Title: An Open-label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Ixazomib in Combination with Lenalidomide and Dexamethasone in Patients with Relapsed and/or Refractory Multiple Myeloma Initially Treated with an Injection of Proteasome Inhibitor-Based Therapy

NCT Number: NCT03416374
Protocol Approve Date: 30-MAY-2019

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

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

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

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

CLINICAL STUDY PROTOCOL

An Open-label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Ixazomib in Combination with Lenalidomide and Dexamethasone in Patients with Relapsed and/or Refractory Multiple Myeloma Initially Treated with an Injection of Proteasome Inhibitor-Based Therapy

Secondary Sponsor:	Takeda Pharmaceutical Company Limited		
Study number:	C16043		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Study Drug:	Ixazomib		
Indication:	Multiple Myeloma	**Phase:**	4
Date:	30 May 2019	**Amendment Number:**	Version 5

1.0 THE PRINCIPLES OF CLINICAL STUDIES AND ADMINISTRATIVE INFORMATION

1.1 Principles of Clinical Studies

This study will be conducted with the highest respect for individual study participants, according to the requirements of this study protocol and the following. This study will also be conducted as a "specified clinical trial" according to the Clinical Research Act (Act No. 16 of 2017):

- The ethical principles based on the Declaration of Helsinki
- Clinical Research Act (Act No. 16 of 2017)
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline E6
- All applicable laws and regulations, including data privacy laws, and regulation and guidelines on conflicts of interest

1.2 Research Implementation Structure

This clinical study will be conducted according to the study protocol with the following implementation system. Other implementation systems are described on a separate sheet.

Research Steering Committee

Research Steering Committee Chair: PPD

Research Steering Committee: PPD

Representative investigator:

PPD

Director of Statistical Analysis:

PPD

1.3 Secondary Sponsor

Takeda Pharmaceutical Company Limited, PPD

Representative: PPD

PPD

Takeda Pharmaceutical Company Limited (hereinafter referred to as "Takeda") will take responsibility for drafting of the study and procurement of the study funds as well as all matters related to the conduct of this clinical study for which the representative investigator is responsible in collaboration with the representative investigator. The method of oversight by subcontractors concerning this clinical study is described in the procedure manual prepared separately.

The fees* required for the administration of this clinical study are borne by Takeda.

*In accordance with the service agreement, fees required for conducting this study, including administration, monitoring, registration, statistical analysis, audit, medical writing, clinical examinations, and data management will be paid by Takeda to the subcontractor. Study sites will be paid agreed fees based on the 'Study cost calculation Guideline' as specified separately.

1.4 Inquiries Concerning Study Protocol

Refer to Supplement 1 of Study Protocol

1.5 Inquiries Concerning Registration Procedures

Refer to Supplement 1 of Study Protocol

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2.0 STUDY SUMMARY

Compound:

Ixazomib citrate

Title of Protocol:

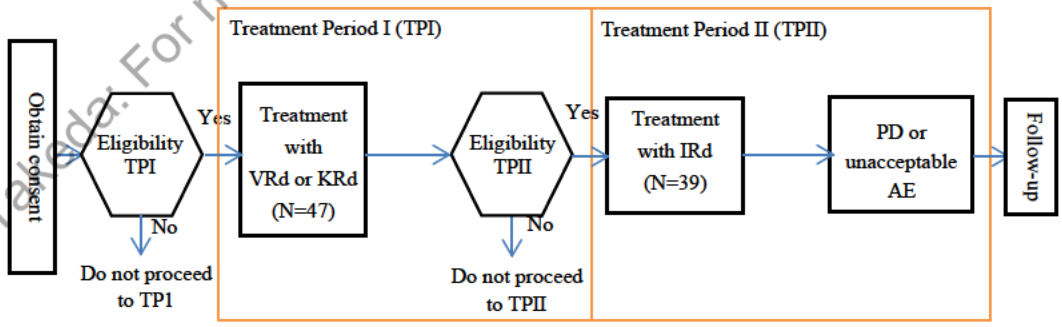
An Open-label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Ixazomib in Combination with Lenalidomide and Dexamethasone in Patients with Relapsed and/or Refractory Multiple Myeloma, Initially Treated with an Injection of Proteasome Inhibitor-Based Therapy

Study Number: C16043	**Phase:** 4

Study Design:

This is a national, multicenter, open-label, single-arm study in patients with relapsed and/or refractory multiple myeloma (RRMM).
The patient population consists adult men and women who have a confirmed diagnosis of MM, and who meet other eligibility criteria. This clinical study consists of two treatment periods, Treatment Period I and Treatment Period II.

After providing consent, patients who meet the eligibility criteria are enrolled into Treatment Period I. Following the baseline evaluations, combination therapy consisting of bortezomib, lenalidomide, and dexamethasone (VRd) or combination therapy consisting of carfilzomib, lenalidomide, and dexamethasone (KRd) is started at the discretion of the investigator or principal investigator. A patient's eligibility for Treatment Period II is then determined 3 cycles after the start of Treatment Period I. Patients who meet these eligibility criteria II subsequently continue into Treatment Period II and change intravenous to oral PI therapy. In Treatment Period II, patients receive combination therapy consisting of ixazomib, lenalidomide, and dexamethasone (IRd). IRd treatment is continued until progressive disease (PD) or an unacceptable adverse event (AE) is observed.



<table>
<tr><td colspan="2">Objective:
To investigate the efficacy and safety of long-term administration of the oral proteasome inhibitor ixazomib as part of IRd therapy in patients with RRMM treated initially with an injectable proteasome inhibitor-based therapy.</td></tr>
<tr><td colspan="2">Subject population: RRMM patients who are able to treatment with an injectable and an oral proteasome inhibitor-based therapy</td></tr>
<tr><td>Number of Subjects:
Treatment Period I: 47
(Treatment Period II: 39)</td><td>Number of Sites:
Approximately 30</td></tr>
<tr><td>Dose Level(s):
Treatment Period I：
Standard dosing is recommended according to the package insert of each drug.
Treatment Period II:
Patients will receive ixazomib (4.0 mg) on Days 1, 8 and 15, plus lenalidomide (25 mg) on Days 1 to 21, and dexamethasone (40 mg) on Days 1, 8, 15 and 22, of a 28-day cycle.</td><td>Route of Administration:
Treatment Period I: follow the package insert
Treatment Period II:
Ixazomib: oral
Lenalidomide: oral
Dexamethasone: oral</td></tr>
<tr><td>Duration of Treatment:
Treatment in Treatment Period II is continued until either PD or an unacceptable AE is observed, whichever comes first.</td><td>Period of Evaluation:
Clinical research implementation scheduled period (enrollment period and study treatment period): 39 months
Enrollment period: 18 months</td></tr>
<tr><td colspan="2">Inclusion Criteria:
Patients satisfying all the following criteria are eligible to participate in this clinical study.
Eligibility for Treatment Period I
1. Men and women of age 20 years or older at the time of enrollment
2. Patients with RRMM
3. Patients who are planned to start combination therapy with bortezomib, lenalidomide, and dexamethasone (VRd), or combination therapy with carfilzomib, lenalidomide, and dexamethasone (KRd) as second, third or fourth line of treatment
4. Patients with measurable disease defined by one or more of the following three measurements</td></tr>
</table>

