study drug treatment to the date of first documented PR or better.
- DOR, measured as the time from the date of first documentation of PR or better to the date of first documented progression among those patients that responded.

5.2.3 Exploratory Endpoints

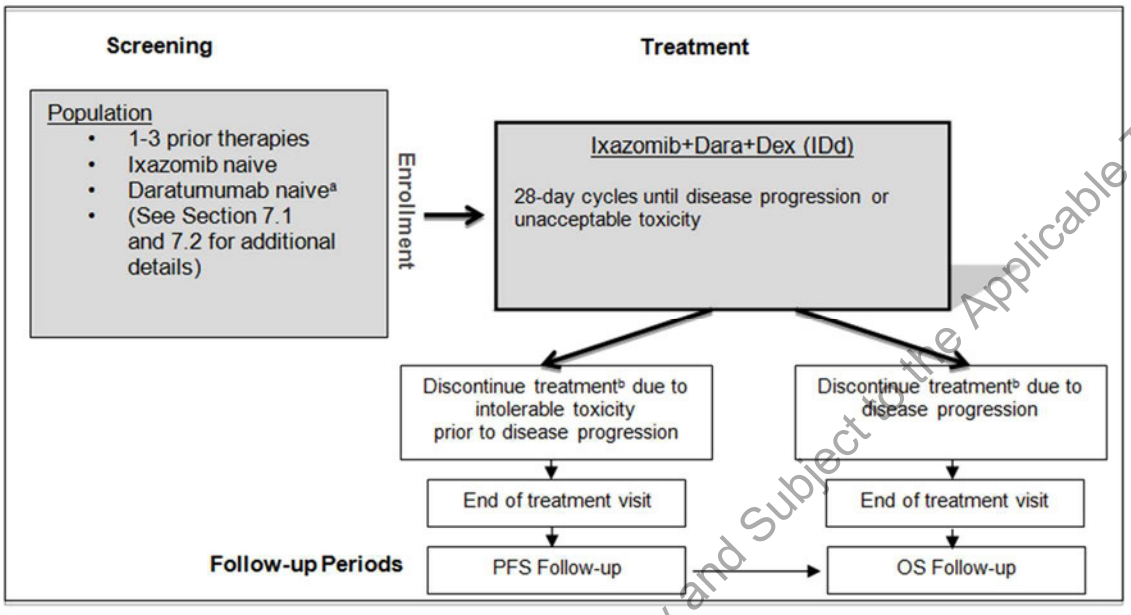
[redacted]

6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a prospective, open-label, multicenter, phase 2 study to evaluate the efficacy and safety of oral ixazomib in combination with daratumumab and dexamethasone in adult patients with MM who have received at least 1 prior therapy. It is expected that approximately 60 patients will be enrolled. The study design is illustrated in Figure 6.a.

Figure 6.a Study Schema



Abbreviations: Dara, daratumumab; Dex, dexamethasone.
(a) Patients must not have received prior daratumumab or other anti-CD38 therapies except as part of initial therapy if this was stopped to move on to SCT and the patient did not progress on anti-CD38 treatment.
(b) Note that treatment discontinuation applies only to discontinuation of the full study treatment regimen (ixazomib, daratumumab, and dexamethasone). For modifications of individual study drugs, see Section 8.3.

6.1.1 Study Population

The patient population will consist of adult patients who have been diagnosed with MM [1,2]. All patients must have documented evidence of PD, as defined by IMWG criteria (see Appendix E), on or after their last regimen [1-3]. All patients must have received between 1 to 3 prior therapies for MM. See Section 7.1 and Section 7.2 for eligibility criteria details.

6.2 Number of Patients

The expected enrollment is approximately 60 patients.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

All patients will receive study therapy until they experience PD, have an unacceptable toxicity, withdraw consent, the study has completed, or until the sponsor terminates the study.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The study will be completed approximately 1 year after 50% of patients have died or experienced PD. The estimated timeframe is approximately 4 years after first patient in (FPI).

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Refer to Table 6.a for disclosure information for all primary and secondary endpoints.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame*
Primary: Rate of VGPR or better	Response of VGPR or better as evaluated by the investigator according to IMWG criteria [1-3].	Up to 3 years
Secondary: PFS	The time from first study drug treatment dose to the first occurrence of confirmed PD, as evaluated by an Investigator, according to IMWG criteria [49], or death from any cause, whichever occurs first.	Up to 5 years
Secondary: TTP	The time from first study drug treatment dose to first documentation of PD.	Up to 5 years
Secondary: OS	The time from first study drug treatment dose to death from any cause.	Up to 5 years
Secondary: ORR	PR, VGPR, or CR, as evaluated by the investigator according to IMWG criteria.	Up to 5 years
Secondary: TTR	The time from first study drug treatment dose to the first documentation of PR or better.	Up to 5 years
Secondary: DOR	The time from the first documentation of PR or better to first documentation of PD.	Up to 5 years

Abbreviations: DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression; TTR, time to response.
*Some endpoints are event-driven and timing may shift.

6.3.4 Total Study Duration

It is anticipated that this study will last for approximately 4 years after FPI. However, the study duration is dependent on rate of accrual and of maturation of the different endpoints.

6.3.5 Posttrial Access

At the conclusion or termination of the study, participants still remaining on ixazomib and/or daratumumab will be given the opportunity to participate in the optional ixazomib (NINLARO) posttrial access (PTA) program in order to continue receiving ixazomib and/or daratumumab if, in the opinion of the investigator and confirmed by the sponsor, the patient continues to receive clinical benefit from ixazomib and/or daratumumab. This is a voluntary program. Alternatively, investigators have the option of transferring their patients to standard-of-care treatment or treating their patients outside of the PTA program.

Duration of Posttrial Access

Participants in the PTA program will be offered ixazomib (NINLARO) until they no longer benefit from ixazomib, the benefit-risk no longer favors the individual, and/or ixazomib is commercially available for the indication under study in the participants' market, and/or the sponsor deems the PTA program is no longer viable. The PTA program may also be terminated in a country or geographical region where the marketing authorization has been rejected, the development of ixazomib has been suspended or stopped by the sponsor, or where ixazomib can no longer be supplied.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

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

- Adult patients (aged ≥18 years) who have been diagnosed with MM according to IMWG criteria [1-3].
- All patients must have measurable disease by at least 1 of the following measurements:
  - Serum M-protein ≥1 g/dL (≥10 g/L).
  - Urine M-protein ≥200 mg/24 hours.
- All patients must have documented evidence of PD on or after their last regimen as defined by IMWG criteria (see Appendix E) [1-3]. All patients must have received between 1 to 3 prior therapies for MM (a prior therapy is defined as 2 or more cycles of therapy given as a treatment plan for MM [eg, a single-agent or combination therapy or a sequence of planned treatments such as induction therapy followed by autologous SCT and then consolidation and/or maintenance therapy]).
- All patients must have achieved a response (PR or better) to at least 1 prior therapy.
- All patients must have an Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2.
- All patients must meet the following laboratory criteria:
  - Absolute neutrophil count (ANC) ≥1000/mm^3.
  - Platelet count ≥75,000/mm^3.

  - Total bilirubin ≤1.5 x the upper limit of the normal range (ULN) (except for Gilbert syndrome: direct bilirubin ≤2 x ULN).
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x ULN.
  - Calculated creatinine clearance ≥50 mL/min.
- Female patients who:
  - Are postmenopausal for at least 1 year before the screening visit, OR
  - Are surgically sterile, OR
  - If they are of childbearing potential, agree to use effective contraceptive measures during and for 90 days following treatment. Advise women using hormonal contraceptives to also use a barrier method of contraception (see Appendix H for details). For women of childbearing potential, a pregnancy test must be negative before the first dose of study treatment is administered.
- Male patients, even if surgically sterilized (ie, status postvasectomy), who:
  - Agree to use effective contraceptive measures during and for 90 days following treatment (see Appendix H for details).
- Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
- Patient is willing and able to adhere to the study visit schedule and other protocol requirements.

7.2 Exclusion Criteria

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

- Patients have undergone prior allogenic bone marrow transplantation.
- Patients have received prior ixazomib at any time or daratumumab or other anti-CD38 therapies, except as part of initial therapy if this was stopped to move on to SCT and the patient did not progress on anti-CD38 treatment.
- Patients are refractory to bortezomib or carfilzomib at the last exposure before this study (defined as patient having PD while receiving bortezomib or carfilzomib therapy or within 60 days after ending bortezomib or carfilzomib therapy).
- Patients planning to undergo SCT prior to PD on this study (ie, these patients should not be enrolled in order to reduce disease burden prior to transplant).
- Patients receiving systemic treatment with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital, St. John's wort) within 14 days before randomization.

- Patient has received autologous SCT within 12 weeks before the date of study treatment.
- Patient has received an investigational drug (including investigational vaccines) within 4 weeks before study treatment (except for investigational antimyeloma agents, which cannot be taken within 2 weeks prior or 5 PK half-lives of the treatment, whichever is longer, before the date of study treatment). The only exception is emergency use of a short course of corticosteroids (equivalent of dexamethasone 40 mg/day for a maximum 4 days) before treatment.
- Patients with known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal. Note: FEV1 testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 is <50% of predicted normal.
  - Patients with Grade 2 or higher residual toxicities from prior therapy (including Grade 2 or higher peripheral neuropathy or any grade neuropathy with pain; excluding alopecia). This includes recovery from any major surgery. Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate. Kyphoplasty or vertebroplasty are not considered major surgery.
- Patients with known allergy to any of the study medications, their analogues, their excipients, mAbs or human proteins or known sensitivity to mammalian-derived products.
- Patient has uncontrolled clinically significant cardiac disease, including myocardial infarction within 6 months before date of study entry or unstable or uncontrolled angina, congestive heart failure, New York Heart Association (NYHA) Class III-IV, uncontrolled cardiac arrhythmia (Grade 2 or higher).
- Patients with ongoing or active systemic infection requiring IV medical management; patients with known HIV-RNA positivity; patients with hepatitis B virus (HBV) surface antigen or core antibody positivity; and patients with known hepatitis C virus-RNA positivity. Patients who have positive hepatitis C antibody can be enrolled but must have hepatitis C virus-RNA negativity.

  Note: Patients who are already enrolled at the time of Amendment 02 should have local HBV testing performed as soon as possible for HBV surface antigen, e antigen, core antibody, and DNA. If any of these tests is positive, consult a physician with expertise in managing HBV for guidance regarding stopping daratumumab, starting HBV antiviral therapy, and remaining on study [50,51]. See Sections 8.3.3.2, 8.7.2, 9.4.3.1, and Appendix A for more information.
- Patient has any concurrent medical condition or disease that is likely to interfere with study procedures, results, or assessment of safety or toxicity or that in the opinion of the investigator would constitute a hazard for participating in this study.
- Patients diagnosed or treated for another malignancy within 2 years before randomization or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

- Patient is pregnant.

8.0 STUDY THERAPY

8.1 Overview

All protocol-specific criteria for administration of study therapy must be met and documented before drug administration. Study therapy will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Daratumumab should be administered by a healthcare professional, with immediate access to emergency equipment and appropriate medical support to manage IRRs if they occur. Refer to DARZALEX prescribing information [20].

Patients should be monitored for toxicity as necessary and doses of the appropriate study therapy should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose holds, and adjustments of the dose (see Section 8.3).

Each AE should be attributed to a specific drug (ie, ixazomib, daratumumab, or dexamethasone), if possible, so that dose modifications can be made accordingly. Only 1 dose modification per cycle will be performed for a given agent when toxicity is suspected to be related primarily to that agent. Reduction, including discontinuation, of 1 agent and not the other is appropriate if the toxicity is suspected to be related primarily to that 1 agent. No dose increases of any agent are allowed. No daratumumab dose reductions are permitted (see Section 8.3.3 for permitted modifications).

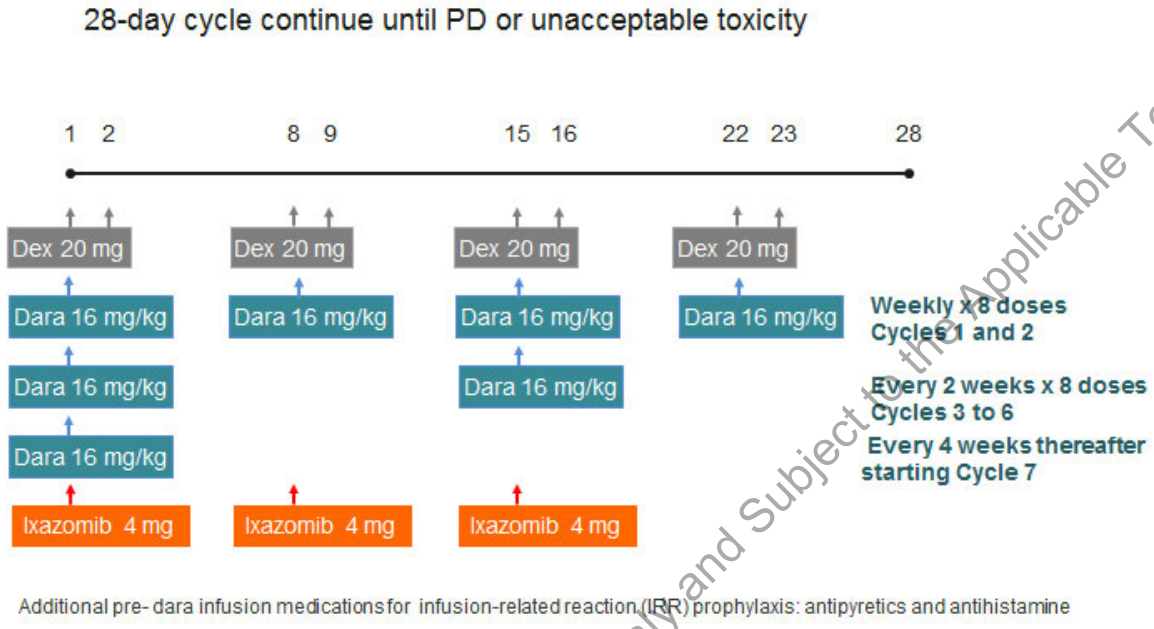
The start of a cycle is defined as the start of either daratumumab or ixazomib. If both daratumumab and ixazomib are held, then this should be reported as a cycle delay.

Every effort should be made to follow the planned dosing schedule; however, occasional changes are allowable for holidays, vacations, and other administrative reasons or for a longer window after discussion with the Takeda project clinician or designee. If the study cycle schedule is shifted, assessments must be shifted to ensure that collection of assessments is completed before dosing.

8.2 Study Treatment Administration

For the purposes of this protocol, study treatment regimen is defined as the combination of ixazomib, daratumumab, and dexamethasone. All cycles are approximately 28 days with treatment given until PD or unacceptable toxicity (see Figure 8.a).

Figure 8.a Study Treatment Administration



Abbreviations: Dara, daratumumab; Dex, dexamethasone; PD, progressive disease.

8.2.1 Order of Study Treatment Administration

In principle, when ixazomib and daratumumab are administered in the same week, they should be administered on the same day of the week to align the dexamethasone premedication, which is given before daratumumab, as noted below in Section 8.2.4.

- For Cycle 1: Due to the potential of IRR with daratumumab, during the first cycle of therapy it is preferable to give the daratumumab dose before the ixazomib dose to allow for accurate safety assessment and management of any IRRs. Given the long daratumumab infusion time during the first cycle, ixazomib should be taken later the same day after resolution of any IRR; however, if there was an IRR that required treatment or prolonged the daratumumab infusion, ixazomib should be given within 24 hours after the start of the daratumumab infusion.
- For Cycle 2 and beyond: If there have been no Grade 3 or higher IRRs in the previous cycle, ixazomib can be given prior to or at approximately the same time as the premedications. The daratumumab infusion should begin approximately 1 hour after the ixazomib administration. To support consistency for patients, the same dexamethasone schedule (split dose on 2 sequential days) will be followed even on weeks without daratumumab infusion (see Figure 8.a).

8.2.2 Daratumumab

Daratumumab will be administered as an IV infusion. Each patient's dose will be calculated on the basis of the patient's weight rounded to the nearest kilogram. The dose does not need to be recalculated for weight changes that are <10% from baseline. All infusions may be performed as outpatient visits.

Patients will receive pre- and postinfusion medications (see Section 8.2.2.1). All patients should have blood pressure monitored before and after all infusions. Additional vital sign monitoring may be done as medically needed. For complete details on daratumumab, refer to the most current local product prescribing information [20].

8.2.2.1 Concomitant Pre-infusion and Postinfusion Medications

Pre-infusion Medication

Administer the following pre-infusion medications to reduce the risk of IRRs to all patients 1 to 3 hours before every infusion of daratumumab:

- Administer 20 mg dexamethasone before every daratumumab infusion (further described below in Section 8.2.4).
  - Note: Dexamethasone is given IV before the first daratumumab infusion and oral administration may be considered before subsequent infusions.
- Antipyretics (oral acetaminophen 650 to 1000 mg).
- Antihistamine (oral or IV diphenhydramine 25 to 50 mg or equivalent).
- Montelukast 10 mg orally.