- Serum M-protein: ≥0.5 g/dL (≥ 5 g/L)
- Urine M-protein: ≥ 200 mg/24 hours
- Serum free light chain assay: involved free light chain concentration ≥ 10 mg/dL (≥ 100 mg/L) provided that the serum free light chain ratio is abnormal

5. Patients with ECOG performance status (PS) 0–2; however, patients with ECOG PS 3 are eligible if they only have symptoms associated with bone lesions.
6. Patients who are considered by the principal investigator or investigator not to be eligible for transplant; or, if considered eligible for transplant, patients who are planned not to undergo transplant for at least 12 months after the start of the study treatment
7. Patients must be registered with, and comply with, the guidelines of the lenalidomide management program (RevMate®)
8. Patients who, before implementing procedures related to clinical research (excluding standard medical practices), understand that they can withdraw consent at any time without suffering from disadvantages to future treatments, and can provide written informed consent

Eligibility for Treatment Period II

9. Patients must have received an injectable proteasome inhibitor (bortezomib or carfilzomib) in each treatment cycle of Treatment Period I

Exclusion Criteria:
Patients meeting any of the following exclusion criteria are not to be enrolled in this clinical study.

Exclusion Criteria for Treatment Period I

1. Women who are nursing or pregnant
2. Patients with another active malignancy, i.e. synchronous active malignancy or previous malignancy with a disease-free period of less than 5 years, except for patients with carcinoma in situ (intraepithelial carcinoma) or intramucosal carcinoma judged to be cured by topical treatment
3. Patients with poorly controlled active thrombosis
4. Patients who have participated in a clinical trial of ixazomib or have been treated with ixazomib
5. Patients who were refractory to either treatment regimen based on lenalidomide and/or proteasome inhibitor(s)

   Note: Refractory MM is defined as PD on therapy or PD within 60 days after the last dose of a given therapy. Patients who have disease progressed 60 days after the last dose of a given therapy will be considered as relapsed in this study.

6. Patients with ongoing or active systemic infection, known hepatitis B virus infection, known hepatitis C virus infection, or known positivity to human immunodeficiency virus (HIV)
7. Patients who underwent major surgery within 14 days prior to enrollment to Treatment Period I. Surgery for bone lesions is not considered as major surgery
8. Patients who received radiation therapy within 14 days prior to enrollment to Treatment Period I. If the radiation field is small, 7 days is considered as a sufficient interval between radiation therapy and chemotherapy
9. Patients who experience Grade 1 peripheral neuropathy accompanied by pain, or Grade ≥2 peripheral neuropathy
10. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmia, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months before enrollment to Treatment Period I
11. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before enrollment into Treatment Period I
12. Patients with central nervous system involvement
13. Inability to swallow oral medications, inability or unwillingness to comply with the drug administration requirements, or gastrointestinal conditions that could interfere with the oral absorption or tolerance of treatment
14. Psychiatric illness/social situation that would limit compliance with study requirements
15. Comorbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the participant inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens

Exclusion Criteria for Treatment Period II

16. Patients who do not achieve at least a minimal response (MR) to VRd or KRd in Treatment Period I per the International Myeloma Working Group (IMWG) response criteria, 2014 revision
17. Patients who experience Grade 1 peripheral neuropathy accompanied by pain, or Grade ≥2 peripheral neuropathy during Treatment Period I
18. Patients with evidence of uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmia, symptomatic congestive heart failure, unstable angina, or myocardial infarction during Treatment Period I
19. Patients using potent CYP3A4 inducing agents (rifampicin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or gingko biloba or St. John's wort

20. Patients with hypersensitivity to any of the IRd study medications, their analogs, or excipients contained in IRd
21. Comorbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the participant inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens

Criteria for Evaluation and Analyses:

Primary endpoint

Progression-free survival (PFS) rate at 12 months from the start of study treatment

Secondary endpoints

Overall survival (OS) from the start of study treatment

PFS from the start of study treatment

Proportion of patients who achieved very good partial response (VGPR) or better

Rate of minimal residual disease (MRD) in bone marrow in patients who achieved complete response (CR)

Best response

Overall response rate (ORR)

Proportion of patients continuing treatment with ixazomib at 12 months from the start of study treatment

Duration of response (DOR)

Patient-reported outcome: health-related quality of life (HRQoL), as evaluated by the EORTC-QLQ-C30 and MY-20 instruments

Evaluation of Quality-Adjusted Life-Years (QALYs)

Healthcare resource utilization (HCRU)

Relative Dose Intensity (RDI)

Bone evaluation

AEs

Statistical methods:

Population for Analyses:

In this clinical study, the patient populations for analysis are classified as the 'Full Analysis Set',, the 'Full Safety Analysis Set', and the 'Safety Analysis Set for Treatment Period II'.

The 'Full Analysis Set' is defined as all patients who enroll in Treatment Period I and who

receive at least one dose of any therapy during the Treatment Period. The 'Full Safety Analysis Set' are defined as all patients who enroll in Treatment Period I and who receive at least one dose of any therapy during the Treatment Period. The 'Safety Analysis Set for Treatment Period II' is defined as all patients who enroll into Treatment Period II and who receive at least one dose of the study drug.

Analysis of effectiveness:

Primary endpoint

For the analysis of the 'Full Analysis Set', a binomial test is conducted on the null hypothesis that PFS rate at 12 months after the start of study Treatment Period I is less than or equal to 36%. The one-sided significance level is 5%. The two-sided 90% confidence intervals based on exact binomial distribution will be calculated.

Secondary endpoint

For the 'Full analysis Set', exact two-sided 95% confidence intervals based on the ratio and binomial distribution, analysis by Kaplan-Meier method and summary statistics are calculated.

Safety analysis

For the 'Full Safety Analysis Set' and 'Safety Analysis Set for Treatment Period II', data on the frequency of AEs will be collected.

Determination of sample size:

The purpose of this clinical study is to investigate the efficacy and safety of long-term administration of PI-based therapy with IRd in RRMM patients who are unable to continue treatment with injectable PI-based therapy. The primary efficacy endpoint of this study is the 12-month PFS rate. The sample size was estimated using the results of a preceding overseas (i.e. non-Japanese) clinical trial, and was set so the expected 12-month PFS rate exceeds the threshold 12-month PFS rate.

In a clinical trial of patients with RRMM treated with VRd therapy, the 12-month PFS rate was 36%; this value was set as the threshold PFS rate. Assuming that the hazard rate follows a constant exponential distribution, the hazard rate was estimated to be 0.085.

To calculate the expected PFS rate at 12 months, it is assumed that injectable PI-based therapy will be continued up to 3 cycles, and that the PFS rate 9 months after changing to IRd therapy can be based on the PFS distribution in the IRd arm of the C16010 study, an international, double-blind, randomized, placebo-controlled phase 3 study conducted in patients with RRMM with 1-3 prior therapies. In the C16010 study, the median PFS of the IRd group was 20.6 months; assuming that the hazard rate for PFS in the IRd group has a constant exponential distribution, the hazard rate with IRd was 0.034. For the present study, assuming that the hazard rate for the first 3 months is 0.085, and assuming that from month 4 – after changing treatment to IRd therapy – the hazard rate is 0.034, the PFS rate at 9 months after switching to IRd therapy is estimated to be 57%, and this is therefore the expected 12-month PFS rate.

With a threshold 12-month PFS rate of 36%, an expected 12-month PFS rate of 57%, a one-sided significance level of 5%, and 80% power, the number of study subjects required is 39.

Based on the considerations above, the minimum number of patients required to be administered IRd in this clinical study is 39. However, estimating that approximately 20% of patients may not meet the inclusion criteria or may discontinue the trial, the number of patients enrolled in Treatment Period I will be 47.

3.0 ABBREVIATIONS

ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
CCI	Charlson comorbidity index
Ccr	creatinine clearance
COI	conflict of interest
CR	complete response
CTCAE	common terminology criteria for adverse events
CVA	cerebrovascular attack
CYP	cytochrome P450
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Module
FFPE	formalin-fixed paraffin-embedded
FLC	free light chain
GCP	Good Clinical Practice
HCRU	Healthcare resource utilization
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
IMiDs	immunomodulatory drugs
ICH	International Conference on Harmonisation
IMWG	International Myeloma Working Group
IRd	ixazomib plus lenalidomide and dexamethasone
ISS	International Staging System
ITT	intent-to-treat
JAN	Japan Accepted Name
JCOG	Japan Clinical Oncology Group

jRCT	Japan Registry of Clinical Trials
KRd	carfilzomib plus lenalidomide and dexamethasone
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging
NDMM	newly diagnosed multiple myeloma
NGS	next-generation sequencing
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PI	proteasome inhibitor
PR	partial response
QALY	quality-adjusted life-year
QOL	quality of life
RDI	relative dose intensity
RRMM	relapsed and/or refractory multiple myeloma
SAE	serious adverse event
SPEP	serum protein electrophoresis
sCR	stringent complete response
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
TIA	transient ischemic attack
UPEP	urine protein electrophoresis
VGPR	very good partial response
VRd	bortezomib plus lenalidomide and dexamethasone

In addition, the terms used in this clinical study protocol are defined as follows.

Study site:

Institution where this clinical study will be conducted.

Principal investigator:

Refers to a person who is participating in the implementation of the study, and who oversees the tasks associated with the study at his or her affiliated study site.

Investigator(s):

A physician taking some of the responsibilities for study-related activities under the direction of the investigator at the study site where this person is employed.

Representative investigator:

An investigator who acts as the representative of all the investigators at multiple study sites when a multicenter study is conducted.

Director of study site:

A person managing and supervising the investigator at the study site where the investigator is employed.

Certified Review Board:

A committee engaged in reviewing and giving opinions about the conduct of clinical studies established in compliance with the Clinical Research Act.

Monitor:

A person who are third party not engaged in this research, nominated by Takeda under responsible representative investigator.

Study subject:

Refers to persons, including those who are deceased, who fall under any of the following categories.

1. Persons on whom the study is conducted, including persons who requested to participate in the study.
2. Persons from whom existing samples and/or information were collected for use in the study.

4.0 INTRODUCTION

4.1 Background

Multiple myeloma (MM) is a clonal disease of plasma cells that is characterized by an increase in serum or urine monoclonal immunoglobulin (M-protein) [1]. MM may result in bone marrow failure, bone destruction, hypercalcemia, and renal failure. MM constitutes approximately 1% of all reported neoplasms and approximately 13% of hematologic cancers worldwide [2]. In the United States in 2017, an estimated 30,280 cases of MM were diagnosed and 12,590 deaths occurred due to the disease [3]. In Europe in 2012, an estimated 38,900 cases of MM were diagnosed and 24,300 deaths occurred due to the disease [4]. In Asian countries, the incidence rate of MM is approaching that seen in Western countries [5,6]. According to the National Cancer Center, the number of new cases of MM in Japan in 2015 was estimated to be approximately 8,600, with approximately 4,200 deaths due to the disease [7]. MM is predominantly a disease of the elderly, and it is estimated that the median age at the time of diagnosis is 65 to 70 years [10]. MM is generally considered incurable with current therapy.

Treatment of MM has undergone major changes in recent years due to the increased understanding of the pathology of disease and improvements in therapeutic strategy. Previously, conventional therapeutic approaches focused on the use of cytotoxic drugs (e.g. alkylating agents, anthracyclines, etc.) and corticosteroids, which showed efficacy as front-line and subsequent therapies. However, proteasome inhibitors (PIs) such as bortezomib and immunomodulatory drugs such as thalidomide and lenalidomide resulted in improved treatment outcomes. Currently, three drug combinations of a PI, an immunomodulatory drug and an antibody formulation are recommended as treatment options for MM. In addition, two drug combination regimens, mainly carfilzomib and dexamethasone, are recommended [8,9].

In recent years, the overall survival (OS) of patients with MM has been extended, associated with the introduction of novel therapeutic agents [11,12]. In a retrospective analysis by the Japanese Myeloma Society, the median OS for patients diagnosed between 2001 and 2012 was 60.6 months, compared with 38.9 months for patients diagnosed between 1990 and 2000 [13]. A separate retrospective study by the Japanese Myeloma Society and the European Myeloma Network showed that the use of new drugs was an independent prognostic factor improving OS for newly diagnosed and relapsed/refractory patients with MM [14]. Regarding the prognostic factors for Japanese patients with MM, retrospective studies suggest that long-term prognosis is poorer with increasing numbers of prior lines of therapy [15]. Currently, a large-scale prospective observational study (JSH-MM-15) on the prognosis of myeloma-related diseases is being conducted by the Japan Society of Hematology. The number of treatment options using new therapeutic agents is increasing, and studies on prognostic factors are progressing. However, MM remains incurable; ultimately, almost all patients will relapse and require further treatment, and so additional novel treatment options are needed.

Ixazomib is a boronic acid compound and the biologically active form of ixazomib citrate. Ixazomib is an oral, small molecule PI developed by Takeda Pharmaceutical Company that selectively targets the 20S proteasome which is activated in MM and other cancers. The

ubiquitin–proteasome cascade is a major regulatory system for maintaining protein homeostasis and an important mechanism for degradation of proteins including those involved in proliferation regulation, cell cycle regulation, and apoptosis. Inhibition of the 20S proteasome system has been shown to be feasible in the treatment of MM and mantle cell lymphoma. Ixazomib selectively binds to the β5 subunit of the 20S proteasome, preventing its chymotrypsin-like activity, and inhibits degradation of misfolded proteins [16]. In addition, at higher concentrations, ixazomib also inhibits the activity of the β1 and β2 subunits. Furthermore, ixazomib has a shorter dissociation half-life compared to bortezomib; it has been shown to be widely distributed in tumor tissue, with more sustained proteasome inhibition, and to exert greater anti-tumor effects in various tumor xenografts [17].