Postinfusion Medication

- Administer 20 mg dexamethasone the day after every daratumumab infusion (further described below in Section 8.2.4).
- In addition, for any patients with a history of COPD, consider prescribing postinfusion medications such as short- and long-acting bronchodilators and inhaled corticosteroids. After the first 4 infusions, if the patient experiences no major IRRs, these additional inhaled postinfusion medications may be discontinued [20]. In addition, these at-risk patients may be hospitalized for monitoring for up to 2 nights after an infusion. If these at-risk patients are hospitalized, then their FEV1 should be measured before discharge. If these patients are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours after all infusions. If no IRR has occurred, the follow-up telephone call 48 hours after the infusion is not required. If the patient did not experience a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as an SAE. Investigators may prescribe bronchodilators, antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after patients are released from the hospital/clinic. If an at-risk subject experiences no major

IRRs, then these postinfusion medications may be waived after 4 doses at the investigator's discretion.

8.2.2.2 Daratumumab Schedule and Administration

Daratumumab will be given on the following schedule (see Appendix A):

- Cycles 1 and 2: Days 1, 8, 15, and 22 (every week; 8 doses in total).
- Cycles 3 to 6: Days 1 and 15 (every 2 weeks; 8 doses in total).
- Cycles 7 and beyond: Day 1 (every 4 weeks).

Daratumumab infusion rates are given in Table 8.a. Incremental escalation of the infusion rate should only be considered in the absence of IRRs.

Upon implementation of Amendment 04, to prioritize the safety of patients during the COVID-19 pandemic, patients may have their infusion duration reduced to no less than 90 minutes if they did not have a history of an IRR at any time after the third dose (Table 8.a and Appendix J).

Table 8.a Infusion Rates for Daratumumab IV Administration

	Dilution Volume	Initial Rate (first hr)	Rate Increment (a)	Maximum Rate
First infusion	1000 mL	50 mL/hr	50 mL/hr every hr	200 mL/hr
Second infusion (b, c)	500 mL	50 mL/hr	50 mL/hr every hr	200 mL/hr
Subsequent infusions (d)	500 mL	100 mL/hr	50 mL/hr every hr	200 mL/hr
To prioritize the safety of patients during the COVID-19 pandemic, subsequent infusions may instead be administered to patients (if they do not have a history of IRR at any time after their third dose) as noted here:	Daratumumab can be administered at an initial rate of 20% of the total dose over 30 minutes, followed by the remaining 80% of the total dose over 60 minutes (no less than a 90-minute total infusion time). The accelerated infusion will be given in a total volume of 500 mL. This allows for a rate of 200 mL/hr for the first 30 minutes and a rate of 400 mL/hr for the final 60 minutes. See Appendix J for the full memo from Janssen-Cilag International NV.			

Source: DARZALEX prescribing information [20].

Abbreviations: COVID-19, coronavirus disease 2019; hr, hour; IV, intravenous; IRR, infusion-related reaction.

(a) Consider incremental escalation of the infusion rate only in the absence of infusion reactions.

(b) Use a dilution volume of 500 mL only if there were no Grade 1 (mild) or greater infusion reactions during the first 3 hours of the first or second infusion. Otherwise, continue to use a dilution volume of 1000 mL and instructions for the first infusion.

(c) Alternative option for second dose is to use 1000 mL dilution volume but start at a faster rate and not decrease to 500 mL dilution volume until dose 3.

(d) Use a modified initial rate for subsequent infusions (ie, third infusion onwards) only if there were no Grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥100 mL/hr in the first 2 infusions. Otherwise, continue to use instructions for the second infusion.

Missed (Held) Daratumumab Doses

Every effort should be made to keep patients on the planned dosing schedule. However, doses given within 3 days of the scheduled dose are permitted, as long as the interval between doses is at least 5 days. If daratumumab administration does not commence within the prespecified window of the scheduled administration date, for toxicity or other reasons, then the dose will be considered a missed (held) dose. Administration may resume at the next planned dosing date. A missed (held) dose will not be made up. If a planned dose of daratumumab is missed (held), bring the situation to the attention of the Takeda project clinician or designee at the earliest possible time.

Patients missing ≥3 consecutive planned doses of daratumumab for reasons other than toxicity should be withdrawn from daratumumab treatment, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon. Any dose hold of more than 28 days due to toxicity will result in permanent discontinuation of daratumumab. Ixazomib dosing may continue if the toxicity was attributable to daratumumab.

See Section 8.3 dose modification and Section 8.7 management of clinical events for more information.

8.2.3 Ixazomib

Ixazomib will be given as an oral dose weekly (Days 1, 8, and 15) for 3 weeks, followed by 1 week without ixazomib in a 28-day cycle (Appendix A). Refer to the Study Manual for additional instructions regarding study therapy administration.

Patients should be instructed to swallow ixazomib capsules whole with water and not to break, chew, or open the capsules. Ixazomib should be taken on an empty stomach, at least 1 hour before or at least 2 hours after food. The capsule should be swallowed with water. A total of approximately 240 mL (8 ounces) of water should be taken with the capsules. Missed doses can be taken as soon as the patient remembers as long as the next scheduled dose is 72 hours or more away. A double dose should 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.

8.2.4 Dexamethasone

Dexamethasone is usually given as 1 dose; however, in this study, it will be given in split doses as follows, as it is being used for both its antimyeloma activity and as prophylaxis for daratumumab-induced IRRs:

- Dexamethasone will be given as 20 mg on Days 1, 2, 8, 9, 15, 16, 22, and 23 in each 28-day cycle, to achieve the standard total of 40 mg per week (2 doses of 20 mg per week).
- Dexamethasone should be given IV before the first daratumumab dose but can be given IV or orally thereafter. The subsequent doses (ie, day after daratumumab infusion) can be given orally.

- For patient consistency and compliance, the same dexamethasone schedule (2 sequential days) will be followed even on weeks without daratumumab infusion (see Figure 8.a).
- The dose of dexamethasone can be reduced to 20 mg once weekly for patients who are older than 75 years, have poorly controlled diabetes, or had prior intolerance to or AE from corticosteroid therapy (see Section 8.3.4). On daratumumab dosing days, the dose of dexamethasone must be given prior to daratumumab infusion (see Section 8.3.4).

Dexamethasone should be administered considering patient tolerability. Ideally it would be taken at approximately the same time each dosing day. If a dose of dexamethasone is missed, the dose should be taken as soon as the patient remembers it. If enough time has elapsed that it is almost time for the next dose (within 6 hours), the missed dose should be skipped and the next dose taken according to the regular dosing schedule. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose. Note the use of dexamethasone as a pre- and postinfusion medication for daratumumab.

8.3 Dose Modification Guidelines

8.3.1 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

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

- ANC $\geq$1000/mm^3.
- Platelet count $\geq$75,000/mm^3 without platelet transfusion support.
- All nonhematologic toxicity considered to be related to treatment with study therapy must have resolved to $\leq$Grade 1, to the patient's baseline values, or to a severity level considered stable and tolerable by the investigator/patient (eg, Grade 2 chronic kidney disease due to underlying MM).

If the patient does not meet the above-cited criteria for retreatment, initiation of the next cycle of IDd should be delayed for 1 week. After 1 week, the patient should be re-evaluated to determine whether the criteria for retreatment have been met. If the patient continues not to meet the previously cited criteria, delay IDd and continue to re-evaluate. Should the start of the next cycle need to be delayed >2 weeks because of incomplete recovery from treatment-related toxicity, consult with the Takeda project clinician or designee. Each AE should be attributed to a specific drug (ie, ixazomib, daratumumab, or dexamethasone), if possible, so that dose modifications can be made accordingly. In cases where the residual toxicity after >2 weeks can clearly be attributed to 1 of the drugs (eg, only to ixazomib or only to daratumumab), continuation of therapy with the other drugs within the study treatment regimen rather than permanent discontinuation of all study treatment can be considered.

8.3.2 Ixazomib Treatment Modification

Patients experiencing AEs attributed to ixazomib may continue in the study but may have doses of ixazomib modified (delayed, held, or reduced by at least 1 dose level [dose reduction levels as per Table 8.b]). When a dose reduction of ixazomib is required because of toxicity, no dose re-escalation will be permitted. Treatment reductions because of ixazomib-related AEs are outlined for hematologic and nonhematologic toxicities in Table 8.c and Table 8.d.

Table 8.b Dose Reduction Steps for Ixazomib

Current Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
4 mg	3 mg	2.3 mg	Discontinue ixazomib

Table 8.c Ixazomib and Daratumumab Dose Modification for Hematologic Toxicities

Hematologic Toxicities	Recommended Actions
Thrombocytopenia (Platelet Count)	
Platelet count less than 25,000/mm^3 without clinically significant bleeding, need for transfusion, or results in 2 weeks or less delay in start of the next cycle of therapy. *Clinically significant bleeding is determined by investigator medical judgement.*	Hold ixazomib and daratumumab until platelet count resolved to ≥75,000/mm^3. Note platelet count must recover to at least 75,000/mm^3 without platelet transfusion support to start a new cycle of therapy as per Section 8.3.1. • Following recovery, resume both ixazomib and daratumumab at the most recent dose.
Platelet count less than 25,000/mm^3 with clinically significant bleeding, need for transfusion, or results in more than a 2-week delay in start of next cycle. *Clinically significant bleeding is determined by investigator medical judgement.*	Hold ixazomib and daratumumab until platelet count resolved to ≥75,000/mm^3. Note platelet count must be to at least 75,000/mm^3 without platelet transfusion support to start a new cycle of therapy as per Section 8.3.1. • Following recovery, resume ixazomib at the next lower dose and resume daratumumab.
Neutropenia (ANC)	
ANC less than 500/mm^3 without febrile neutropenia, infection, or results in 2 weeks or less delay in start of the next cycle of therapy.	Withhold ixazomib and daratumumab until ANC resolved to at least 1000/mm^3. Consider adding granulocyte colony-stimulating factor (G-CSF) as per clinical guidelines. • Following recovery, resume ixazomib and daratumumab at the most recent dose
ANC less than 500/mm^3 with febrile neutropenia, infection, or results in more than a 2 week delay in start of next cycle.	Withhold ixazomib and daratumumab until ANC resolved to at least 1000/mm^3. Symptomatic management per clinical practice. Consider adding G-CSF as per clinical guidelines. • Following recovery, resume ixazomib at the next lower dose and resume daratumumab.

ANC, absolute neutrophil count; G-CSF, granulocyte colony stimulating factor.

Table 8.d Ixazomib Dose Modification for Nonhematologic Toxicities

Nonhematologic Toxicities	Recommended Actions
Rash	
Grade 2 or 3	Withhold ixazomib until rash recovers to Grade 1 or lower. Supportive care and prophylaxis are recommended (see Section 8.7). • Following recovery, resume ixazomib at the next lower dose. Note: if Stevens-Johnson syndrome occurs, ixazomib should be discontinued
Grade 4	Discontinue ixazomib.
Peripheral Neuropathy	
Grade 1 Peripheral Neuropathy with Pain or Grade 2 Peripheral Neuropathy	Withhold ixazomib until peripheral neuropathy recovers to Grade 1 or lower without pain or patient's baseline. • Following recovery, resume ixazomib at the most recent dose.
Grade 2 Peripheral Neuropathy with Pain or Grade 3 Peripheral Neuropathy	Withhold ixazomib. Toxicities should, at the physician's discretion, generally recover to patient's baseline condition or Grade 1 or lower prior to resuming ixazomib. • Following recovery, resume ixazomib at the next lower dose.
Grade 4 Peripheral Neuropathy	Discontinue ixazomib.
Other Nonhematologic Toxicities	
Other Grade 3 or 4 Nonhematologic Toxicities	Withhold ixazomib. Toxicities should, at the physician's discretion, generally recover to patient's baseline condition or Grade 1 or lower prior to resuming ixazomib. • If attributable to ixazomib, resume ixazomib at the next lower dose following recovery.

8.3.3 Daratumumab Treatment Modification

Increasing the frequency of daratumumab dosing is not permitted at any point. Also no daratumumab dose reductions are permitted.

8.3.3.1 Infusion Rates and Management of IRRs

Administer daratumumab infusion IV at the infusion rate described above in Table 8.a. Consider incremental escalation of the infusion rate only in the absence of infusion reactions.

For infusion reactions of any grade/severity, immediately interrupt the daratumumab infusion and manage symptoms. Management of IRRs may further require reduction in the rate of infusion, or treatment discontinuation, of daratumumab as outlined below:

- Grade 1 or 2 (mild to moderate): Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as clinically appropriate, up to the maximum rate of 200 mL/hour (Table 8.a).
- Grade 3 (severe): Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in Table 8.a. Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or higher IRR.
- Grade 4 (life threatening): Permanently discontinue daratumumab treatment.

No daratumumab dose reductions are permitted. If any of the following criteria are met and the event is ascribed to daratumumab, the daratumumab infusion must be held to allow for recovery from toxicity:

- Hematologic toxicities are overlapping toxicities with ixazomib and daratumumab, thus also note Table 8.c above for dose modification considerations.
- Grade 3 or higher nonhematologic toxicities with the following exceptions:
  - Grade 3 nausea or Grade 3 vomiting that responds to antiemetic treatment.
  - Grade 3 diarrhea that responds to antidiarrheal treatment.
  - Grade 3 fatigue or asthenia that lasts for <7 days after the last administration of daratumumab.

Daratumumab treatment should be resumed when the toxicity has resolved to ≤Grade 2 (see Section 8.3.1 and Table 8.c). If daratumumab administration does not commence within the prespecified window of the scheduled administration date, then the dose will be considered a missed (held) dose (see Section 8.2.2.2). Administration may resume at the next planned dosing date (see Table 8.e). A missed (held) dose will not be made up.

Table 8.e Daratumumab-Related Toxicity Management

Daratumumab-Related Toxicity Management

Cycles	Dosing Frequency	Dose Miss	Dosing Resumption
1 and 2	Weekly (QW)	>3 days	next planned weekly dosing date
3 to 6	Biweekly (Q2W)	>7 days	next planned biweekly dosing date
7+	Every 4 weeks (Q4W)	>21 days	next planned every 4 weeks dosing date

A daratumumab dose held for more than 3 days after the per-protocol administration date for any reason other than toxicities suspected to be related to daratumumab should be brought to the attention of the sponsor at the earliest possible time. Patients missing ≥3 consecutive planned doses of daratumumab for reasons other than toxicity should be withdrawn from treatment, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

Any dose hold of more than 28 days due to toxicity will result in permanent discontinuation of daratumumab. Ixazomib dosing may continue if the toxicity was attributable to daratumumab.

8.3.3.2 Management of HBV Reactivation

Patients who are already enrolled at the time of Amendment 02 should undergo local HBV testing as soon as possible for HBV surface antigen, e antigen, core antibody, and DNA. If any of these tests is positive, consult a physician with expertise in managing HBV for guidance regarding stopping daratumumab, starting HBV antiviral therapy, and remaining on study. These patients should be monitored every cycle during, and for at least 6 month after the end of, daratumumab treatment for clinical and laboratory signs of HBV reactivation (ie, positive HBV surface antigen, positive HBV e antigen, or positive HBV DNA) [50,51]. If this monitoring reveals HBV reactivation, further treatment, including stopping daratumumab if relevant, should be discussed with a physician with expertise in managing HBV. The sponsor's study clinician (or designee) should be consulted about the continued administration of the other study drugs (ixazomib and dexamethasone).

See Section 9.4.3.1 and Appendix A for more information.

8.3.4 Dexamethasone Treatment Modification

Patients experiencing AEs attributed to dexamethasone may have doses of dexamethasone modified. When a dose reduction of dexamethasone is required because of toxicity, no dose re-escalation will be permitted. All dexamethasone treatment modifications are according to the local prescribing information.

After Cycle 6, the dose of dexamethasone may be reduced to a minimum of 20 mg/week at the investigator's discretion (see Section 8.2.4). The 20 mg dose of dexamethasone given before the infusion (whether given IV or orally) on the day of daratumumab dosing must not be decreased. When dexamethasone is reduced to 20 mg/week and is given as pre-infusion medication, patients may receive low-dose methylprednisolone (≤20 mg) orally (or equivalent in accordance with local standards) for the prevention of delayed IRRs as clinically indicated. If the patient isn't tolerating dexamethasone at 20 mg/week, alternative low-dose corticosteroids may be considered in accordance with local standards and in consultation with the Takeda project clinician or designee.

8.4 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study.

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

- Strong cytochrome P-450 3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital, and St John's wort.

Refer to the local prescribing information for drug-drug interaction information for daratumumab [19,20].

The following procedures are prohibited during the treatment period of the study:

- Any antineoplastic treatment with activity against MM, other than study therapy.
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates PD; "spot" radiation for areas of pain is permitted).

8.5 Permitted Concomitant Medications and Procedures

All necessary supportive care consistent with optimal patient care will be available to patients, as necessary. All blood products and concomitant medications received from the signing of the informed consent form (ICF) until 30 days after the final dose of study therapy will be recorded in the electronic case report forms (eCRFs).