Results of two clinical trials of ixazomib in Japanese patients have been reported. One was a domestic phase 1 trial of patients with relapsed/refractory multiple myeloma (RRMM), which was conducted following the availability of data from non-Japanese phase 1 clinical trial in solid tumors and hematologic malignancies. The domestic phase 1 trial was an open-label, non-comparative study of the safety and pharmacokinetics of ixazomib 4.0 mg, alone or in combination with lenalidomide and dexamethasone (Rd), administered orally once a day on days 1, 8, and 15 of a 28 day-cycle. Ixazomib was administered to 14 patients (7 patients each in the monotherapy and combination therapy arms). No deaths were observed in this study; in the first cycle, which was considered as the evaluation period for dose-limiting toxicity (DLT), DLT was observed in 1 of 6 patients in the monotherapy arm (diarrhea, nausea, hypokalemia, hyponatremia, and hypertension [all Grade 3], and Grade 4 thrombocytopenia), and 1 of 6 patients in the combination therapy arm (thrombocytopenia and neutropenia, both Grade 4).

Japanese patients were also treated with ixazomib in another clinical trial – the international, double-blind, randomized, placebo-controlled phase 3 TOURMALINE-MM1 trial (C16010 study) in patients with RRMM. The study compared the efficacy and safety of ixazomib administered with Rd (IRd; ixazomib group) with placebo administered with Rd (placebo group). Ixazomib 4.0 mg or placebo was administered orally on days 1, 8, and 15 of a 28-day cycle. Lenalidomide 25 mg was administered orally on days 1 to 21, and dexamethasone 40 mg was administered orally on days 1, 8, 15, and 22. Treatment was continued until the health condition of the patient met the discontinuation criteria. The intent-to-treat (ITT) population consisted of 722 randomized patients, which included 41 Japanese patients. At the first planned interim analysis, at which the median follow-up was approximately 15 months, IRd was associated with a significant benefit compared to placebo-Rd in the primary endpoint of progression-free survival (PFS) by independent review committee assessment. Median PFS was 20.6 months in the ixazomib group and 14.7 months in the placebo group, a difference of approximately 6 months. The hazard ratio for progression or death was 0.74 (p=0.01), representing a 35% improvement in PFS in the ixazomib group compared with the placebo group [18]. OS was a secondary endpoint; median OS was not reached in either group at a subsequent analysis (median follow-up of approximately 23 months with data cut-off on July 12, 2015), and so the trial is continuing in a double-blind fashion to the next planned interim analysis for OS. The proportion of patients with very good partial response (VGPR) or better (i.e. sCR, CR, or VGPR) was significantly higher in the ixazomib group (48.1%) compared with the placebo group (39.0%).

Safety was analyzed in 720 patients. The mortality rate during treatment or within 30 days after the last dose of study drug was 4% (15/361) in the ixazomib group and 6% (23/359) in the placebo group. The incidence of all adverse events (AEs) was 98% (355/361) and 99% (357/359) in the ixazomib and placebo groups, respectively, and the incidence of Grade ≥3 AEs was 74% (267/361) and 69% (247/359), respectively. AEs for which the incidence in the ixazomib group was 10 percentage points higher than in the placebo group were thrombocytopenia (31% and 16%, respectively) and vomiting (23% and 12%, respectively). The QOL evaluation results were comparable in both groups. Ixazomib was approved in the United States in November 2015 and in Europe in November 2016, in combination with Rd, for the treatment of MM patients who have received at least one prior treatment. In Japan, ixazomib was approved for the treatment of patients with RRMM in March 2017.

4.2 Rationale for the Proposed Study

In the international, double-blind, randomized, placebo-controlled phase 3 trial of ixazomib in patients with RRMM, 70% of the patients had prior treatment with a PI, and 69% had prior treatment with bortezomib. Furthermore, carfilzomib has been approved in Japan for use in patients with RRMM since August 2016. CCI [redacted] CCI The primary endpoint of this study is PFS rate at 12 months from the start of study treatment. In order to investigate the influence on physical, social, and emotional functioning by the continued administration of oral PIs after treatment with injectable PIs, QOL will be evaluated in this study as secondary endpoint.

5.0 STUDY OBJECTIVE

5.1 Objectives

To investigate the efficacy and safety of long-term administration of the oral proteasome inhibitor ixazomib as part of IRd therapy in patients with RRMM treated initially with an injectable proteasome inhibitor-based therapy.

5.2 Endpoints

5.2.1 Primary Endpoint

Progression-free survival (PFS) rate at 12 months from the start of study treatment

5.2.2 Secondary Endpoints

- Overall survival (OS) from the start of study treatment
- PFS from the start of study treatment
- Proportion of patients who achieved very good partial response (VGPR) or better
- Rate of minimal residual disease (MRD) in bone marrow in patients who achieved complete response (CR)
- Best response
- Overall response rate (ORR)
- Proportion of patients continuing treatment with ixiazomib at 12 months from the start of study treatment
- Duration of response (DOR)
- Patient-reported outcome: health-related quality of life (HRQoL), as evaluated by the EORTC-QLQ-C30 and MY-20 instruments
- Evaluation of Quality-Adjusted Life-Years (QALYs)
- Healthcare resource utilization (HCRU)
- Relative Dose Intensity (RDI)
- Bone evaluation
- AEs

6.0 STUDY DESIGN

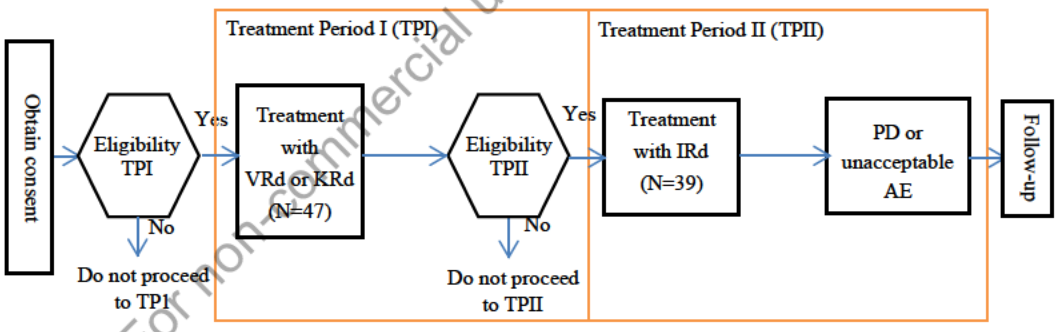
6.1 Overall Study Design and Plan: Description

This clinical study is a national, multicenter, open-label, single-arm study to evaluate the effectiveness and safety of IRD in patients with RRMM. Adult patients diagnosed with MM who satisfy eligibility criteria will be enrolled in this study. This study consists of the Treatment Period I and Treatment Period II.

After providing consent, patients who meet the eligibility criteria are enrolled into Treatment Period I . Following the baseline evaluations, combination therapy with bortezomib, lenalidomide and dexamethasone (VRd), or combination therapy with carfilzomib, lenalidomide and dexamethasone (KRd) is started at the discretion of the principle investigator or investigator. A patient's eligibility for Treatment Period II is then determined 3 cycles after the start of Treatment Period I. Patients who meet the eligibility criteria II are subsequently enrolled into Treatment Period II and receive IRd. In Treatment Period II, patients receive combination therapy consisting of ixazomib, lenalidomide and dexamethasone (IRd). IRd treatment is continued until PD or an unacceptable AE is observed.

A schematic diagram of clinical study design is shown in Figure 6.a. See Appendix A: Schedule of events, for the schedule of screening, observation, and evaluation.

Figure 6.a A Schematic Diagram of Clinical Study Design



6.2 Termination or Suspension of Study or Study Site

6.2.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study

- New information or other evaluation regarding the safety or efficacy of ixazomib that indicates a change in the known risk/benefit profile of the compound is obtained, such that the risk/benefit profile is no longer acceptable for patients participating in the study.

- A significant violation of the Clinical Research Act, or of ICH Good Clinical Practice (GCP), that compromises the safety of the study participants.
- A regulatory authority decides to terminate the clinical study.

6.2.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the study site (including the investigator) is found in significant violation of the Clinical Research Act, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise agreed by the contractual agreement.

6.2.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the representative investigator,Takeda, or the Certified Review Board elects to terminate or suspend the study or the participation of an study site, a study-specific procedure for early termination or suspension will be provided by the CRO; the applicable study site will follow procedure during the course of termination or study suspension.

6.3 Procedures for Revision of Protocol

If the protocol needs to be revised, the representative investigator and Takeda shall consider and decide whether the revision is possible or not. The principal investigator of each site shall be informed of the details of each protocol revision.

Revising clinical study implementation plan

1. Change or addition of objective(s)
2. Change or addition of evaluation method for efficacy or safety
3. Additional procedures (including frequency) for which the burden on the study participant increases
4. Significant change to, or addition of, inclusion or exclusion criteria
5. Change in the number of planned participants
6. Change in the plan or description, due to the occurrence of serious AEs
7. A change determined to be serious as a result of consultation between the representative investigator and Takeda.

Following notification regarding such a protocol revision, the principal investigator of each study site must obtain the approval from the director of the study site, according to the regulations of each study site.

7.0 STUDY SUBJECTS

All entry criteria, including test results, need to be confirmed prior to start of treatment for Treatment Period I or Treatment Period II.

7.1 Inclusion Criteria

Patients satisfying all the following criteria are eligible to participate in this clinical study.

Eligibility for Treatment Period I

1. Men and women aged 20 years or older at the time of enrollment
2. Patients with RRMM
3. Patients who are planned to start combination therapy VRd or KRd as second, third or fourth line of treatment
4. Patients with measurable disease defined by one or more of the following three measurements
   - Serum M-protein: ≥0.5 g/dL (≥ 5 g/L)
   - Urine M-protein: ≥ 200 mg/24 hours
   - Serum free light chain assay: involved free light chain concentration ≥ 10 mg/dL (≥ 100 mg/L) provided that the serum free light chain ratio is abnormal
5. Patients with ECOG performance status (PS) 0–2; however, patients with ECOG PS 3 are eligible if they only have symptoms associated with bone lesions
6. Patients who are considered by the principal investigator or investigator not to be eligible for transplant; or, if considered eligible for transplant, patients who are planned not to undergo transplant for at least 12 months after the start of the study treatment
7. Patients must be registered with, and comply with, the guidelines of the lenalidomide management program (RevMate®)
8. Patients who, before implementing procedures related to clinical research (excluding standard medical practices), understand that they can withdraw consent at any time without suffering from disadvantages to future treatments, and can provide written informed consent

Eligibility for Treatment Period II

9. Patients must have received an injectable proteasome inhibitor (bortezomib or carfilzomib) in each treatment cycle of Treatment Period I

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in this clinical study.

Eligibility for Treatment Period I

1. Women who are nursing or pregnant
2. Patients with another active malignancy, i.e. synchronous active malignancy or previous malignancy with a disease-free period of less than 5 years, except for patients with carcinoma in situ (intraepithelial carcinoma) or intramucosal carcinoma judged to be cured by topical treatment
3. Patients with poorly controlled active thrombosis
4. Patients who have participated in a previous clinical trial of ixazomib or who have been previously treated with ixazomib
5. Patients who were refractory to either treatment regimen based on lenalidomide and/or proteasome inhibitor(s)

   Note: Refractory MM is defined as PD on therapy or PD within 60 days after the last dose of a given therapy. Patients who have disease progressed 60 days after the last dose of a given therapy will be considered as relapsed in this study.
6. Patients with ongoing or active systemic infection, known hepatitis B virus infection, known hepatitis C virus infection, or known positivity to human immunodeficiency virus (HIV)
7. Patients who underwent major surgery within 14 days prior to enrollment to Treatment Period I. Surgery for bone lesions is not considered as major surgery
8. Patients who received radiation therapy within 14 days prior to enrollment to Treatment Period I. If the radiation field is small, 7 days is considered as a sufficient interval between radiation therapy and chemotherapy
9. Patients who experience Grade 1 peripheral neuropathy accompanied by pain, or Grade ≥2 peripheral neuropathy
10. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmia, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months before enrollment to Treatment Period I
11. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before enrollment into Treatment Period I
12. Patients with central nervous system involvement
13. Inability to swallow oral medications, inability or unwillingness to comply with the drug administration requirements, or gastrointestinal conditions that could interfere with the oral absorption or tolerance of treatment
14. Psychiatric illness/social situation that would limit compliance with study requirements

15. Comorbid systemic illnesses or other severe concurrent disease which, in the judgment of the principal investigator or investigator, would make the participant inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens

Eligibility for Treatment Period II

16. Patients who do not achieve at least a MR to VRd or KRd in Treatment Period I per the IMWG response criteria, 2014 revision
17. Patients who experience Grade 1 peripheral neuropathy accompanied by pain, or Grade ≥2 peripheral neuropathy during Treatment Period I
18. Patients with evidence of uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmia, symptomatic congestive heart failure, unstable angina, or myocardial infarction during Treatment Period I
19. Patients using potent CYP3A4 inducing agents (rifampicin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or gingko biloba or St. John's wort
20. Patients with hypersensitivity to any of the IRd study medications, their analogs, or excipients contained in IRd
21. Comorbid systemic illnesses or other severe concurrent disease which, in the judgment of the principal investigator or investigator, would make the participant inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens

7.3 Study Registration

Patients are enrolled into the study after providing consent, and are registered on the web-based registration site at the start of treatment.

All patients who provided consent are registered. Refer to Section 9.1.22 for procedures concerning the record of the study subject who discontinued before the start of the study treatment.

For all patients who underwent treatment during Treatment Period I, the results of eligibility for Treatment Period II is recorded on the web-based registration site at the start of the treatment for Treatment Period II.

8.0 STUDY DRUG

This section describes the treatment used in this clinical study. All treatments employed in this study were prescription medicines and were administered or monitored from investigational sites. For details and handling of medications, refer to the latest package insert.

8.1 Study Drugs

8.1.1 Study Drugs for Treatment Period I

Either of the following regimens are used as therapy in Treatment Period I.

1. VRd
   Combination of bortezomib, lenalidomide and dexamethasone
2. KRd
   Combination of carfilzomib, lenalidomide and dexamethasone

8.1.2 Study Drugs for Treatment Period II

Ixazomib was administered as part of a combination regimen with lenalidomide and dexamethasone (i.e. IRd therapy), in Treatment Period II.