The following medication is mandatory during the study:

- Unless there is a clinical contraindication, prophylactic varicella-zoster virus antiviral therapy is required for all patients while receiving study treatment. Examples of acceptable antiviral therapy include acyclovir (eg, 400 mg given orally, 3 times a day), famciclovir (eg, 125 mg given orally, twice a day), or valacyclovir (eg, 500 mg given orally, twice a day) or standard of care/local practice.

The following medications and procedures are permitted during the study:

- Myeloid growth factors (eg, G-CSF) are permitted. Use should follow the local prescribing information, published guidelines, and/or institutional practice; however, alternative usage may be reviewed with the Takeda project clinician or designee.
- Patients should be transfused with red cells and platelets as clinically indicated except to meet study inclusion criteria or within 3 days of the start of the next cycle as a means to meet platelet thresholds to start the next cycle.
- Patients with previously identified lytic destruction of bone or with osteopenia can receive treatment with bisphosphonates or denosumab, if available for patients with MM, according to the American Society of Clinical Oncology Clinical Practice Guidelines or institutional practice in accordance with the local prescribing information, unless specifically contraindicated.

- Patients with evidence of HBV exposure or reactivation may receive HBV therapy as clinically indicated by a physician with expertise in managing HBV [50,51].
- Supportive measures consistent with optimal patient care may be given throughout the study.

8.6 Precautions and Restrictions

Fluid deficit should be promptly corrected before initiation of, and during treatment with, ixazomib.

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

Caution should be used when administering contrast materials for imaging in patients with impaired renal function, as per standard practice.

It is not known what effects ixazomib and daratumumab have on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients who:

- Are postmenopausal for at least 1 year before the screening visit, OR
- Are surgically sterile, OR
- If they are of childbearing potential, agree to use effective contraceptive measures during and for 90 days following treatment. Dexamethasone is known to be a weak to moderate inducer of CYP3A4 as well as other enzymes and transporters. Because ixazomib is administered with dexamethasone, the risk for reduced efficacy of contraceptives needs to be considered. Advise female patients using hormonal contraceptives to also use a barrier method of contraception (see Appendix H for details).

Male patients, even if surgically sterilized (ie, status postvasectomy), agree to use effective contraceptive measures during and for 90 days following treatment (see Appendix H for details).

8.7 Management of Clinical Events

8.7.1 Ixazomib

Symptomatic measures for ixazomib-related AEs are detailed below. Refer to Section 8.3 for information on dose modifications.

Prophylaxis Against Risk of Reactivation of Herpes Infection

Patients may be at an increased risk of infection including reactivation of herpes zoster and herpes simplex viruses. Unless there is a clinical contraindication, prophylactic antiviral therapy is

required for every patient while receiving study treatment (see Section 8.5 for examples of acceptable antiviral therapy).

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 is permitted.

Management of a Grade 3 rash may require IV antihistamines or corticosteroids. Administration of ixazomib should be modified per protocol and reinitiated at a reduced level from where rash was noted (see Table 8.d). In line with clinical practice, dermatology consult and biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a patient has previously developed a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body or oral or topical antihistamines).

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

Thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol, with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib administration should be modified according to dose modification recommendations in the protocol when thrombocytopenia occurs (see Table 8.c). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenia purpura and hemolytic uremic syndrome (HUS), 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 it 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 when neutropenia occurs (see Table 8.c). Febrile neutropenia should be managed as per local guidelines. Therapy can be reinitiated at a reduced level upon recovery of 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 ixazomib 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 ixazomib and as needed during treatment to avoid dehydration.

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome 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

(MRI) or computed tomography (CT). If the syndrome is diagnosed or suspected, symptom-directed treatment should be maintained until the condition is reversed by control of hypertension or other instigating factors. Ixazomib therapy should be discontinued.

Transverse Myelitis

Transverse myelitis has been reported with ixazomib. It is not known whether ixazomib causes transverse myelitis; however, because transverse myelitis has happened in patients 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

Overdose has been reported in patients taking ixazomib, and the symptoms of overdose are generally consistent with the known risks of ixazomib. Reports of accidental overdose have been associated with SAEs, such as severe nausea, aspiration pneumonia, multiple organ failure, and death.

Health care providers should instruct patients and caregivers that only 1 dose of ixazomib should be taken at a time, and only at the prescribed interval (1 capsule, once a week, on Days 1, 8, and 15 of a 28-day cycle). The importance of carefully following all dosage instructions should be discussed with patients starting treatment.

There is no known specific antidote for ixazomib overdose. If an overdose occurs, consider admitting the patient to the hospital for IV hydration, monitoring for adverse drug reactions, monitoring of vital signs, and appropriate supportive care. Gastric lavage and administration of charcoal may be considered if instituted within 1 hour of ingestion of an ixazomib overdose.

8.7.2 Daratumumab

See the daratumumab local prescribing information for more information.

Infusion-Related Reactions

Daratumumab can cause serious IRRs, including anaphylaxis. Approximately half of all patients experienced an IRR, most during the first infusion. Monitor patients throughout the infusion and the postinfusion period. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, and hypertension, laryngeal edema and pulmonary edema. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting, and nausea. Fatal outcomes have been reported. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension (refer to Section 8.2.2 for additional risk minimization strategies).

Thrombocytopenia and Neutropenia

Daratumumab may increase thrombocytopenia and neutropenia induced by background therapy [20]. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Daratumumab dose delay may

be required to allow recovery of platelets, as specified in Table 8.c. No dose reduction of daratumumab is recommended. Consider supportive care with transfusions (see Section 8.5).

Monitor patients with neutropenia for signs of infection. Daratumumab dose delay may be required to allow recovery of neutrophils, as specified in Table 8.c. No dose reduction of daratumumab is recommended. Consider supportive care with growth factors (see Section 8.5).

Interference With Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs Test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum [20,52]. The determination of a patient's ABO and Rh blood type are not impacted [20]. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received daratumumab. Type and screen patients prior to starting daratumumab or follow applicable local institutional guidelines.

If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.

Overdose

The dose of daratumumab at which severe toxicity occurs is not known. In the event of an overdose, monitor patients for any signs or symptoms of adverse effects and provide appropriate supportive treatment. See the daratumumab local prescribing information for more information [20].

Reactivation of HBV

Daratumumab can be associated with potential HBV reactivation. Patients found to have positive HBV serology (ie, positive HBV surface antigen or positive HBV core antibody) during screening are excluded.

Patients who are already enrolled at the time of Amendment 02 should be tested locally as soon as possible for HBV surface antigen, e antigen, core antibody, and DNA. If any of these tests is positive, consult a physician with expertise in managing HBV for guidance regarding stopping daratumumab, starting HBV antiviral therapy, and remaining on study. These patients should be monitored every cycle during, and for at least 6 months after the end of, daratumumab treatment for clinical and laboratory signs of HBV reactivation (ie, positive HBV surface antigen, positive HBV e antigen, or positive HBV DNA) [50,51]. If this monitoring reveals HBV reactivation, further treatment, including stopping daratumumab if relevant, should be discussed with a physician with expertise in managing HBV. The sponsor's study clinician (or designee) should be consulted about the continued administration of the other study drugs (ixazomib and dexamethasone).

8.7.3 Dexamethasone

See the dexamethasone local prescribing information for management of any dexamethasone-related clinical events.

8.8 Blinding and Unblinding

This is an open-label study; thus there is no blinding or unblinding.

8.9 Description of Investigational Agents

8.9.1 Ixazomib

8.9.1.1 Preparation, Reconstitution, and Dispensation

Ixazomib is dispensed in blister packaging in a child-resistant carton. For the 2.3, 3.0, and 4.0 mg capsule strengths, there are 3 capsules in each wallet/carton.

Ixazomib is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised during handling. See the Pharmacy Manual for more information.

8.9.1.2 Packaging and Labeling

Ixazomib will be provided by Takeda. The ixazomib local prescribing information will fulfill all requirements specified by governing regulations.

8.9.1.3 Storage, Handling, and Accountability

On receipt at the investigative site, ixazomib should remain in the blister packaging and carton provided until use or dispensation. For storage conditions, refer to the Pharmacy Manual or equivalent. All excursions from the temperature storage guidelines 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. If circumstances due to the COVID-19 pandemic prevent a patient from attending the study site, sites may use alternative strategies to deliver ixazomib 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.

Ixazomib dispensed to the patient for take-home dosing should remain in the blister packaging and carton and stored as directed until the point of use. Patients taking ixazomib should be given only 1 cycle of medication at a time; more than 1 cycle of medication may be dispensed (except in France; patients in France must not be dispensed more than 1 cycle of medication at a time) on a case-by-case basis for holidays, travel, or other circumstances upon discussion with the investigator and sponsor's project clinician/designee. The investigator and/or health care provider must review the proper dosing instructions with the patient to avoid the potential for incorrect self-administration or overdose of medication. Patients should be instructed to store the medication as indicated in the Pharmacy Manual or equivalent. 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 his/her next visit for take-home medication. If circumstances due to the COVID-19 pandemic prevent a patient from attending the study site, drug packs and dosing diaries should be returned at the next available on-site clinic visit. Any excursions in temperature should be reported and dealt with on a case-by-case basis.

Ixazomib is an anticancer drug and, as with other potentially toxic compounds, caution should be exercised during handling. 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 cleanup operation. The product may be harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during cleanup 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 treatment is to be taken as intact capsules.

Refer to the Pharmacy Manual for this study for additional instructions.

8.9.2 Daratumumab

8.9.2.1 Preparation, Reconstitution, and Dispensation

Daratumumab is dispensed as a colorless to pale yellow preservative-free solution for IV infusion in single-dose vials as described in the local prescribing information [19,20].

Daratumumab is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised during handling.

8.9.2.2 Packaging and Labeling

Daratumumab will be supplied from the manufacturer.

8.9.2.3 Storage, Handling, and Accountability

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

8.9.3 Dexamethasone

8.9.3.1 Preparation, Reconstitution, and Dispensation

Dexamethasone is dispensed as a solution for IV administration or tablet for oral administration, as described in the local prescribing information [53].

8.9.3.2 Packaging and Labeling

Dexamethasone is to be dispensed from local site supplies, where possible. Dexamethasone may be supplied by the site from commercial sources or from the sponsor, depending on regional availability. Additional details are provided in the prescribing information.

8.9.3.3 Storage, Handling, and Accountability

Dexamethasone should be stored according to the manufacturer's prescribing information.

8.10 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 with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

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

9.1 Study Personnel and Organizations

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

For 24-hour contact information, please refer to the Study Manual or equivalent.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. Advertisements should be reviewed by the institutional review board (IRB)/independent ethics committee (IEC) and Takeda (or designee). In France, investigators participating in the study approached patients who were potentially eligible for the study to explain the study and provide further information. Patients

were provided with a copy of the ICF and had as much time as needed for reflection and questions before signing; this was expected to be between 1 and 2 weeks.

9.3 Treatment Group Assignments

This is a single-arm, open-label study. After written informed consent has been obtained, the patient will be enrolled in the study. Patient eligibility will be confirmed by a Takeda project clinician or designee before the study. Procedures for completion of the enrollment information are described in the Study Manual.

9.4 Study Procedures

Refer to the updated Schedule of Events (Appendix A) for timing of assessments (the previous Schedule of Events is now moved to Appendix I for reference only). Additional details are provided as necessary in the sections that follow. After the final analysis is conducted, the sponsor will notify the investigators and sites when the new Schedule of Events in Appendix A, will go into effect.

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 who are impacted by these unavoidable circumstances, any procedures not conducted per the study protocol will be documented in the eCRF.

Alternative methods for administering study procedures/assessments may be considered when it is not possible for the patient to come to the study site due to the COVID-19 pandemic. Alternative methods should be considered for performing the assessments by other means than the patient presenting to the clinic (eg, remote assessment, having lab assessment performed at a facility closer to the patient's home, etc). If an in-clinic visit is not possible, the permitted alternatives are as follows (see Appendix A). These assessments/procedures may be waived: symptom-directed physical examination, ECOG performance status, vital signs, weight, whole blood, and serum sample for antibody titers. These assessments/procedures may be deferred until the next in-clinic visit: soft-tissue plasmacytoma, SPEP, UPEP, serum free light-chain assay, immunofixation, quantification of immunoglobulins, BMA, and biopsy. These assessments/procedures may be performed locally if possible and, if not, may be deferred until the next in-clinic visit: HBV testing and hematology and chemistry laboratory tests.

9.4.1 Assessments During the Treatment Period

Patients will have study assessments performed at regular intervals while they are participating in the study (see Appendix A for details). Patients will receive study therapy until documented,

confirmed PD (on the basis of the IMWG criteria [Appendix E]), intolerable toxicities, withdrawal of consent, or sponsor termination of study, whichever comes first.

At every cycle during the treatment period, the investigator will assess disease response and progression, per IMWG criteria, for the purpose of treatment decisions. ECOG performance score and AEs will be assessed, and laboratory values and vital signs will be obtained to evaluate the safety and tolerability of the study therapy. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective date 14 June 2010. Clinical, laboratory, response, [redacted] data will be collected.

Unscheduled visits may occur between treatment cycles as required. For example, symptomatic pain progression should result in an interim unscheduled visit, as would ongoing Grade 3 or worse AEs.

Patients will attend an end of treatment (EOT) visit up to 30 days (+1 week) after receiving their last dose of study therapy.

Note: Related SAEs occurring during follow-up periods after the EOT visit must be reported to the Takeda Global Pharmacovigilance department or designee. This includes deaths that the investigator considers related to study therapy that occur during post-treatment follow-up. In addition, new primary malignancies that occur during follow-up periods, irrespective of causality to study therapy, must be reported to the Takeda Global Pharmacovigilance department or designee. Refer to Section 10.3 for details regarding definitions, documentation, and reporting of SAEs.

9.4.2 Assessments During the Follow-Up Periods: PFS and OS

After a patient completes the EOT visit or a patient discontinues study therapy before confirmed PD, he/she will enter a follow-up period.

Patients who have stopped treatment for any reason other than PD will first enter the PFS follow-up period. During this period, follow-up will occur every 4 weeks until the occurrence of PD.

After PD occurs during the PFS follow-up period, or if a patient has PD while on study therapy during the treatment period, the patient will enter into the OS follow-up period, in which patients will be followed every 12 weeks until death or termination of the study by the sponsor. During the OS follow-up period, assessments do not require a clinic visit. Data may be collected by methods that include, but are not limited to, telephone, email, mail, social security indexes, and other public records as permitted by local regulations. Both the patient and the current treating physician will be contacted by the site study team during the OS follow-up period to provide information about all MM treatments (best response, date of progression, drug regimen, start/stop date). [redacted].

Information about any new primary malignancies will be collected during the study, including during both follow-up periods.

9.4.3 Clinical Laboratory Evaluations

If the screening laboratory tests were performed more than 14 days before the first dose (Cycle 1 Day 1), the chemistry/hematology tests and serum free light chain, UPEP, SPEP, and pregnancy tests will be repeated before dosing. The test closest to the first dose will be considered baseline. In contrast, collection of whole blood for immune profiling and immune cell function assays, whole blood for T-cell clonality, serum for antibody titers, and BMA need not be repeated.

Hematology and chemistry laboratory samples will be collected centrally and may be collected up to 3 days before dosing, as specified in the Schedule of Events (Appendix A). Local laboratory evaluations may be done more frequently at the investigator's discretion (ie, for acute management of TEAEs and dosing decisions).

Upon implementation of Amendment 07, centralized clinical laboratory evaluations of efficacy and safety are no longer required, and thus either central or local laboratory evaluations may be used, depending on the site's decision (Appendix A). Abnormal hematology and chemistry laboratory data should be entered into the eCRF only if required to document or support a TEAE. For dosing decisions and all other safety assessments for the patient, local hematology and chemistry laboratory results should be used and do not need to be entered into the eCRF. Local laboratory evaluations may be done more frequently at the investigator's discretion (ie, for acute management of TEAEs), per the investigator's judgement of standard of care.

9.4.3.1 Clinical Chemistry and Hematology

Blood samples for analysis of the clinical chemistry and hematologic 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	
Hemoglobin	Albumin	Lactate dehydrogenase
Leukocytes with complete differential [total and percent neutrophils (ANC), lymphocytes, monocytes, eosinophils and basophils]	Alkaline phosphatase (ALP)	Magnesium
	Alanine aminotransferase (ALT)	Potassium
	Aspartate aminotransferase (AST)	Sodium
Platelet (count)	β2-microglobulin	
	Bilirubin (a)	
	Blood urea nitrogen	
	Calcium	
	Chloride	
	Creatinine	

(a) Direct bilirubin if patient has known Gilbert's syndrome.

Serology Antibody Titers
Measles
Varicella-zoster virus
Tetanus

In addition, HBV testing should be performed, on the basis of a newly identified safety risk of potential HBV reactivation with daratumumab (also see Sections 8.3.3.2 and 8.7.2 and Appendix A) [50,51].