Study drug (Ixazomib)

Common name: Ixazomib citrate (JAN)

Chemical name: 2,2'-{2-[(1R)-1-({[(2,5-Dichlorobenzoyl)amino]acetyl}amino)-3-methylbutyl]-5-oxo-1,3,2-dioxaborolane-4,4-diyl}diacetic acid

Lenalidomide

Common name: lenalidomide hydrate (JAN)

Dexamethasone

Common name: dexamethasone

8.2 Definition of Study Treatment

The study treatment period is defined as the period from the start of the treatment in Treatment Period I to the end of the treatment in Treatment Period II. The principal investigator or investigator administers the therapeutic agent (therapeutic agents for Treatment Period I and therapeutic agents for Treatment Period II) according to the clinical research schedule (Appendix A).

In Treatment Period I, the study treatment is discontinued when the PI is not used in each cycle. The cycle start date is the earliest administration start date of any of the three drugs.

8.3 Dose and Regimen of Study Drugs in Treatment Period I

Standard drug administration is recommended according to the latest package insert of each drug. In addition, administration of treatments against varicella zoster virus and *P. jirovecii* infection is allowed as necessary, as recommended supportive care.

8.4 Dose and Regimen of Study Drugs in Treatment Period II

In Treatment Period II, investigators administer to the patient a combination of ixazomib, lenalidomide, and dexamethasone. The dosing schedule for each drug in a cycle is shown in Figure 8.a Administration Schedule of Ixazomib, Lenalidomide, and Dexamethasone. Each drug is administered according to the latest package insert. However, if necessary, changes in the method of administration for each drug may be considered (refer to Section 8.4.2).

Figure 8.a Administration Schedule of Ixazomib, Lenalidomide, and Dexamethasone

	Week 1							Week 2							Week 3							Week 4						
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Ixazomib	○	–	–	–	–	–	–	○	–	–	–	–	–	–	○	–	–	–	–	–	–	–	–	–	–	–	–	–
Lenalidomide	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	–	–	–	–	–	–	–
Dexamethasone	○	–	–	–	–	–	–	○	–	–	–	–	–	–	○	–	–	–	–	–	–	○	–	–	–	–	–	–

In addition, administration of treatments against varicella zoster virus and *P. jirovecii* infection is allowed as necessary, as recommended supportive care.

8.4.1 Administration Schedule of Study Drugs in Treatment Period II

The recommended dose and administration route for each drug used in Treatment Period II are described in **Table 8.a**. A guideline for the starting dose of lenalidomide in patients with impaired renal function is given in **Table 8.b**.

Table 8.a Study Drug and Administration Method

Drug to be administered	Recommended dose	Recommended administration method
Ixazomib	Once a day 4.0 mg	After oral administration once weekly for 3 weeks (1, 8 and 15 days), withdrawal for 13 days. Fasting administration
Lenalidomide	Once a day 25 mg	After oral administration for 21 days, washout for 7 days
Dexamethasone	Once a day 40 mg	Orally administered once a week (days 1, 8, 15 and 22)

Table 8.b Estimated Starting Dose of Lenalidomide when Administered to Patients

with Impaired Renal Function (Quoted from Revlimid® Suitability Guide [24])

Renal function (Ccr)	Recommended administration method
Moderate renal dysfunction: 30 < Ccr <60 mL/min	Start with 10 mg of lenalidomide once daily and increase to 15 mg if tolerable after 2 cycles
Severe renal dysfunction (no dialysis required): Ccr <30 mL/min	Lenalidomide 15 mg administered once every 2 days
Severe kidney function disorder (dialysis necessary): Ccr <30 mL/min	Lenalidomide 5 mg once daily (on dialysis day after dialysis)

8.4.2 Revised Guidelines for Administering Agents in Treatment Period II

(for reference)

AEs are evaluated according to CTCAE (JCOG Japanese translation version v 4.03). For dosing changes within a treatment cycle, refer to 8.4.2.1–8.4.2.5; to determine the start of the next treatment refer to Section 8.4.3.

Where more than one AE is observed, dose adjustment and/or delay are carried out according to the criteria of the most severe AE.

In order to ensure the safety of the patient while maximizing the exposure of the study drug, another dose modification may be recommended.

The dose reduction steps for ixazomib, lenalidomide, or dexamethasone are shown in **Table 8.c**, **Table 8.d**, and **Table 8.e**, respectively.

Table 8.c Dose Reduction Steps for Ixazomib

Starting dose	First dose reduction	Second dose reduction	Third dose reduction
4.0 mg	3.0 mg	2.3 mg	Discontinue

Table 8.d Dose Reduction Steps for Lenalidomide

Starting dose	First dose reduction	Second dose reduction	Third dose reduction
25 mg	15 mg	10 mg	Discontinue

* Patients with moderate renal dysfunction (30 < Ccr < 60 mL/min) will receive lenalidomide from the starting dose of 10mg, first dose reduction of 5 mg, and discontinued at the second dose reduction. In the C16028 study, there were no reports of

lenalidomide treatment in patients with severe renal dysfunction (Ccr < 30 mL/min). Considering the recommendations for dose adjustments for patients with MDS, the patients with severe renal dysfunction may receive lenalidomide from the starting dose of 5 mg, first dose reduction of 2.5 mg twice a week, but careful administration is recommended.

Table 8.e Dose Reduction Steps for Dexamethasone

Starting dose	First dose reduction	Second dose reduction	Third dose reduction
40 mg	20 mg	8 mg	Discontinue

8.4.2.1 Dose Adjustments for Rash: Ixazomib and Lenalidomide

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

- Occurrence of Grade 2 rash

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

In this study, 'events manageable by supportive care' is defined as events for which symptomatic treatment allows for continued study treatment without dose interruptions or reductions, while 'events not manageable by supportive care' is defined as events that cannot be managed only by supportive care, and require dose interruptions or reductions.

In severe situations, alternative dose modification may be made as needed. Angioedema and Grade 4 rash have been reported after the use of lenalidomide, and in such cases, lenalidomide should be discontinued [24]. Refer to **Table 8.f** for dose modification of lenalidomide if angioedema, Stevens-Johnson syndrome, or toxic epidermal necrolysis (TEN) is observed.

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

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

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

8.4.2.2 Dose Adjustments for Hematologic Toxicity: Ixazomib and Lenalidomide

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

Table 8.g Dose Reduction Steps for Ixazomib and Lenalidomide for Thrombocytopenia

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

Table 8.h Dose Reduction Steps for Ixazomib and Lenalidomide for Neutropenia

Platelet Count	Action on Ixazomib	Action on Lenalidomide	Action
First reduction to <500/mm^3	Interrupt treatment	Interrupt treatment	Follow complete blood count (CBC) weekly
Return to ≥500/mm^3 within the same cycle	Resume and maintain dose level	Resume at next lower dose level	Eg, if lenalidomide dose was 25 mg, reduce to 15 mg
Second reduction to <500/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly
Return to ≥500/mm^3 within the same cycle	Resume at next lower dose level	Resume at maintain dose level	Eg, if ixazomib dose was 4 mg, reduce to 3 mg
Third reduction to <500/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly
Return to ≥500/mm^3 within the same cycle	Resume and maintain dose level	Resume at next lower dose level	Eg, if lenalidomide dose was 15 mg, reduce to 10 mg
Fourth reduction to <500/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly
Return to ≥500/mm^3 within the same cycle	Resume at next lower dose level	Resume and maintain dose level	Eg, if ixazomib dose was 3 mg, reduce to 2.3 mg Do not reduce below 2.3 mg
Fifth reduction to <500/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly
Return to ≥500/mm^3 within the same cycle	Resume and maintain dose level	Resume at next lower dose level	Eg, if lenalidomide dose was 10 mg, reduce to 5 mg Do not reduce below 5 mg

8.4.2.3 Ixazomib Treatment Modification

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

Table 8.i Ixazomib Treatment Modifications (Delays, Reductions, and Discontinuations) Due to AEs

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

8.4.2.4 Lenalidomide Treatment Modification

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

Table 8.j Lenalidomide Treatment Modifications (Delays, Reductions, and Discontinuations) Due to Non-Hematologic AEs

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

8.4.2.5 Dexamethasone Treatment Modification

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

Table 8.k Dexamethasone Treatment modifications (Delays, Reductions, and Discontinuations) Due to AEs

AEs (Severity)		Action on Dexamethasone [24]
Gastrointestinal disorder	Dyspepsia, gastric, or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)	Treat with histamine-2 blockers, sucralfate, or omeprazole. If symptoms persist despite these measures, decrease dexamethasone by 1 dose level.
	Dyspepsia, gastric, or duodenal ulcer, gastritis ≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms are adequately controlled. Restart and decrease 1 dose level of current dose along with concurrent therapy with histamine-2 blockers, sucralfate, or omeprazole. If symptoms persist despite these measures, discontinue dexamethasone and do not resume.
	Acute pancreatitis	Discontinue dexamethasone and do not resume.
Cardiovascular disorder	Edema ≥ Grade 3 (limiting function and unresponsive to therapy, or anasarca)	Diuretics as needed and decrease dexamethasone by 1 dose level. If edema persists despite these measures, decrease dose another level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Neurological disorder	Confusion or mood alteration ≥ Grade 3	Hold dexamethasone until symptoms resolve. After the symptoms resolved, restart with 1 dose level reduction. If symptoms persist despite these measures, discontinue dexamethasone and do not resume.

Musculoskeletal disorder	Muscle weakness ≥ Grade 3 (interfering with function ± interfering with ADL)	Decrease dexamethasone dose by 1 dose level. If weakness persists despite these measures, decrease dose by 1 dose level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Metabolic disorder	Hyperglycemia ≥ Grade 3	Treatment with insulin or oral hypoglycemic as needed. If uncontrolled despite these measures, decrease dexamethasone dose by 1 dose level until levels are satisfactory.

8.4.3 Criteria for Toxicity Recovery Before Beginning the Next Cycle of Treatment in Treatment Period II

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

- ANC ≥1,000/mm^3
- Platelet count ≥75,000/mm^3
- Other clinically significant non-hematologic toxicities ≤ Grade 1 or to the patient's baseline condition.

If the beginning the next cycle of treatment are delayed by more than 4 weeks, discontinue administration (exclude when the principal investigator or investigator judge it clinically beneficial).

If the patient does not recover completely from the treatment-related toxicity, see Section 8.4.2.1–8.4.2.5 for recommended dose reduction.

8.5 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study patient, at a dose above that which is assigned to that individual patient according to the study protocol.

All overdose should be recorded in the case report using the appropriate forms, by the principal investigator or investigator, in order to record any data on study drug overdose into a database. Any AEs due to overdose of treatment should be recorded according to section 10.0.

Furthermore, any serious AEs due to overdose of treatment should be recorded according to section 10.2.2.

If overdose occurs, consider close observation for hemodynamics and supportive care under hospitalization in study site.

8.6 Excluded Concomitant Medications and Procedures

The following medications are prohibited during the study.

- Any antineoplastic therapy effective against MM other than the study medication
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates PD)

Participants are advised by the principal investigator or investigators not to take any medications, including marketed drugs, other than the drugs as instructed without prior consultation.

8.7 Discontinuation of Study Treatment per Patient

In any of the following study treatment discontinuation criteria, the study treatment is discontinued. The principal investigators or investigators must record the main reason for discontinuation of clinical study in the case report form, according to the following classifications. For cases where the patient discontinued before treatment medication was administered, see section 9.1.23.

1. Lack of efficacy (or exacerbation of disease), defined as PD according to IMWG criteria (Appendix E).
2. Adverse event
   If an AE requiring an early discontinuation, or if the patient does not wish to continue with the study due to AE, the patient will be discontinued to avoid unacceptable risk to the health of the patient. In case the patient dies during the study treatment, it is classified as death during study treatment.
   Furthermore, if the AE caused a delay of a treatment cycle of more than 4 weeks during the Treatment Period II.
3. If the patient does not meet the inclusion criteria for Treatment Period II, or meets the exclusion criteria. The investigator to record the corresponding criteria(s) in the case report.
4. Voluntary withdrawal by patient
   When the patient wish to stop participating in the clinical study. If the reason for discontinuation is known, the investigator to record the reason(s) in the case report. Investigators should attempt to make the reasons for voluntary discontinuation as clear as possible; note that discontinue due to AEs or lack of efficacy is not classified as voluntary discontinuation.
5. Death during study treatment

   If the patient dies before the decision of discontinuation of the study treatment, the investigator to record the date of death in the case report.

6. Significant deviation from study protocol
   After start of treatment, if it becomes known that the patient did not meet the inclusion criteria of the study protocol; or, if there is a possibility that continued clinical study may result in an unacceptable risk to the patient's health because the patient or investigators did not comply with the study protocol.
7. Lost to follow-up
   Defined as if the patient did not visit the hospital and the investigator could not contact the patient. In this case, investigator should record that an attempt had been made to contact the patient in the original document.
8. Termination of study
   See section 6.2.1 for details.
9. Pregnancy
   When a female patient's pregnancy becomes known.
   Note: If a female patient's pregnancy is known, the patient must immediately discontinue participating in the clinical study. For the discontinuation protocol, see section 9.1.22.
10. Other
    For other reasons, if the principal investigator or investigator judges that it is necessary to stop the study treatment, the investigator will describe the details in the case report.

8.8 Procedure for Discontinuation of Clinical Study by the Enrolled Patient

The principal investigator or investigator will discontinue the trial if the patient violates the criteria described in Section 8.7.

In addition, the patient may discontinue participating in the study at any time without explanation.

If the patient discontinues the study, the principal investigator or investigator will record the main reason in the case report. The investigator must perform all inspections, observations and evaluations that should be performed at the time of discontinuation.

9.0 STUDY PLAN

9.1 Study Procedures

The following section describe the study procedures and data to be collected by the principal investigator or investigator. For each procedure, patients are to be tested/observed/assessed by the same principal investigator or investigator whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The protocol for obtaining informed consent is described in Section 15.3. Each patient must provide written informed consent before any study-related procedures are conducted.