- Patients who are already enrolled at the time of Amendment 02 should undergo local HBV testing as soon as possible for HBV surface antigen, e antigen, core antibody, and DNA. If any of these tests is positive, consult a physician with expertise in managing HBV for guidance regarding stopping daratumumab, starting HBV antiviral therapy, and remaining on study. These patients should be monitored every cycle during, and for at least 6 months after the end of, daratumumab treatment for clinical and laboratory signs of HBV reactivation (ie, positive HBV surface antigen, positive HBV e antigen, or positive HBV DNA) [50,51]. If this monitoring reveals HBV reactivation, further treatment, including stopping daratumumab, should be discussed with a physician with expertise in managing HBV. The sponsor's study clinician (or designee) should be consulted about the continued administration of the other study drugs (ixazomib and dexamethasone).
- Patients being considered for study enrollment should be tested during screening for HBV serology: test patients locally for HBV surface antigen and HBV core antibody; if either of these tests is positive, then exclude the patient from the study.

If creatinine clearance is to be estimated, the Cockcroft-Gault formula will be employed as follows:

Estimated creatinine clearance

= ([140 – Age] × Weight [kg]) / (72 × serum creatinine [mg/dL])

For female patients, the result of the formula above should be multiplied by 0.85.

9.4.3.2 Clinical Laboratory Evaluations for Disease Assessments

A blood sample will be collected during screening for measurement of serum β_2-microglobulin and albumin for determination of disease stage according to the International Staging System; these results will be sent to the central laboratory for evaluation and recorded on the eCRF.

Clinical laboratory evaluations for disease assessments, SPEP, 24-hour UPEP, serum free light-chain, immunofixation, and total immunoglobulin levels must be sent to the central laboratory for evaluation.

Immunofixation will also be done to confirm CR. As daratumumab is a monoclonal IgG kappa antibody, the SPEP and IFE can be positive due to daratumumab. Therefore, an automated MM reflex at Covance will trigger interference testing whenever the SPEP values reach ≤0.2 g/dL for 2 consecutive disease evaluations. Currently, if the interference test results come back POSITIVE,

then the assay is considered positive for endogenous protein, and thus there is still disease present. If the interference test results come back NEGATIVE, then the assay is considered negative for endogenous protein, and thus the remaining protein is likely daratumumab. This is communicated back to the sites, and the sites can proceed to perform a confirmatory BMA evaluation for possible CR if not already performed earlier.

Blood samples for IgM, IgG, and IgA will be obtained at screening and throughout the study at the time points specified in the Schedule of Events (Appendix A). Quantitative IgD and IgE will be done at screening only. For the rare patient with documented IgD or IgE MM, the quantitative test for that antibody will be followed at the same time points as IgG and IgA.

BMA or biopsy disease assessment is to be performed at a local laboratory to assess disease status at screening. BMA will be repeated if the patient is considered possibly to have resolution of serum and urine M-protein consistent with CR or to investigate suspected PD. A clinically indicated BMA or biopsy drawn before consent is acceptable for the baseline assessment provided that it is collected within 42 days before the first dose.

9.4.3.3 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at screening and within 3 days prior to the first dose of study drug treatment. The results from these tests must be available and negative before the first dose of study drug treatment is administered. If Cycle 1 Day 1 serum pregnancy results will not be available before dosing, a urine pregnancy test may be performed.

Pregnancy tests will be performed at Day 1 of every cycle during the study if requested by an IEC/IRB or if required by local regulations.

9.4.4 Disease Assessment

Disease will be assessed using IMWG criteria (see Appendix E) based on central laboratory results along with local BMA and imaging results. After the final analysis, disease will be assessed on the basis of local laboratory results.

9.4.4.1 Radiographic Assessment of Disease

Skeletal survey or CT scan (according to institutional practice) will be performed at screening to document lytic bone and/or extramedullary disease. Patients with documented soft tissue extramedullary disease must have radiographic disease assessments (CT, CT/positron emission tomography [PET], or CT/MRI) performed as outlined in Appendix A, until PD. The same imaging technique should be used throughout the study to allow for consistent disease assessment. Additional imaging assessments can be done at the discretion of the investigator (ie, for suspected increased or new bone lesions).

9.4.4.2 Bone Marrow

BMA will be obtained at screening for (1) clinical staging performed by the local laboratory (unless a biopsy is used for this purpose instead; see Section 9.4.4.2); [redacted]

[redacted] The BMA first, second, and third pulls should correspond to the purposes listed above. [redacted]

Patients suspected of achieving a CR should have a BMA obtained to document CR per IMWG criteria. Determination of percentage plasma cells will be done by local laboratory. [redacted]

Suspected CR is defined independently of the immunofixation result; BMA is to be performed when the M-protein measurement in SPEP (for heavy-chain patients) or UPEP (for light-chain patients) becomes below detection limits/nonquantifiable.

Further details about MRD testing are in Appendix A and below in Section 13.1.5.

[redacted]

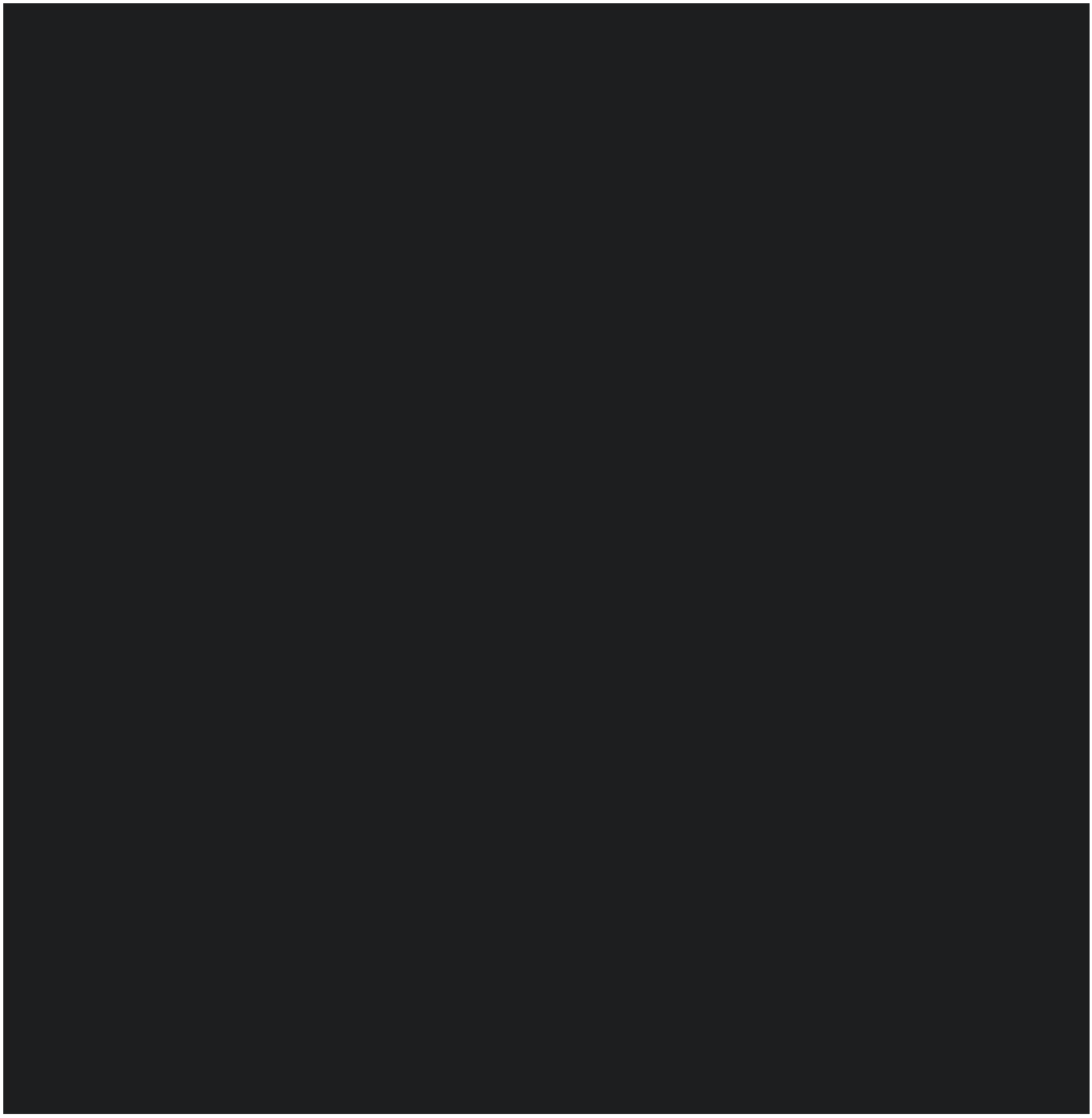


Table 9.b Primary Specimen Collection Table

Specimen Name in Schedule of Procedures	Primary Specimen	Primary Specimen Derivative 1	Primary Specimen Derivative 2	Description of Intended Use	Sample Collection
[redacted]					
Plasma sample for ixazomib PK	Plasma	N/A	N/A	PK Measurements	Mandatory

Abbreviation: [redacted] N/A, not applicable; PK, pharmacokinetics.

[redacted]

9.5 PK Measurements

Plasma concentrations of ixazomib (the complete hydrolysis product of ixazomib citrate) will be measured using a validated liquid chromatography tandem-mass spectrometry assay. Details regarding the preparation, handling, and shipping of the PK samples are provided in the Study Manual. Blood samples (3 mL) for the determination of plasma concentrations of ixazomib will be collected during Cycles 1 through 5 as indicated in Appendix I.

Upon implementation of Amendment 04, PK sample collection will be considered complete and no additional PK samples will be collected.

9.6 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed the study when they have died or have had PD or when the sponsor terminates the study.

9.7 Discontinuation of Treatment With Study Drug Treatment and Patient Replacement

Study therapy must be permanently discontinued for patients meeting any of the following criteria:

- Withdrawal by subject.
- Pregnancy.

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

- AE.
- PD.
- Unsatisfactory therapeutic response.
- Initiation of hematopoietic stem cell transplant.
- Protocol deviation.
- Study terminated by sponsor.
- Lost to follow-up.
- Physician decision.
- Other.

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

Note that some patients may discontinue study therapy for reasons other than PD before completing the full treatment course; these patients will remain in the study for PFS follow-up assessments as outlined in the Schedule of Events (Appendix A) until PD occurs. Unless the patient withdraws consent to follow-up, PFS and/or OS follow-up assessments will continue to be conducted as outlined in the Schedule of Events (Appendix A). Public records may be consulted as permitted per local regulations.

Patients remaining on study therapy at the time of study closure (whether completion of the study or any other reason) will be provided continued access to study therapy by the sponsor, either through commercial drug supply (where available and reimbursable) or through continued treatment in another extension or rollover study (see Section 6.3.5).

9.8 Withdrawal of Patients From Study

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

- Death.
- Study terminated by sponsor.
- Withdrawal by subject.
- Lost to follow-up.
- Other.

The consequence of a patient withdrawing consent from further treatment and follow-up is that no new information will be collected from the withdrawn patient and added to the existing data or any database. However, every effort will be made to follow all patients for safety. Data collected during patient consent, however, must be included in the database.

9.9 Study Compliance

Study drug treatment 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 treatment receipt and dispensing.

9.10 Study Closure

The study will be considered complete approximately 4 years after enrollment of the first patient, at the time of follow-up of approximately 1 additional year after 50% of patients have died or progressed. Patients remaining on ixazomib after study closure (whether completion of the study or any other reason) will be provided continued access to ixazomib by the sponsor (see Section 9.7).

Within 90 days of the end of the study, the sponsor will notify the competent authorities and the IECs in all member states where the study is being carried out that the study has ended.

Within 1 year after the end of the study, a summary of the clinical study results will be submitted to the competent authorities and IECs in all member states involved in the study.

Study participation by individual sites or the entire study may be prematurely terminated if, in the opinion of the investigator or Takeda, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Takeda by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients.
- Failure to enter patients at an acceptable rate.
- Insufficient adherence to protocol requirements.

- Insufficient, incomplete, and/or unevaluable data.
- Determination of efficacy based on an interim analysis.
- Plans to modify, suspend, or discontinue the development of the study drug treatment.

Should the study be closed prematurely, the site will no longer be able to access the electronic data capture (EDC) application, will not have a right to use the EDC application, and will cease using the password or access materials once its participation in the study has concluded. In the event that any access devices for the EDC application have been provided, these will be returned to Takeda once the site's participation in the study has concluded.

Within 15 days after premature closure, Takeda must notify the competent authorities and IECs of any member state where the study is being conducted, providing the reasons for study closure.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

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

10.1.2 AE Definition

An AE 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 treatment.

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

10.1.3 SAE Definition

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 4.03, effective date 14 June 2010 [54]. 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 (WBC) count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting AEs and SAEs

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

Regardless of causality, SAEs must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours after becoming aware of the event. This should be done by transmitting an EDC SAE report. If transmission of an EDC SAE report is not feasible, then a facsimile of the completed Takeda paper-based SAE form should be sent. A sample of the paper-based SAE form and reporting

instructions are in the Study Manual. Information in the SAE report or form must be consistent with the data provided on the eCRF.

SAE Follow-Up

If information not available at the time of the first report becomes available at a later date, then the investigator should transmit a completed follow-up EDC SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

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

SAE Reporting Contact Information

US and Canada

Cognizant

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

Email: takedaoncocases@cognizant.com

All Other Countries Except Japan

Cognizant

Fax #: 1-202-315-3560

Email: takedaoncocases@cognizant.com

Planned hospital admissions or surgical procedures for an illness or disease that existed before study drug treatment was given 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 treatment administration.

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

Relationship of the event to study drug treatment administration (ie, its causality) will be determined by the investigator responding YES (related) or NO (unrelated) to this question: "Is there a reasonable possibility that the AE is associated with the study drug treatment?"

10.3 Monitoring of AEs and Period of Observation

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

- AEs will be reported from the signing of informed consent through 30 days after administration of the last dose of study therapy and recorded in the eCRFs. AEs ongoing at EOT should be monitored until they are resolved, return to baseline, are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es), the start of second-line alternative therapy, or 6 months after PD has occurred whichever comes first.
- SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of informed consent through 30 days after administration of the last dose of study therapy 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 return to baseline or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). In addition, all cases of new primary malignancy must be immediately reported to the Takeda Department of Pharmacovigilance or designee, irrespective of causality to the study treatment regimen, from the time of first dose of the study treatment regimen through death (including the follow-up periods) or until termination of the study by the sponsor, whichever comes first.
- For the purposes of this study, HBV reactivation will be considered a medically significant event and should be reported as an SAE in the eCRF.

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 treatment. The sponsor must also be contacted immediately by transmitting a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee. 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 transmitting a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee. 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 this to ctmcomplaint@takeda.com.

Product complaints or medication errors in and of themselves are not AEs. If a product complaint or medication error 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 EMA 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

In accordance with Takeda standard operating procedures, each clinical trial is evaluated to determine whether a Drug Safety Monitoring Board (DSMB) should be convened. Applicable regulation and guidance (including the guidance set forth by the FDA as described in the Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees [www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf]) are used to evaluate each trial in terms of potential confounding factors that complicate evaluation of the study safety and/or efficacy data, and potential risks of the study design or treatment to study participants.

A DSMB is not indicated at this time for this study given that Takeda's standards and processes, which include continuous review and evaluation of safety data reported from all participating sites through the conduct of the study, are appropriate for the ongoing monitoring of patient safety and

data integrity. However, the decision to convene a DSMB could be made at any time during the conduct of Study C16047 (see below and Section 13.2 for a description of an internal interim safety review).

Though a formal DSMB will not be formed, a steering committee is planned that may include but is not limited to, a subset of study investigators, trial clinician, and a sponsor senior clinical and pharmacovigilance representative. This committee will examine the internal safety interim review described in Section 13.1.9. This review will be prepared by the sponsor and provided to this committee for review and possible study conduct recommendations.

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 eCRFs

Completed eCRFs are required for each subject who signs an ICF.

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, contract research organization (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 following procedure is applied for all countries involved in this study. 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 ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), 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

This phase 2 study is designed to evaluate the safety and efficacy of IDd. Approximately 60 patients will be enrolled. The primary endpoint is the rate of confirmed VGPR or better (CR+VGPR) as defined by IMWG criteria and evaluated by the investigator. An interim safety review will be conducted after the first 15 patients have been enrolled and have had the chance to have been treated for 4 cycles. The first interim analysis, of the CR+VGPR rate, will be conducted 6 months after the last patient is enrolled. The second interim analysis will be conducted after 50% of the PFS events (ie, death or PD) have occurred. The final analysis will be conducted 1 year after 50% of the PFS events have occurred.

A statistical analysis plan (SAP) will be prepared and finalized before database lock for the first interim analysis. Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the final clinical study report.

13.1.1 Analysis Sets

The populations used for analysis will include the following:

- Safety population: Patients who receive at least 1 dose of any study treatment regimen.

- Response-evaluable population: Patients who receive at least 1 dose of ixazomib, have measurable disease during the screening period, and have at least 1 postbaseline disease assessment.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

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

13.1.3 Efficacy Analyses

13.1.3.1 Primary Efficacy

The primary endpoint is the rate of VGPR or better. The first interim analysis, which is the primary efficacy analysis, will be based on the response-evaluable population. Estimates of the rate of VGPR or better will be presented with 2-sided 95% exact binomial confidence intervals. This analysis will occur 6 months after the last patient is enrolled.

13.1.3.2 Secondary Efficacy

The secondary efficacy parameters include PFS, TTP, OS, ORR, TTR, and DOR. The second interim analysis, which is the secondary efficacy analysis, will be conducted after 50% of the PFS events have occurred.

PFS is defined as the time from the date of first dose of study treatment to the date of first documented PD or death, whichever occurs first. Patients without PD or death will be censored at the date of last response assessment that is stable disease or better.

TTP is defined as the time from the date of first dose of study treatment to the date of first documentation of PD. Patients without PD will be censored at the date of last response assessment that is stable disease or better.

OS is defined as the time from the date of first dose of study treatment to the date of death. Patients without death will be censored at the date last known to be alive.

ORR is defined as the pooled rate of PR, VGPR, and CR, as evaluated by the investigator according to IMWG criteria.

TTR is defined as the time from the date of first dose of study treatment to the date of the first documentation of a confirmed response.

DOR is defined as the time from the date of first documentation of a confirmed response to the date of first documented PD.

PFS, TTP, and OS will be analyzed for the safety population. TTR and DOR, measured in the population of patients with a confirmed response, will be analyzed for the response-evaluable population. These data will be analyzed using standard survival analysis techniques based on

Kaplan-Meier estimates and will be summarized by 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals, as well as percentage of censored observations.

The response rates will be analyzed for the response-evaluable population. The response rates will be analyzed similarly to the primary endpoint.

13.1.4 PK Analysis

PK data collected in this study will contribute to future population PK analyses of ixazomib. These analyses may include data from other ixazomib clinical studies. The plan for the population PK analysis will be defined separately and the results will be reported separately. The PK data collected in this study may also contribute to exposure-response (safety/efficacy) analyses. The results of any exposure-response analyses will be reported separately.

[redacted]

time. This will be repeated for all subscales of the EORTC QLQ-C30 and QLQ-MY20 with specific interest on the global QOL summary score, physical functioning, fatigue, nausea/vomiting, pain, dyspnea, appetite loss, and constipation/diarrhea. The change in score from baseline will also be presented using cumulative distribution function figures. The number and percentage of patients with an improvement in score from baseline based on minimally important differences will be summarized over time. The scores will also be analyzed using repeated measures linear mixed models.

13.1.9 Safety Analysis

Safety data will be included in data listings and tabulations. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and changes from baseline in the patient's vital signs, weight, and clinical laboratory results in the safety population. Exposure to study therapy and reasons for discontinuation will be tabulated.

TEAEs that occur after administration of the first dose of study therapy and through 30 days after the last dose of study therapy will be tabulated.

AEs will be tabulated according to MedDRA and will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 TEAEs.
- Grade 4 or higher TEAEs.
- Grade 3 drug-related TEAEs.
- Grade 4 or higher drug-related TEAEs.
- The most commonly reported TEAEs (ie, those reported by ≥10% of all patients).
- All SAEs.
- New primary malignancies.
- Any AE resulting in dose modification or discontinuation of any study therapy.
- Any other AE that in the opinion of the investigator is a clinically significant event.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Shift tables for laboratory parameters will be generated for changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the ixazomib safety profile.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and weight will be tabulated by scheduled time point. ECOG performance scores will be summarized using a shift table.

Incidence rate will be calculated for the safety population based on the new primary malignancy assessment:

- Incidence proportions, defined as the percentage of the subjects reporting any new primary malignancy in the safety population with available information, along with 95% confidence intervals, will be calculated.

Analyses of new primary malignancies may be performed separately for hematologic and nonhematologic malignancies.

All concomitant medications collected from the first dose of study therapy throughout the study period will be classified to preferred terms according to the WHO Drug Dictionary.

An interim safety review will be conducted after the first 15 patients have been enrolled and have had the chance to have been treated for 4 cycles. A descriptive evaluation of the available data from these patients will include toxicity characterization (Grade 3 or 4 AEs, SAEs, all grades of peripheral neuropathy, and treatment discontinuation) and study drug treatment exposure. The study will continue during this safety review, which will be conducted by a steering committee (see Section 11.0) and reviewed with at least a subset of study investigators.

Additional safety analyses may be performed to more clearly enumerate rates of toxicities and to further define the safety profile of ixazomib in combination with daratumumab and dexamethasone.

13.2 Interim Analysis and Criteria for Early Termination

Two interim analyses will be conducted: the first, 6 months after the last patient is enrolled in the study; the second, after 50% of PFS events have occurred.

13.3 Determination of Sample Size

Statistical assumption was based on observed CR+VGPR rates in clinical studies with ixazomib [4], bortezomib [5], and daratumumab [6].

The sample size is calculated using the binomial exact test for single proportion based on the rate of VGPR or better of the IDd treatment regimen. With 54 response-evaluable patients, there will be 95% power to test a null hypothesis of a rate of VGPR or better of 30% and an alternative hypothesis of a rate of VGPR or better of 55% at 2-sided significance level of α=0.05. Therefore, assuming 10% of patients are not response-evaluable, the total enrollment will be approximately 60 patients.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and 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 (as long as blinding is not jeopardized), including but not limited to the IB, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), 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 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, if required. For France, alternative monitoring approaches should be used only if approved as a contingency measure by ANSM (French Agency for Medicines and Health Products Safety) and permitted by the IEC, if required.

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 sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it will be reported to regulatory authorities as a serious breach of GCP and the protocol.

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 IEC, 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.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it will be reported to regulatory authorities as a serious breach of GCP and 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. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, 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 IB, a copy of the ICF, 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, ICF) reviewed; and state the approval date. If required by either country or regional regulations or procedures, approval from the Competent Regulatory Authority will be obtained before commencement of the study or implementation of a substantial amendment. 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 ICF, 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 ICF, 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 ICF 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 ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and if applicable, the subject authorization form. The ICF, 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 ICF, 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 ICF, 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 ICF 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 ICF 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 ICF, 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 ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs 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 ICF.

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 eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by

law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. 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 and www.clinicaltrialsregister.eu, as well as on 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 treatment 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. Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20(9):1467-73.
2. Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011;117(18):4691-5.
3. Palumbo A, Rajkumar SV, San Miguel JF, Larocca A, Niesvizky R, Morgan G, et al. International myeloma working group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. J Clin Oncol 2014;32(6):587-600.
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.
5. Moreau P, Pylypenko H, Grosicki S, Karamanesht I, Leleu X, Grishunina M, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. Lancet Oncol 2011;12(5):431-40.
6. Palumbo A, Chanan-Khan A, Weisel K, Nooka A, Masszi T, Beksac M, et al. Phase 3 Randomised Controlled Study of Daratumumab, Bortezomib and Dexamethasone Versus Bortezomib and Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma: Castor. 2016. 21st Congress of the European Hematology Association, LB2236.
7. Rajkumar SV, Richardson P, San Miguel JF. Guidelines for determination of the number of prior lines of therapy in multiple myeloma. Blood 2015;126(7):921-2.
8. Morgan GJ, Walker BA, Davies FE. The genetic architecture of multiple myeloma. Nature Reviews Cancer 2012;12(5):335-48.
9. Munshi NC, Anderson KC. New strategies in the treatment of multiple myeloma. Clinical Cancer Research 2013;19(13):3337-44.
10. Mikhael JR, Dingli D, Roy V, Reeder CB, Buadi FK, Hayman SR, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. Mayo Clin Proc 2013;88(4):360-76.
11. Boyd KD, Ross FM, Chiecchio L, Dagrada GP, Konn ZJ, Tapper WJ, et al. A novel prognostic model in myeloma based on co-segregating adverse FISH lesions and the ISS: analysis of patients treated in the MRC Myeloma IX trial. Leukemia 2012;26(2):349-55.
12. Rajkumar SV, Hayman SR, Lacy MQ, Dispenzieri A, Geyer SM, Kabat B, et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. Blood 2005;106(13):4050-3.

13. NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma version 1.2014. National Comprehensive Cancer Network. 2013.
14. Laubach J, Garderet L, Mahindra A, Gahrton G, Caers J, Sezer O, et al. Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group. Leukemia 2016;30(5):1005-17.
15. Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. N Engl J Med 2016;375(8):754-66.
16. NINLARO (ixazomib) [Summary of Product Characteristics]. Denmark: Takeda Pharma A/S, 2016.
17. NINLARO (ixazomib) capsules, for oral use [prescribing information]. Cambridge, MA: Takeda Pharmaceutical Company Limited.
18. Moreau P, van de Donk NW, Miguel JS, Lokhorst H, Nahi H, Ben-Yehuda D, et al. Erratum to: Practical Considerations for the Use of Daratumumab, a Novel CD38 Monoclonal Antibody, in Myeloma. Drugs 2016;76(9):989-90.
19. Darzalex (daratumumab). Summary of Product Characteristics. United Kingdom: Janssen-Cilag Ltd, 16 June 2016.
20. DARZALEX (daratumumab) [prescribing information]. USPI. Horsham, PA: Janssen Biotech, Inc., November, 2015.
21. VELCADE (bortezomib) [package insert]. Cambridge, MA: Millennium Pharmaceuticals, Inc.
22. Hou J, Jin J, Xu Y, Wu D, Ke X, Zhou D, et al. Randomized, double-blind, placebo-controlled phase III study of ixazomib plus lenalidomide-dexamethasone in patients with relapsed/refractory multiple myeloma: China Continuation study. Journal of Hematology & Oncology 2017;10(137):13.
23. Kumar SK, Berdeja JG, Niesvizky R, Lonial S, Laubach JP, Hamadani M, et al. Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma: an open-label phase 1/2 study. Lancet Oncology 2014;15(13):1503-12.
24. Kumar S, Berdeja J, Niesvizky R, Lonial S, Laubach J, Hamadani M, et al. Deep and durable responses with weekly ixazomib, lenalidomide and dexamethasone in patients with newly diagnosed multiple myeloma: long-term follow-up of patients who did not undergo SCT. European Hematology Association; June 24, 2017.
25. Richardson P, Hofmeister C, Rosenbaum C, Htut M, Vesole D, Berdeja J, et al. Twice-weekly ixazomib plus lenalidomide-dexamethasone in patients with newly diagnosed multiple myeloma: long-term follow-up data for patients who did not undergo stem cell transplantation (SCT). European Hematology Association; June 25, 2017. S780.

26. Laubach JP, Tai YT, Richardson PG, Anderson KC. Daratumumab granted breakthrough drug status. Expert Opin Investig Drugs 2014;23(4):445-52.

27. Usmani SZ, Weiss BM, Plesner T, Bahlis NJ, Belch A, Lonial S, et al. Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma. Blood 2016;128(1):37-44.

28. Lonial S, Weiss BM, Usmani SZ, Singhal S, Chari A, Bahlis NJ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet 2016;387(10027):1551-60.

29. Little L, Powles R. Daratumumab; challenges of integrating this new therapy into standard care. EHA Learning Center 2017. 182693.

30. van der Veer MS, de Weers M, van Kessel B, Bakker JM, Wittebol S, Parren PW, et al. The therapeutic human CD38 antibody daratumumab improves the anti-myeloma effect of newly emerging multi-drug therapies. Blood Cancer J 2011;1(10):e41.

31. Nijhof IS, Groen RW, Noort WA, van Kessel B, de Jong-Korlaar R, Bakker J, et al. Preclinical Evidence for the Therapeutic Potential of CD38-Targeted Immuno-Chemotherapy in Multiple Myeloma Patients Refractory to Lenalidomide and Bortezomib. Clin Cancer Res 2015;21(12):2802-10.

32. Kong S-Y, Li X-F, Nahar S, Song W, de Weers M, Parren P, et al. Daratumumab directly induces human multiple myeloma cell death and acts synergistically with conventional and novel anti-myeloma drugs. Blood 2010;116:3013.

33. Phipps C, Chen Y, Gopalakrishnan S, Tan D. Daratumumab and its potential in the treatment of multiple myeloma: overview of the preclinical and clinical development. Ther Adv Hematol 2015;6(3):120-7.

34. Bonnet A, Moreau P. Safety of ixazomib for the treatment of multiple myeloma. Expert Opin Drug Saf 2017;16(8):973-80.

35. REVLIMID (lenalidomide) [prescribing information]. Summit, NJ: Celgene Corporation, 2016.

36. Revlimid 2.5 mg hard capsules (lenalidomide) [Summary of Product Characteristics]. United Kingdom: Penn Pharmaceutical Services Limited, 2015.

37. NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. Version 3.2017. National Comprehensive Cancer Network. 2016.

38. Moreau P, San Miguel J, Sonneveld P, Mateos MV, Zamagni E, Avet-Loiseau H, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-updagger. Ann Oncol 2017.

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

40. Foroni L, Coyle LA, Papaioannou M, Yaxley JC, Sinclair MF, Chim JS, et al. Molecular detection of minimal residual disease in adult and childhood acute lymphoblastic leukaemia reveals differences in treatment response. Leukemia 1997;11(10):1732-41.
41. Liu H, Johnson JL, Koval G, Malnassy G, Sher D, Damon LE, et al. Detection of minimal residual disease following induction immunochemotherapy predicts progression free survival in mantle cell lymphoma: final results of CALGB 59909. Haematologica 2012;97(4):579-85.
42. Moreton P, Kennedy B, Lucas G, Leach M, Rassam SM, Haynes A, et al. Eradication of minimal residual disease in B-cell chronic lymphocytic leukemia after alemtuzumab therapy is associated with prolonged survival. Journal of Clinical Oncology 2005;23(13):2971-9.
43. Pott C. Minimal residual disease detection in mantle cell lymphoma: technical aspects and clinical relevance. Seminars in Hematology 2011;48(3):172-84.
44. Paiva B, Vidriales MB, Cervero J, Mateo G, Perez JJ, Montalban MA, et al. Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation. Blood 2008;112(10):4017-23.
45. Sarasquete ME, Garcia-Sanz R, Gonzalez D, Martinez J, Mateo G, Martinez P, et al. Minimal residual disease monitoring in multiple myeloma: a comparison between allelic-specific oligonucleotide real-time quantitative polymerase chain reaction and flow cytometry. Haematologica 2005;90(10):1365-72.
46. Martinez-Sanchez P, Montejano L, Sarasquete ME, Garcia-Sanz R, Fernandez-Redondo E, Ayala R, et al. Evaluation of minimal residual disease in multiple myeloma patients by fluorescent-polymerase chain reaction: the prognostic impact of achieving molecular response. British Journal of Haematology 2008;142(5):766-74.
47. Paiva B, Martinez-Lopez J, Vidriales MB, Mateos MV, Montalban MA, Fernandez-Redondo E, et al. Comparison of immunofixation, serum free light chain, and immunophenotyping for response evaluation and prognostication in multiple myeloma. Journal of Clinical Oncology 2011;29(12):1627-33.
48. Krejcik J, Casneuf T, Nijhof IS, Verbist B, Bald J, Plesner T, et al. Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. Blood 2016;128(3):384-94.
49. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncology 2014;15(12):e538-48.
50. Wang B, Mufti G, Agarwal K. Reactivation of hepatitis B virus infection in patients with hematologic disorders. Haematologica 2019;104(3):435-43.
51. Bessone F, Dirchwolf M. Management of hepatitis B reactivation in immunosuppressed patients: An update on current recommendations. World J Hepatol 2016;8(8):385-94.

52. Chapuy CI, Nicholson RT, Aguad MD, Chapuy B, Laubach JP, Richardson PG, et al. Resolving the daratumumab interference with blood compatibility testing. Transfusion 2015;55(6 Pt 2):1545-54.

53. DECADRON® (dexamethasone) tablets [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.

54. Common Terminology Criteria for Adverse Events (CTCAE). National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services Series v4.03. June 14, 2010. Publication No. 09-5410.

55. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016;17(8):e328-46.

Appendix A Schedule of Events

A-1 Schedule of Events (28-Day Cycle) for Use Until Final Analysis

Study Procedure	Treatment Period (a)	EOT	Follow-Up	
	Cycle X and Beyond, Day 1 of Each 28-Day Cycle	Up to 30 Days After Last Dose	PFS Q4 Wk Until PD	OS Q12 Wk After PD
	Window, ± 2 days	Window, +1 wk	Window, ±1 wk	
Informed Consent (Reconsent)	X (b)			
Complete Physical Examination		X		
Symptom-Directed Physical Examination (c)	X			
HBV Testing (c)	X (d)	X (d)	X (d)	X (c, e)
ECOG Performance Status (c)	X	X		
Vital Signs (c, f)	X	X		
Weight in kg (c)	X	X		
EORTC QLQ-C30 (g)	X (h)	X (h)	X (h)	X (h)
EORTC QLQ-MY20 (g)	X (h)	X (h)	X (h)	X (h)
Soft-tissue plasmacytoma (c, i)	X (i)		X (i)	
Investigator's assessment of disease response/status	X	X	X	X
AE reporting (j)	New onset recorded from signing of ICF through 30 days after last dose of study therapy			
	SAEs collected from signing of ICF through 30 days after last dose of study therapy (see Section 10.3)			
Monitoring of concomitant medications/procedures	Recorded from signing of ICF through 30 days after last dose of study therapy			
New primary malignancy	Assessment continuous from start of study drug administration until death or termination of study by the sponsor (see Section 10.3)			
Survival				X
Subsequent therapy				X (k)
Study Therapy Administration				
Dexamethasone (l)	Days 1, 2, 8, 9, 15, 16, 22, and 23 in each cycle			
Daratumumab (m)	IV infusion Q4 wk (from Cycle 7) until PD			
Ixazomib (m)	Days 1, 8, and 15 of each cycle			
Samples/Laboratory Assessments				
Hematology laboratory tests (c, n)	X	X		
Chemistry laboratory tests (c, n)	X	X		
Urinalysis		X		

Study Procedure	Treatment Period (a)	EOT	Follow-Up	
	Cycle X and Beyond, Day 1 of Each 28-Day Cycle	Up to 30 Days After Last Dose	PFS Q4 Wk Until PD	OS Q12 Wk After PD
	Window, ± 2 days	Window, +1 wk	Window, ±1 wk	
Whole blood for immune profiling and immune cell function assays (c, o)	X	X		
Whole blood for T-cell clonality (c, p)	X	X		
Serum sample for antibody titers (c, q)	X	X		
M-protein measurements (SPEP) (c)	X	X	X	
M-protein measurements (UPEP [24-hr urine collection]) (c)	X	X	X	
Serum free light-chain assay (c)	X	X	X	
Immunofixation - serum and urine (c, r)	X	X	X	
Quantification of immunoglobulins (c, s)	X	X	X	
BMA or biopsy for disease assessment (c) [redacted]	X (u, v)	X (u)	X (u)	

Abbreviations: AE: adverse event; BMA, bone marrow aspirate; COVID-19, coronavirus disease 2019; CR, complete response; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-MY20, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Multiple Myeloma Module; EOT, end of treatment; GCP, Good Clinical Practice; HBV, hepatitis B virus; hr, hour; ICF: informed consent form; IMWG: International Myeloma Working Group; IRB, institutional review board; IRR, infusion-related reaction; IV, intravenous; MRI, magnetic resonance imaging; [redacted]; OS, overall survival; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; Q, every; wk, week; SPEP, serum protein electrophoresis; TEAE, treatment-emergent adverse event; UPEP, urine protein electrophoresis; WBC, white blood cell.

(a) Tests and procedures should be performed on schedule, but, unless otherwise specified, occasional changes are allowable within a 2-day window for holidays, vacations, and other administrative reasons. If a visit or procedure cannot be performed within the window, then the Takeda project clinician or designee should be consulted. If the study schedule is shifted, assessments should be shifted to be aligned with the new schedule.

(b) Before dosing on Day 1 of the next full treatment cycle upon implementation of Amendment 04, patients remaining on study treatment will need to be reconsented. Reconsenting should be done in person. Remote reconsenting is permitted as long as the process adheres to site, IRB/IEC, and GCP standards and local regulations.

(c) Alternative methods for administering study procedures/assessments may be considered when it is not possible for the patient to come to the study site due to the COVID-19 pandemic. Alternative methods should be considered for performing the assessments by other means than the patient presenting to the clinic (eg, remote assessment, having lab assessment performed at a facility closer to the patient's home, etc). If an in-clinic visit is not possible, the permitted alternatives are as follows. These assessments/procedures may be waived: symptom-directed physical examination, ECOG performance status, vital signs, weight, whole blood, and serum sample for antibody titers. These assessments/procedures may be deferred until the next in-clinic visit: soft-tissue plasmacytoma, SPEP, UPEP, serum free light-chain assay, immunofixation, quantification of immunoglobulins, BMA, and biopsy. These assessments/procedures may be performed locally if possible and, if not, may be deferred until the next in-clinic visit: HBV testing and hematology and chemistry laboratory tests.

(d) Patients who are already enrolled at the time of Amendment 02 should undergo local testing as soon as possible, on the basis of a newly identified safety risk of potential HBV reactivation with daratumumab. The HBV testing should consist of tests for HBV surface antigen, e antigen, core antibody, and DNA. If any of these tests is positive, consult a physician with expertise in managing HBV for guidance regarding stopping daratumumab, starting HBV antiviral therapy, and remaining on study. These patients should be monitored every cycle during, and for at least 6 months after the end of, daratumumab treatment for clinical and laboratory signs of HBV reactivation (ie, positive HBV surface antigen, positive HBV e antigen, or positive HBV DNA) [50,51]. If this monitoring reveals HBV reactivation, further treatment, including stopping daratumumab if relevant, should be discussed with a physician with expertise in managing HBV. The sponsor's study clinician (or designee) should be consulted about the continued administration of the other study drugs (ixazomib and dexamethasone).

(e) Patients undergoing monitoring for HBV reactivation must visit the clinic for testing during the OS follow-up period.

(f) Measurement of blood pressure and heart rate is to be performed during the treatment period; temperature and respiratory rate are collected only as clinically indicated. Blood pressure must be checked before and after each daratumumab infusion.

(g) Patient-reported outcomes should be completed before any other study procedures are performed or study therapy is administered.

(h) Patient-reported outcome questionnaires are to be provided to patients at every other cycle starting at Cycle 2. If the patient discontinues treatment for a reason unrelated to PD, then EORTC QLQ-C30 and QLQ-MY20 completion should continue every 8 weeks until PD. After progression, EORTC QLQ-C30 and QLQ-MY20 should be completed at first 2 OS follow-up visits. Patient-reported outcome questionnaires are preferred to be completed by patients in the clinic, but if needed during the COVID-19 pandemic, the EORTC QLQ-C30 and QLQ-MY20 may be completed at the patient's home using mailed paper versions of the questionnaires; if self-reporting by a patient is not possible at the clinic or at home, the questionnaires may be completed over the telephone.

(i) Imaging to assess extramedullary disease will be done at screening (within 8 weeks before enrollment) for all patients by means of CT, MRI, or PET/CT. In patients for whom extramedullary disease is found at screening, additional assessments should be done, using the same modality, at Cycle 2 Day 1 and every other cycle thereafter during the treatment period (ie, Cycle 4 Day 1, Cycle 6 Day 1), and every 8 weeks during PFS follow-up until the patient has PD. Imaging should be done at EOT if it supports PD, unless progression has already been shown on imaging acceptable to the investigator; otherwise it may be done at the physician's discretion.

(j) AEs ongoing at EOT should be monitored until they are resolved, return to baseline, are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es), until start of second-line alternative therapy, or 6 months after PD has occurred whichever comes first.

(k) For subsequent therapy, type of therapy, start and end date, best response, and date of progression should be recorded in the eCRF if available.

(l) Dexamethasone is usually given as 1 dose; however in this study it will be given in split doses as follows: dexamethasone will be given as 20 mg on Day 1, 2, 8, 9, 15, 16, 22, and 23 in each 28-day cycle, to achieve the standard total of 40 mg per week (2 doses of 20 mg per week). During weeks when the patient receives an infusion of daratumumab, the first dexamethasone dose will be given before the daratumumab infusion, with the second dexamethasone dose given the day after. Dexamethasone should be given IV before the first daratumumab dose; but can be given IV or orally thereafter. The dose of dexamethasone can be reduced to 20 mg once weekly for patients who are older than 75 years, have poorly controlled diabetes, or had prior intolerance to or AE from corticosteroid therapy. See Section 8.2.4 for more details on dexamethasone administration.

(m) Pre-infusion medication of oral antipyretics and oral antihistamine will be administered. If ixazomib and daratumumab are to be administered in the same week, they should be administered on the same day of the week. With the potential of IRRs with daratumumab, during the first cycle of therapy it is preferable to give the daratumumab dose before the ixazomib dose to allow for the correct safety assessment and management of any IRR. If no Grade 3 or higher IRR occurred during the previous cycle, starting with Cycle 2 and with subsequent cycles on daratumumab infusion days, ixazomib may be administered prior to or at approximately the same time as the premedications. The daratumumab infusion should then begin approximately 1 hour after the ixazomib administration. See Section 8.2.2 for more details on daratumumab administration and Section 8.2.3 for more details on ixazomib administration.

(n) Hematology and chemistry laboratory samples will be collected centrally and may be collected up to 3 days before Day 1 dosing and within 24 hours before Days 8 and 15 dosing, where required. Local laboratory evaluations may be done more frequently at the investigator's discretion (ie, for acute management of TEAEs) and may be used for dosing decisions. A differential WBC count with absolute lymphocyte count is requested approximately 3 months after EOT, if feasible.

(o) Whole blood measurements are to be taken for immune profiling to measure changes in immune cell subsets, T-cell clonality, titers of noninvolved immunoglobulins, etc. Samples to be taken at study entry (predose) and then blood collected every cycle for the first 6 cycles and then every 3 cycles thereafter until PD; a sample is also requested at relapse if feasible.

(p) Whole blood measurements are to be taken for analysis of immune cell function. Samples to be taken on Day 1 of each cycle up to Cycle 6 and then every 3 cycles thereafter until progression; a sample is also requested at relapse if feasible.

(q) Samples for antibody titers to be taken on Day 1 of each cycle up to Cycle 6 and then every 3 cycles thereafter until progression.

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

(s) Blood samples for IgM, IgG, and IgA will be obtained at screening and throughout the study at the time points specified. For the rare patient with documented IgD or IgE MM, the quantitative test for that antibody will be followed at the same time points as for IgG and IgA.

[redacted]

A-2 Schedule of Events After Final Analysis

Study Procedure	Treatment Period (a)	EOT
	Cycle X and Beyond, Day 1 of Each 28-Day Cycle	**Up to 30 Days After Last Dose**
	Window, ± 2 days	**Window, +1 wk**
Informed consent (reconsent)	X (b)	
Physical examination (c)		X
HBV testing (d)	X (e)	X (e)
Vital signs (d, f)	X	X
Weight in kg (d)	X	X
Investigator's assessment of disease response/status	X	X
AE reporting (g)	New onset recorded from signing of ICF through 30 days after last dose of study therapy	
	SAEs collected from signing of ICF through 30 days after last dose of study therapy (see Section 10.3)	
Monitoring of concomitant medications/procedures	Recorded from signing of ICF through 30 days after last dose of study therapy	
New primary malignancy	Assessment continuous from start of study drug administration until death or termination of study by the sponsor (see Section 10.3)	
Study Therapy Administration		
Dexamethasone (h)	Days 1, 2, 8, 9, 15, 16, 22, and 23 in each cycle	
Daratumumab (i)	IV infusion Q4 wk (from Cycle 7) until PD	
Ixazomib (i)	Days 1, 8, and 15 of each cycle	
Samples/Laboratory Assessments		
Hematology laboratory tests (d, j)	X	X
Chemistry laboratory tests (d, j)	X	X
Pregnancy test (k)	X	

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; EOT, end of treatment; GCP, Good Clinical Practice; HBV, hepatitis B virus; ICF, informed consent form; IEC, independent ethics committee; IRB, institutional review board; IRR, infusion-related reaction; IV, intravenous; OS: overall survival; PD, progressive disease; Q, every; wk, week; SAE: serious adverse event; TEAE, treatment-emergent adverse event; WBC, white blood cell; wk: week.

Note: After the final analysis is conducted, the sponsor will notify the investigators and sites when this new Schedule of Events will go into effect. At this time, an end of study form should be completed for any patient in OS follow up.

(a) Tests and procedures should be performed on schedule, but, unless otherwise specified, occasional changes are allowable within a 2-day window for holidays, vacations, and other administrative reasons. If a visit or procedure cannot be performed within the window, then the Takeda project clinician or designee should be consulted. If the study schedule is shifted, assessments should be shifted to be aligned with the new schedule.

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

(c) Assessment will be performed at the discretion of the investigator.

(d) Alternative methods for administering study procedures/assessments may be considered when it is not possible for the patient to come to the study site due to the COVID-19 pandemic. Alternative methods should be considered for performing the assessments by other means than the patient presenting to the clinic (eg, remote assessment, having laboratory assessment performed at a facility closer to the patient's home). If an in-clinic visit is not possible, the permitted alternatives are as follows. These assessments/procedures may be waived: physical examination, vital signs, and weight. These assessments/procedures may be performed locally if possible and, if not, may be deferred until the next in-clinic visit: HBV testing and hematology and chemistry laboratory tests.

(e) Patients who are already enrolled at the time of Amendment 02 should undergo local testing as soon as possible, on the basis of a newly identified safety risk of potential HBV reactivation with daratumumab. The HBV testing should consist of tests for HBV surface antigen, e antigen, core antibody, and DNA. If any of these tests is positive, consult a physician with expertise in managing HBV for guidance regarding stopping daratumumab, starting HBV antiviral therapy, and remaining on study. These patients should be monitored every cycle during, and for at least 6 months after the end of, daratumumab treatment for clinical and laboratory signs of HBV reactivation (ie, positive HBV surface antigen, positive HBV e antigen, or positive HBV DNA) [50,51]. If this monitoring reveals HBV reactivation, further treatment, including stopping daratumumab if relevant, should be discussed with a physician with expertise in managing HBV. The sponsor's study clinician (or designee) should be consulted about the continued administration of the other study drugs (ixazomib and dexamethasone).

(f) Measurement of blood pressure and heart rate is to be performed during the treatment period; temperature and respiratory rate are collected only as clinically indicated. Blood pressure must be checked before and after each daratumumab infusion.

(g) Patients should be assessed and treated per standard of care. All AEs/SAEs will be recorded in the eCRF according to the criteria outlined in Section 10.0. Patient safety outside the protocol assessments should be monitored during the time between on-site visits at the investigator's discretion, per standard of care. At minimum, there will be a phone call with an investigator within the specified-visit window timeframe, which will include an assessment of AEs/SAEs.

(h) Dexamethasone is usually given as 1 dose; however in this study it will be given in split doses as follows: dexamethasone will be given as 20 mg on Day 1, 2, 8, 9, 15, 16, 22, and 23 in each 28-day cycle, to achieve the standard total of 40 mg per week (2 doses of 20 mg per week). During weeks when the patient receives an infusion of daratumumab, the first dexamethasone dose will be given before the daratumumab infusion, with the second dexamethasone dose given the day after. Dexamethasone should be given IV before the first daratumumab dose; but can be given IV or orally thereafter. The dose of dexamethasone can be reduced to 20 mg once weekly for patients who are older than 75 years, have poorly controlled diabetes, or had prior intolerance to or AE from corticosteroid therapy. See Section 8.2.4 for more details on dexamethasone administration.

(i) Pre-infusion medication of oral antipyretics and oral antihistamine will be administered. If ixazomib and daratumumab are to be administered in the same week, they should be administered on the same day of the week. With the potential of IRRs with daratumumab, during the first cycle of therapy it is preferable to give the daratumumab dose before the ixazomib dose to allow for the correct safety assessment and management of any IRR. If no Grade 3 or higher IRR occurred during the previous cycle, starting with Cycle 2 and with subsequent cycles on daratumumab infusion days, ixazomib may be administered prior to or at approximately the same time as the premedications. The daratumumab infusion should then begin approximately 1 hour after the ixazomib administration. See Section 8.2.2 for more details on daratumumab administration and Section 8.2.3 for more details on ixazomib administration.

(j) Patients should be assessed and treated according to standard of care using either central or local laboratory evaluations, depending on the site's decision. Abnormal hematology and chemistry data are to be collected and recorded in the eCRF only to the extent that they are needed to document or support an AE. Laboratory assessments to inform dosing decisions and routinely monitor patients do not need to be recorded in the eCRF.

(k) Pregnancy tests will be performed at Day 1 of every cycle during the study upon request by IECs/IRBs or if required by local regulations.

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. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
7. 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.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH, and local regulations, are met.
9. 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 ICF 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 ICF 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.
10. 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.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor. This responsibility lies on the appropriate individual, designated by the site in Japan.
13. 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, US, 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 Eastern Cooperative Oncology Group Scale for Performance Status

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

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology 1982;5(6):649-55.

Appendix E IMWG Uniform Response Criteria for MM

Table 3. Response Criteria

Response	Criteria
CR	Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow; in patients for whom only measurable disease is by serum FLC level, normal FLC ratio of 0.26 to 1.65 in addition to CR criteria is required; two consecutive assessments are needed
sCR	CR as defined plus normal FLC ratio and absence of clonal plasma cells by immunohistochemistry or two- to four-color flow cytometry; two consecutive assessments of laboratory parameters are needed
Immunophenotypic CR	sCR as defined plus absence of phenotypically aberrant plasma cells (clonal) in bone marrow with minimum of 1 million total bone marrow cells analyzed by multiparametric flow cytometry (with > four colors)
Molecular CR	CR as defined plus negative allele-specific oligonucleotide polymerase chain reaction (sensitivity 10[-5])
VGPR	Serum and urine M component detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M component plus urine M component < 100 mg/24 h; in patients for whom only measurable disease is by serum FLC level, > 90% decrease in difference between involved and uninvolved FLC levels, in addition to VGPR criteria, is required; two consecutive assessments are needed
PR	≥ 50% reduction of serum M protein and reduction in 24-hour urinary M protein by ≥ 90% or to < 200 mg/24 h If serum and urine M protein are not measurable, ≥ 50% decrease in difference between involved and uninvolved FLC levels is required in place of M protein criteria If serum and urine M protein and serum FLC assay are not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M protein, provided baseline percentage was ≥ 30% In addition, if present at baseline, ≥ 50% reduction in size of soft tissue plasmacytomas is required Two consecutive assessments are needed; no known evidence of progressive or new bone lesions if radiographic studies were performed
MR for relapsed refractory myeloma only	≥ 25% but ≤ 49% reduction of serum M protein and reduction in 24-hour urine M protein by 50% to 89% In addition, if present at baseline, 25% to 49% reduction in size of soft tissue plasmacytomas is also required No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
SD	Not meeting criteria for CR, VGPR, PR, or PD; no known evidence of progressive or new bone lesions if radiographic studies were performed
PD	Increase of 25% from lowest response value in any of following: Serum M component with absolute increase ≥ 0.5 g/dL; serum M component increases ≥ 1 g/dL are sufficient to define relapse if starting M component is ≥ 5 g/dL and/or; Urine M component (absolute increase must be ≥ 200 mg/24 h) and/or; Only in patients without measurable serum and urine M protein levels: difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL); Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC level, bone marrow plasma cell percentage (absolute percentage must be ≥ 10%) Development of new or definite increase in size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia that can be attributed solely to plasma cell proliferative disorder Two consecutive assessments before new therapy are needed

NOTE. Data adapted.[8,9,30a]
Abbreviations: CR, complete response; FLC, free light chain; M, monoclonal; MR, minimal response; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

Source: Palumbo 2014 [3]

Appendix F EORTC QLQ-C30 (version 3)

EORTC QLQ-C30 (version 3)

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

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

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

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

Please go on to the next page

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Appendix G EORTC QLQ-MY20

EORTC Multiple Myeloma Module (QLQ-MY20)

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

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

Please turn to next page

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

Appendix H Acceptable Methods of Contraception

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 ICF, for 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)
Intra-Uterine Devices (IUD)	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 1 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, due to 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)
Vasectomy	Latex or nonlatex condom with or without a spermicidal agent
	Diaphragm with spermicide; cervical cap with spermicide; sponge with spermicide
If 1 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 I Schedule of Events (28-Day Cycle) Previous to Amendment 02

Study Procedures	Screening	Treatment Period (a)												EOT	Follow-Up	
		28-Day Cycles													PFS	OS
Cycle		Cycle 1				Cycles 2-3				Cycle 4 Onward				Up to 30 Days After Last Dose	Every 4 Weeks Until PD	Every 12 Weeks After PD
Days	-28 to -1	1	8	15	22	1	8	15	22	1	8	15	22			
Window		± 2 days												+1 wk	±1 wk	±1 wk
Informed Consent	X															
Inclusion/Exclusion Criteria (b)	X															
Demographics	X															
Complete Medical History	X															
Complete Physical Exam	X													X		
Symptom-Directed Physical Exam	X	X				X				X						
HBV Testing	X (c)	X (d)				X (d)				X (d)				X (d)	X (d)	X (e)
ECOG Performance Status	X	X				X				X				X		
Vital Signs (f)	X	X				X				X				X		
Height (cm)	X															
Weight (kg)	X	X				X				X				X		
Forced expiratory testing for patients with known or suspected COPD	X															

Footnotes are on last table page.

Schedule of Events (28-Day Cycle) Previous to Amendment 02 (continued)

Study Procedures	Screening	Treatment Period (a)												EOT	Follow-Up	
		28-Day Cycles													PFS	OS
Cycle		Cycle 1				Cycles 2-3				Cycle 4 Onward				Up to 30 Days After Last Dose	Every 4 Weeks Until PD	Every 12 Weeks After PD
Days	-28 to -1	1	8	15	22	1	8	15	22	1	8	15	22			
Window		± 2 days												+1 wk	±1 wk	±1 wk
Blood type assessment prior to first dose of daratumumab only	X															
EORTC QLQ-C30 (g)	X	X				X (h)				X (h)				X (h)	X (h)	X (h)
EORTC QLQ-MY20 (g)	X	X				X (h)				X (h)				X (h)	X (h)	X (h)
Imaging Disease Assessments																
Bone (i)	X															
Soft-tissue plasmacytoma (j)	X (j)					X (j)				X (j)					X (j)	
Investigator's assessment of disease response/status	X					X				X				X	X	X
AE reporting (k)	New onset recorded from the signing of ICF through 30 days after last dose of study therapy.															
	SAEs collected from the signing of ICF through 30 days after last dose of study therapy (see Section 10.3).															
Monitoring of concomitant medications/procedures	Recorded from the signing of ICF through 30 days after last dose of study therapy.															
New Primary Malignancy	Assessment continuous from the start of study drug administration until death or termination of the study by the sponsor (see Section 10.3).															
Survival																X
Subsequent therapy																X (l)

Footnotes are on last table page.

Schedule of Events (28-Day Cycle) Previous to Amendment 02 (continued)

Study Procedures	Screening	Treatment Period (a)												EOT	Follow-Up	
		28-Day Cycles													PFS	OS
Cycle		Cycle 1				Cycles 2-3				Cycle 4 Onward				Up to 30 Days After Last Dose	Every 4 Weeks Until PD	Every 12 Weeks After PD
Days	-28 to -1	1	8	15	22	1	8	15	22	1	8	15	22			
Window		± 2 days												+1 wk	±1 wk	±1 wk
Study Therapy Administration																
Dexamethasone (m)		Days 1, 2, 8, 9, 15, 16, 22, and 23 in each cycle.														
Daratumumab (n)		IV infusion weekly in Weeks 1 through 8 (corresponding to Cycles 1 and 2; total of 8 doses) Every 2 weeks in Weeks 9 through 24 (corresponding to Cycles 3 through 6; total of 8 doses), and every 4 weeks (from Cycle 7) thereafter until PD.														
Ixazomib (n)		Days 1, 8, and 15 of each cycle														

Footnotes are on last table page.

Schedule of Events (28-Day Cycle) Previous to Amendment 02 (continued)

Study Procedures	Screening	Treatment Period (a)												EOT	Follow-Up	
		28-Day Cycles													PFS	OS
Cycle		Cycle 1				Cycles 2-3				Cycle 4 Onward				Up to 30 Days After Last Dose	Every 4 Weeks Until PD	Every 12 Weeks After PD
Days	-28 to -1	1	8	15	22	1	8	15	22	1	8	15	22			
Window		± 2 days												+1 wk	±1 wk	±1 wk
Samples/Laboratory Assessments																
Pregnancy test (o)	X	X														
Hematology laboratory tests (p)	X	X	X	X		X		X		X				X		
Chemistry laboratory tests (p)	X	X				X				X				X		
Urinalysis	X													X		
Archival Tumor Sample (q)	X															
Whole blood for immune profiling and immune cell function assays (r)	X	X				X				X				X		
Whole blood for T-cell clonality (s)	X	X				X				X				X		
Serum sample for antibody titers (t)	X	X				X				X				X		

Footnotes are on last table page.

Schedule of Events (28-Day Cycle) Previous to Amendment 02 (continued)

Study Procedures	Screening	Treatment Period (a)												EOT	Follow-Up	
		28-Day Cycles													PFS	OS
Cycle		Cycle 1				Cycles 2-3				Cycle 4 Onward				Up to 30 Days After Last Dose	Every 4 Weeks Until PD	Every 12 Weeks After PD
Days	-28 to -1	1	8	15	22	1	8	15	22	1	8	15	22			
Window		± 2 days												+1 wk	±1 wk	±1 wk
Samples/Laboratory Assessments																
M-protein measurements (SPEP)	X	X (u)				X				X				X	X	
M-protein measurements (UPEP [24-hr urine collection])	X	X (u)				X				X				X	X	
Albumin and β2-microglobulin	X															
Serum free light-chain assay	X	X (u)				X				X				X	X	
Immunofixation - serum and urine (v)	X	X (u)				X				X				X	X	
Quantification of immunoglobulins (w)	X	X				X				X				X	X	
BMA or biopsy for disease [redacted]	X (x,y,z)					X (aa)				X (aa,bb)				X (aa)	X (aa)	
[redacted]																

Abbreviations: EOT, end of treatment; HBV, hepatitis B virus; hr, hour; OS, overall survival; PFS, progression-free survival; wk, week.

(a) Tests and procedures should be performed on schedule, but, unless otherwise specified, occasional changes are allowable within a 2-day window for holidays, vacations, and other administrative reasons. If a visit or procedure cannot be performed within the window, then the Takeda project clinician or designee should be consulted. If the study schedule is shifted, assessments should be shifted to be aligned with the new schedule.

(b) Confirmation of patient eligibility by a Takeda project clinician or designee is required before enrollment. Cycle 1 Day 1 should be no later than 7 days after the date of enrollment call in interactive response technology.

(c) HBV testing should be performed during screening, on the basis of a newly identified safety risk of potential HBV reactivation with daratumumab. The HBV testing should occur as follows: test patients locally for HBV surface antigen and HBV core antibody; if either of these tests is positive, then exclude the patient from the study.

(d) Patients who are already enrolled at the time of Amendment 02 should undergo local testing as soon as possible, on the basis of a newly identified safety risk of potential HBV reactivation with daratumumab. The HBV testing should consist of tests for HBV surface antigen, e antigen, core antibody, and DNA. If any of these tests is positive, consult a physician with expertise in managing HBV for guidance regarding stopping daratumumab, starting HBV antiviral therapy, and remaining on study. These patients should be monitored every cycle during, and for at least 6 months after the end of, daratumumab treatment for clinical and laboratory signs of HBV reactivation (ie, positive HBV surface antigen, positive HBV e antigen, or positive HBV DNA) [50,51]. If this monitoring reveals HBV reactivation, further treatment, including stopping daratumumab if relevant, should be discussed with a physician with expertise in managing HBV. The sponsor's study clinician (or designee) should be consulted about the continued administration of the other study drugs (ixazomib and dexamethasone).

(e) Patients undergoing monitoring for HBV reactivation must visit the clinic for testing during the OS follow-up period.

(f) Measurement of blood pressure and heart rate is to be performed during the treatment period; temperature and respiratory rate are collected only as clinically indicated. Blood pressure must be checked before and after each daratumumab infusion.

(g) Patient-reported outcomes should be completed before any other study procedures are performed or study therapy is administered.

(h) Patient-reported outcome questionnaires are to be provided to patients at every other cycle starting at Cycle 2. If the patient discontinues treatment for a reason unrelated to PD, then QLQ-C30 and MY20 should continue every 8 weeks until PD. After progression, QLQ-C30 and MY20 should be completed at first 2 OS follow-up visits; during OS follow-up only the questionnaires may be completed over the telephone if the patient does not attend clinic in person.

(i) Imaging to assess status of bone disease will be done at screening (within 8 weeks before enrollment) for all patients by means of skeletal survey, CT, MRI, or PET/CT. Additional assessments for bone disease can be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD) and should be done by the same modality.

(j) Imaging to assess extramedullary disease will be done at screening (within 8 weeks before enrollment) for all patients by means of CT, MRI, or PET/CT. In patients for whom extramedullary disease is found at screening, additional assessments should be done, using the same modality, at Cycle 2 Day 1 and every other cycle thereafter during the treatment period (ie, Cycle 4 Day 1, Cycle 6 Day 1), and every 8 weeks during PFS follow-up until the patient has PD. Imaging should be done at EOT if it supports PD, unless progression has already been shown on imaging acceptable to the investigator; otherwise it may be done at the physician's discretion.

(k) AEs ongoing at EOT should be monitored until they are resolved, return to baseline, are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es), until start of second-line alternative therapy, or 6 months after PD has occurred whichever comes first.

(l) For subsequent therapy, type of therapy, start and end date, best response, and date of progression should be recorded in the eCRF if available.

(m) Dexamethasone is usually given as 1 dose; however in this study it will be given in split doses as follows: dexamethasone will be given as 20 mg on Day 1, 2, 8, 9, 15, 16, 22, and 23 in each 28-day cycle, to achieve the standard total of 40 mg per week (2 doses of 20 mg per week). During weeks when the patient receives an infusion of daratumumab, the first dexamethasone dose will be given before the daratumumab infusion, with the second dexamethasone dose given the day after. Dexamethasone should be given IV before the first daratumumab dose; but can be given IV or orally thereafter. The dose of dexamethasone can be reduced to 20 mg once weekly for patients who are older than 75 years, have poorly controlled diabetes, or had prior intolerance to or AE from corticosteroid therapy. See Section 8.2.4 for more details on dexamethasone administration.

(n) Pre-infusion medication of oral antipyretics and oral antihistamine will be administered. If ixazomib and daratumumab are to be administered in the same week, they should be administered on the same day of the week. With the potential of IRRs with daratumumab, during the first cycle of therapy it is preferable to give the daratumumab dose before the ixazomib dose to allow for the correct safety assessment and management of any IRR. If no Grade 3 or higher IRR occurred during the previous cycle, starting with Cycle 2 and with subsequent cycles on daratumumab infusion days, ixazomib may be administered prior to or at approximately the same time as the premedications. The daratumumab infusion should then begin approximately 1 hour after the ixazomib administration. See Section 8.2.2 for more details on daratumumab administration and Section 8.2.3 for more details on ixazomib administration.

(o) For women of childbearing potential, 2 pregnancy tests (with 1 or both being a serum test) must be performed and results must be available and negative before dosing. The Cycle 1 Day 1 pregnancy test may be collected up to 3 days prior. Pregnancy tests will be performed at Day 1 of every cycle during the study upon request by IECs/IRBs or if required by local regulations.

(p) Hematology and chemistry laboratory samples will be collected centrally and may be collected up to 3 days before Day 1 dosing and within 24 hours before Days 8 and 15 dosing, where required. Local laboratory evaluations may be done more frequently at the investigator's discretion (ie, for acute management of TEAEs) and may be used for dosing decisions. A differential

WBC count with absolute lymphocyte count is requested approximately 3 months after EOT, if feasible.

(q) The material should consist of (in order of preference) unstained slides; BMA as a formalin-fixed, paraffin-embedded block; or stained slides. Bone marrow biopsy samples will not be accepted. This is a mandatory sample if available.

(r) Whole blood measurements are to be taken for immune profiling to measure changes in immune cell subsets, T-cell clonality, titers of noninvolved immunoglobulins, etc. Samples to be taken at study entry (predose) and then blood collected every cycle for the first 6 cycles and then every 3 cycles thereafter until PD; a sample is also requested at relapse if feasible.

(s) Whole blood measurements are to be taken for analysis of immune cell function. Samples to be taken on Day 1 of each cycle up to Cycle 6 and then every 3 cycles thereafter until progression; a sample is also requested at relapse if feasible.

(t) Samples for antibody titers to be taken on Day 1 of each cycle up to Cycle 6 and then every 3 cycles thereafter until progression.

(u) Clinical laboratory evaluations for disease assessments (SPEP, UPEP, serum free light-chain, immunofixation, and immunoglobulin) must be sent to the central laboratory for evaluation until the secondary endpoint of PFS has been evaluated in this study. At that time, all central efficacy and investigator assessments for protocol purposes will be stopped and not recorded in the eCRF.

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

(w) Blood samples for IgM, IgG, and IgA will be obtained at screening and throughout the study at the time points specified. For the rare patient with documented IgD or IgE MM, the quantitative test for that antibody will be followed at the same time points as for IgG and IgA.

(x) Bone marrow biopsy or, if BMA used instead of biopsy, first pull of BMA to be used to assess disease status at screening. Assessment to be performed at a local laboratory. A clinically indicated BMA or biopsy drawn prior to consent is acceptable for the baseline assessment provided that it is collected within 42 days before the first dose.

[redacted] t.

[redacted] Day 1 (± 1 week) for evaluation of immune profiling. If a patients is suspected to be in CR or has PD at this time, then the sequence of BMA pulls should be as described for those timepoints.

Appendix I Previous Table A - PK Sampling Schedule (completed as of Amendment 04)

Cycle 1			Cycle 2		Cycle 3		Cycle 4	Cycle 5
Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15	Day 1	Day 1
Predose (a)								
X	X	X	X	X	X	X	X	X

(a) If a PK sample is collected on an ixazomib dosing day, the predose PK sample can be collected at any time before administration of ixazomib. If a PK sample is collected on a non-ixazomib dosing day, the PK sample can be collected at any time during the study visit.

Note: If a predose PK sample is collected from the patient and the patient does not receive a dose of ixazomib on that protocol visit day, a second predose sample does not need to be collected on the subsequent visit where the dose is administered. All future visits should be performed per the protocol.

Appendix J COVID-19 Trial Communication Letter from Janssen-Cilag International NV

COVID-19 Trial Communication Letter

DARZALEX® (daratumumab): Urgent changes to company sponsored daratumumab trials in response to COVID-19

Dear Investigator,

Janssen-Cilag International N.V. would like to inform you about two changes that are being implemented in company sponsored research and development (R&D) DARZALEX® (daratumumab) trials.

Summary

Janssen-Cilag International N.V. has made the following provision to company sponsored daratumumab R&D clinical trials to prioritize the safety of subjects during the COVID-19 pandemic:

- For patients receiving intravenous daratumumab, the duration of infusion may be shortened starting in cycle 2 onwards to a 90-minute infusion for subjects without a history of an infusion related reaction after the third dose of daratumumab

Given the unprecedented challenges associated with the pandemic, this change has been implemented under an urgent safety measure (USM).

Background

During the current COVID-19 pandemic, Janssen-Cilag International N.V.is committed to ensuring that all subjects on company sponsored clinical trials for daratumumab can receive access to study treatment understanding the challenges that exist for subjects risking exposure to COVID-19 and the constraints on the health care systems globally.

Shortened Daratumumab Infusions

The median time for Intravenous daratumumab administration is 7 hours for the 1st infusion and a minimum of 3 hours for subsequent infusions. This requires a subject to remain on-site for a prolonged period and additional resources from the site for monitoring purposes during the administration. A 90-minute administration of daratumumab has been evaluated in a single center trial in the US that studied 28 subjects. All subjects received an accelerated infusion of daratumumab after at least two prior doses were administered without an infusion related reaction (IRR). There was no grade 3 or higher IRRs reported (Barr et al. Blood 2017 130: 1889). Additionally, this accelerated infusion has been implemented in a company sponsored phase 2 trial in the US, 54767414MMY2004, and multiple investigator-initiated trials.

Based on the experience with accelerated administration of daratumumab, Janssen-Cilag International N.V. is updating the trial- specific IPPI or SIPPM or protocol (where applicable) in all company sponsored R&D trials that include intravenous daratumumab to allow for physicians to administer intravenous daratumumab in 90 minutes for any subject without a history of an IRR after the third dose of daratumumab. Daratumumab can be administered at an initial rate of 20% of the total dose over 30 minutes, followed by the remaining 80% of the total dose over 60 minutes (90-minute total infusion time). The accelerated infusion will be given in a total volume of 500 mL. This allows for a rate of 200 mL/hr for the first 30 minutes and a rate of 400 mL/hr for the final 60 minutes. Pre-medications should continue to be given as outlined in the protocol.

These actions have been taken to support investigators to provide the best care to their patients during this challenging period and is in line with new guidance from Health Authorities on managing clinical trials during the COVID-19 pandemic. Please notify your ethics committee or institutional review board as appropriate.

Janssen-Cilag International N.V. will continue to explore all possible options to address the needs of the subjects during the COVID-19 pandemic.

If you have further questions or require additional information, please contact your site manager or study team directly.

Appendix K Amendment 07 Detailed Summary of Changes

The primary sections of the protocol affected by the changes in Amendment 07 are indicated. The corresponding text has been revised throughout the protocol.

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

The change occurs on the Cover Page, in the Sponsor row:

Initial wording:	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited 40 Landsdowne Street Cambridge, MA 02139, USA Telephone: +1 (617) 679-7000 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:	**Takeda Development Center Americas, Inc**~~Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited~~ ~~40 Landsdowne Street~~**95 Hayden Avenue** ~~Cambridge~~**Lexington**, MA 02~~139~~**421**, USA Telephone: +1 (617) 679-7000 ~~Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium," "Sponsor," or "Takeda".~~

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

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 3.5 Corporate Identification.
- Section 4.2 Ixazomib.

Change 2: Add a new Schedule of Events to Appendix A for future use, after the final analysis has been conducted.

The primary change occurs in to Appendix A Schedule of Events:

Description of change:	• Added new Schedule of Events

The following sections also contain this change:

- Section 9.4 Study Procedures.
- Section 9.4.4 Disease Assessment.
- Appendix I Schedule of Events (28-Day Cycle) Previous to Amendment 02.

Change 3: Add language on local clinical laboratory evaluations for efficacy and safety after implementation of Amendment 07.

The primary change occurs in to Section 9.4.3:

Initial wording:	If the screening laboratory tests were performed more than 14 days before the first dose (Cycle 1 Day 1), the chemistry/hematology tests and serum free light chain, UPEP, SPEP, and pregnancy tests will be repeated before dosing. The test closest to the first dose will be considered baseline. In contrast, collection of whole blood for immune profiling and immune cell function assays, whole blood for T-cell clonality, serum for antibody titers, and BMA need not be repeated. Hematology and chemistry laboratory samples will be collected centrally and may be collected up to 3 days before dosing, as specified in the Schedule of Events (Appendix A). Local laboratory evaluations may be done more frequently at the investigator's discretion (ie, for acute management of TEAEs and dosing decisions).
Amended or new wording:	If the screening laboratory tests were performed more than 14 days before the first dose (Cycle 1 Day 1), the chemistry/hematology tests and serum free light chain, UPEP, SPEP, and pregnancy tests will be repeated before dosing. The test closest to the first dose will be considered baseline. In contrast, collection of whole blood for immune profiling and immune cell function assays, whole blood for T-cell clonality, serum for antibody titers, and BMA need not be repeated. Hematology and chemistry laboratory samples will be collected centrally and may be collected up to 3 days before dosing, as specified in the Schedule of Events (Appendix A). Local laboratory evaluations may be done more frequently at the investigator's discretion (ie, for acute management of TEAEs and dosing decisions). **Upon implementation of Amendment 07, centralized clinical laboratory evaluations of efficacy and safety are no longer required, and thus either central or local laboratory evaluations may be used, depending on the site's decision. Abnormal hematology and chemistry laboratory data should be entered into the eCRF only if required to document or support a TEAE. For dosing decisions and all other safety assessments for the patient, local hematology and chemistry laboratory results should be used and do not need to be entered into the eCRF. Local laboratory evaluations may be done more frequently at the investigator's discretion (ie, for acute management of TEAEs), per the investigator's judgement of standard of care.**

The following sections also contain this change:

- Section 9.4 Study Procedures.
- Section 9.4.3.1 Clinical Chemistry and Hematology.
- Appendix A, Table A-2, footnote j and g

Change 4: Clarify 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 addresses provided below.

Product	Call Center	Phone Number	E-mail	Fax
NINLARO (ixazomib)	Dohmen Life Science Services (DLSS)	1-844-617-6468 (1-844-N1-POINT)	GlobalOncologyMedinfo@takeda.com	1-800-881-6092

Product complaints or medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, the SAE should be reported.

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 or medication errors in and of themselves are not AEs. If a product complaint or medication error 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 addresses provided below~~ **to Cognizant (refer to Section 10.2).**

~~Product~~	~~Call Center~~	~~Phone Number~~	~~E-mail~~	~~Fax~~
~~NINLARO (ixazomib)~~	~~Dohmen Life Science Services (DLSS)~~	~~1-844-617-6468 (1-844-N1-POINT)~~	~~GlobalOncologyMedinfo@takeda.com~~	~~1-800-881-6092~~

~~Product complaints or medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, the SAE should be reported.~~

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

Change 5: Clarify language about study conduct regarding the coronavirus disease 2019 (COVID-19) pandemic.

The change occurs in Section 8.9.1.3 Storage, Handling, and Accountability:

Initial wording:	On receipt at the investigative site, ixazomib should remain in the blister packaging and carton provided until use or dispensation. For storage conditions, refer to the Pharmacy Manual or equivalent. All excursions from the temperature storage guidelines 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. In case of extenuating circumstances that prevent a patient from attending the study site (eg, the COVID-19 pandemic), sites may use alternative strategies to deliver ixazomib 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.
Amended or new wording:	On receipt at the investigative site, ixazomib should remain in the blister packaging and carton provided until use or dispensation. For storage conditions, refer to the Pharmacy Manual or equivalent. All excursions from the temperature storage guidelines 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. ~~In case of extenuating~~ **If** circumstances **due to the COVID-19 pandemic**~~that~~ prevent a patient from attending the study site ~~(eg, the COVID-19 pandemic)~~, sites may use alternative strategies to deliver ixazomib 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.

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

The following sections also contain this change:

- Section 9.4 Study Procedures.
- Appendix A Schedule of Events.

Change 6: Update the Management of Clinical Events section for ixazomib to reflect evolving data, including the addition that ixazomib should be discontinued if SJS occurs.

The change occurs in Section 8.7.1 Ixazomib:

Initial wording:

Erythematous Rash With or Without Pruritus

…

The rare risks of Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), and pemphigus vulgaris have been reported in oncology studies when ixazomib (or placebo) was given with concomitant medications that are known to cause rash (eg, Bactrim, lenalidomide, aspirin), and/or in the setting of confounding TEAEs. These severe, potentially life-threatening or deadly conditions may involve rash with skin peeling and mouth sores and should be clinically managed according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator. 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 as outlined in the protocol, with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib administration should be modified according to dose modification recommendations in the protocol when thrombocytopenia occurs (see Table 8.c). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenia purpura and hemolytic uremic syndrome (HUS), are rare, serious blood disorders that cause low levels of platelets and red blood cells and result in blood clots in small blood vessels. Symptoms may include fatigue, fever, bruising, nose bleeds, and decreased urination. These disorders, including fatal cases, have been reported in patients receiving ixazomib. TMA should be managed according to standard medical practice.

…

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. If an overdose occurs, consider close observation including hospitalization for hemodynamic support. Gastric lavage may be considered if instituted within 1 hour of ingestion of an ixazomib overdose.

Amended or new wording:

Erythematous Rash With or Without Pruritus

…

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

Thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol, with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib administration should be modified according to dose modification recommendations in the protocol when thrombocytopenia occurs (see Table 8.c). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenia purpura and hemolytic uremic syndrome (HUS), 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 ~~should be managed~~ **is suspected, consider withdrawal of the suspected causative agent and manage it** according to standard medical practice.

…

Transverse Myelitis

Transverse myelitis has been reported with ixazomib. It is not known whether ixazomib causes transverse myelitis; however, because transverse myelitis **has** happened ~~to a patient~~ **in patients** 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, and the symptoms of overdose are generally consistent with the known risks of ixazomib. Reports of accidental overdose have been associated with SAEs, such as severe nausea, aspiration pneumonia, multiple organ failure, and death.

Health care providers should instruct patients and caregivers that only 1 dose of ixazomib should be taken at a time, and only at the prescribed interval (1 capsule, once a week, on Days 1, 8, and 15 of a 28-day cycle). The importance of carefully following all dosage instructions should be discussed with patients starting treatment.

There is no known specific antidote for ixazomib overdose. If an overdose occurs, consider ~~close observation including hospitalization for hemodynamic support~~ **admitting the patient to the hospital for IV hydration, monitoring for adverse drug reactions, monitoring of vital signs, and appropriate supportive care.** Gastric lavage **and administration of charcoal** may be considered if instituted within 1 hour of ingestion of an ixazomib overdose.

Rationale for Change: Added management suggestion for erythematous rash with or without pruritus (including the addition that ixazomib should be discontinued if SJS occurs), thrombocytopenia, removed reference to 1 patient for transverse myelitis, and updated the overdose section.

The following sections also contain this change:

- Section 8.3.2 Ixazomib Treatment Modification, Table 8.d Ixazomib Dose Modification for Nonhematologic Toxicities.

Change 7: Incorporate changes from France-specific Protocol Amendments 01 and 05.

Changes from France-specific Protocol Amendment 01:

#1: The inclusion criterion detailing requirements for female patients has been clarified to state that women of childbearing potential must have a negative pregnancy test before the first dose of study drug treatment is administered.

The change occurs in Section 7.1 Inclusion Criteria:	
Added text:	Female patients who: … – If they are of childbearing potential, agree to use effective contraceptive measures during and for 90 days following treatment. Advise women using hormonal contraceptives to also use a barrier method of contraception (see Appendix H for details). **For women of childbearing potential, a pregnancy test should be negative before the first dose of study drug treatment is administered.**
Rationale for Change: Clarification of the study procedures.	
#2: An exclusion criterion has been added to clarify that pregnant women are not permitted to enroll in the study.	
The change occurs in Section 7.2 Exclusion Criteria:	
Added text:	• **Patient is pregnant.**
Rationale for Change: Clarification of the inclusion/exclusion criteria in the study.	
#3: Information about the process and timing of obtaining informed consent has been clarified.	
The change occurs in Section 9.2 Arrangements for Recruitment of Patients:	
Added text:	Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. Advertisements should be reviewed by the institutional review board (IRB)/independent ethics committee (IEC) and Takeda (or designee). **In France, investigators on the study approached patients who were potentially eligible for the study to explain the study and provide further information. Patients were provided with a copy of the ICF and had as much time as needed for reflection and questions before signing; this was expected to be between 1 and 2 weeks.**
Rationale for Change: Clarification of the study patient recruitment and informed consent processes.	
#4: Footnote "t" and associated reference has been added to the Schedule of Events to clarify the use of bone marrow aspirates (BMA).	
The change occurs in Section Appendix A Schedule of Events:	
Added text:	**In France, confirmation of a CR by laboratory criteria is part of the standard-of-care evaluation of MM, per the IMWG criteria, to confirm a CR. In addition, the IMWG guidance recommends evaluating MRD status at a minimum of 1 year following initial confirmation of MRD negativity for the response criteria of "sustained MRD-negative status" [55].**

Rationale for Change: Clarification of the study procedures.

Change from France-specific Protocol Amendment 05:

#5: To add flexibility in study conduct 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 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, if required. **For France, alternative monitoring approaches should be used only if approved as a contingency measure by ANSM (French Agency for Medicines and Health Products Safety) and permitted by the IEC, if required.**

Rationale for Change: Clarification of the study procedures.

Rationale for Change: Added the text from the France-specific protocols to the Global protocol.

Change 8: Update the terms of the Posttrial Access program.

The change occurs in Section 6.3.5 Posttrial Access:

Initial wording:

6.3.5 Posttrial Access

At the conclusion or termination of the study, participants still on ixazomib treatment will be given the opportunity to enroll in a separate open-label rollover study in order to continue receiving ixazomib if, in the opinion of the investigator and confirmed by the sponsor, they have experienced a clinically important benefit from the ixazomib that they received in the study, have no alternative therapeutic option, and would be harmed without continued access.

Duration of Posttrial Access

Continued access to ixazomib for participants will be terminated for those individuals who no longer benefit from ixazomib, the benefit-risk no longer favors the individual, or ixazomib is available either commercially or via another access mechanism, or when an alternative appropriate therapy becomes available. Posttrial access may be terminated in a country or geographical region where the marketing authorization has been rejected, the development of ixazomib has been suspended or stopped by the sponsor, or where ixazomib can no longer be supplied.

Amended or new wording:

6.3.5 Posttrial Access

At the conclusion or termination of the study, participants still **remaining** on ixazomib **and/or daratumumab** ~~treatment~~ will be given the opportunity to ~~enroll in a separate open-label rollover study~~ **participate in the optional ixazomib (NINLARO) posttrial access (PTA) program** in order to continue receiving

ixazomib **and/or daratumumab** if, in the opinion of the investigator and confirmed by the sponsor, ~~they have experienced a clinically important~~ **the patient continues to receive clinical** benefit from ~~the~~ ixazomib **and/or daratumumab** ~~that they received in the study, have no alternative therapeutic option, and would be harmed without continued access~~. **This is a voluntary program. Alternatively, investigators have the option of transferring their patients to standard-of-care treatment or treating their patients outside of the PTA program.**

Duration of Post**t**trial Access

~~Continued access to ixazomib for~~ Participants **in the PTA program** will be ~~terminated for those individuals who~~**offered ixazomib (NINLARO) until they** no longer benefit from ixazomib, the benefit-risk no longer favors the individual, ~~or ixazomib~~ **and/or ixazomib is** ~~available either~~ commercially ~~or via another access mechanism, or when an alternative appropriate therapy becomes available~~ **available for the indication under study in the participants' market, and/or the sponsor deems the PTA program is no longer viable**. **The PTA program may also** ~~Posttrial access may~~ be terminated in a country or geographical region where the marketing authorization has been rejected, the development of ixazomib has been suspended or stopped by the sponsor, or where ixazomib can no longer be supplied.

Rationale for Change: Updated the language to be consistent with the current PTA program.

Change 9: Clarify the daratumumab infusion time period.

The change occurs in Section 8.2.2.2 Daratumumab Schedule and Administration:

Initial wording:	Upon implementation of Amendment 04, to prioritize the safety of patients during the COVID-19 pandemic, patients may have their infusion duration reduced to 90 minutes if they did not have a history of an IRR at any time after the third dose (Table 8.a and Appendix J).
Amended or new wording:	Upon implementation of Amendment 04, to prioritize the safety of patients during the COVID-19 pandemic, patients may have their infusion duration reduced to **no less than** 90 minutes if they did not have a history of an IRR at any time after the third dose (Table 8.a and Appendix J).

Rationale for Change: Updated the language to clarify that the daratumumab infusion can be reduced per the guidance in Appendix J.

Table 8.a Infusion Rates for Daratumumab IV Administration also contains this change.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Science Approval	30-Mar-2022 14:23 UTC
	Clinical Science Approval	30-Mar-2022 14:54 UTC
	Biostatistics Approval	30-Mar-2022 15:38 UTC