A unique patient identifier (subject ID) will be assigned to each patient at the time that informed consent is obtained; this subject ID will be used throughout the study and will remain unchanged.

9.1.2 Patient Demographics

Demographic information to be obtained will include.

- Date of birth (if it is not provided, use the age at registration)
- Sex
- Initial diagnosis of MM: Initial date of diagnosis NDMM
- M-protein isotype (IgG κ･λ, IgA κ･λ, IgD κ･λ, IgE κ･λ, IgM κ･λ, Bence Jones type κ･λ, non-secretory type, unknown, others)
- Clinical stage according to ISS (Appendix C)
- Chromosome abnormality at the initial diagnosis: t (4;14), t (14;16), t (11;14), del17p, 1q gain
- Chromosomal abnormalities at disease recurrence: del17p, 1q gain
- Evaluation of bone lesions and extramedullary disease
  (If imaging test is performed at the start of the study treatment, the investigator evaluates the presence or absence of bone lesions or extramedullary disease (bone-delivered, or soft tissue-delivered or others). In addition, the investigator evaluates the longest diameter and shortest diameter of the largest extramedullary plasmacytoma of all observed extramedullary disease. As a substitute, the most recent image evaluation until the consent acquisition may be used

9.1.3 Comorbidity

Investigators must investigate patient comorbidities at the beginning of the clinical study using the Charlson comorbidity index (CCI) [26] (Appendix B).

In addition, investigators evaluate the presence or absence, and Grade, of peripheral neuropathy and rash for the patients at the start of study.

9.1.4 Medical History

The investigator will record prior radiation therapy, antineoplastic therapy, or hematopoietic stem cell transplantation for therapy of MM.

- Prior antineoplastic therapies: drug name, reason for termination (i.e. PD or 'other')
- Prior radiation therapy
- Prior hematopoietic stem cell transplantation

9.1.5 Physical Examination

Physical examination based on symptoms, and evaluation (by the investigator) of the organ system related to those symptoms.

Regarding the results of the examination after the start of study treatment, the investigator evaluates the presence or absence of abnormality which is clinically considered to be a problem compared with the examination result before the start of the examination treatment.

9.1.6 Body Weight, Height

Weight and height are measured at each site.

Height is measured in centimeters with only integers and weight is measured in kilograms up to the first decimal place.

E.g.: Height = 176 cm, weight = 79.2 kg

9.1.7 Vital signs

Blood pressure and pulse rate are measured as vital signs.

9.1.8 Status of Study Treatment

The principal investigator or investigator records the following information related to the study drug in the case report

- Dosing of each drug used for study treatment (start date of a treatment cycle, number of cycle days of Treatment Period I, date and dose administered of each PI, start dose administered of lenalidomide and dexamethasone, frequency administered of lenalidomide and dexamethasone)
  Note: The start date of a treatment cycle is defined as the earliest date of the 3 drug start dates within Treatment Period I and within Treatment Period II.

9.1.9 Performance Status

Performance Status determined according to ECOG PS according to Appendix D.

9.1.10 Clinical Laboratory Examinations

Laboratory tests are conducted at each study site. For parameters measured, see **Table 9.a**.

Table 9.a Laboratory tests

Hematologic	Blood biochemistry
WBC count	albumin
Hemoglobin	total bilirubin
Platelet count	AST
Neutrophil count	ALT
	ALP
	LDH
	Creatinine
	Ccr (measured value) *if available in clinical records
	calcium
	β2-microglobulin

Ccr (estimated value) is calculated by using the formula below; the Cockcroft-Gault equation using serum creatinine value may also be used.

For men:

$$\text{Ccr} = \frac{(140 - \text{age [years]}) \times \text{weight [kg]}}{72 \times \text{serum creatinine [mg/dL]}}$$

For women:

$$\text{Ccr} = \frac{0.85\ (140 - \text{age [years]}) \times \text{weight [kg]}}{72 \times \text{serum creatinine [mg/dL]}}$$

9.1.11 Evaluation of QOL

Patients' QOL will be evaluated by the investigators using EORTC-QLQ-C30 (Appendix F)[27] and MY-20 (Appendix G)[28].

Evaluation of QOL shall be conducted before study drug is administered. During Treatment Period II, QOL will be evaluated every 3 cycles (i.e. Cycles 1, 4, 7, 10 etc.). Patients ineligible for Treatment Period II (i.e. those who did not meet Eligibility for Treatment Period II) are required to have a QOL evaluation once prior to the start of next treatment.

9.1.12 Determination of M-protein

M-protein in blood samples and urine samples will be measured at each study site. If it is not possible to measure serum and urine M-protein, it can be substituted with serum FLC (free light chain) level.

9.1.13 Response Assessment

The principal investigator or investigators will determine the clinical response of the patient according to the IMWG criteria (2014 version), based on serum M-protein, urine M-protein, and serum FLC, plus other parameters as required (Appendix E).

9.1.14 Bone Marrow Aspiration

Investigators will perform bone marrow aspiration. If a patient is suspected to have achieved CR, the investigator will collect specimens for evaluation of the presence of minimal residual disease (MRD). Re-assessment is possible from 6 months after bone marrow aspiration until completion of this clinical study. Bone marrow aspiration must take place on Monday through Friday, and must not take place on Saturday, Sunday or the holiday. The collected sample of bone marrow aspirate will be used to measure MRD.

- MRD measurement:

  MRD was measured by the PPD flow method using bone marrow aspiration at the time of CR assessment, and it was measured by the NGS method using both FFPE samples of preserved bone marrow aspiration at the study sites and bone marrow aspiration at the time of CR assessment.

9.1.15 Supportive Therapy

Investigators will record the use and timing (name of drugs, start date and discontinuation date) of supportive therapies for varicella zoster and *P. jirovecii* infection (e.g. ST combination drug) in the patient from the start of the study treatment to the discontinuation of the study treatment.

9.1.16 Image Inspection

When the investigator performs either a CT scan or MRI on the patient, the presence or absence of new extramedullary plasmacytomas will be evaluated, and the longest diameter and the short diameter of the largest extramedullary plasmacytoma measured.

9.1.17 Adverse Events

AEs (serious and non-serious) will be monitored throughout the study period. For details of defining, recording and reporting of AEs and serious AEs, see section 10.0.

9.1.18 Scheduled Outpatient Clinic and Hospitalization

If the patient visits the clinic as an outpatient or is hospitalized during the clinical study, the investigator will record the date of outpatient visit and hospitalization (admission date and discharge date). Duration of Treatment Period I and II are defined as;

Treatment Period I: from the start date of study drug administration for Treatment Period I to the day before the start date of study drug administration for Treatment Period II. For patients who discontinued after Treatment Period I, from the cycle start date to the decision date of discontinuation of the study treatment.

Treatment Period II: from the start date of study drug administration for Treatment Period II to the decision date of discontinuation of the study treatment.

9.1.19 Follow-up Assessments

Patients who discontinue administration of study treatment before disease progression in Treatment Period II are subject to follow-up surveillance to determine PFS. Follow-up is conducted every 3 months by hospital visits, until death or the patient is lost to follow-up.

All patients who discontinue administration of study treatment in Treatment Period II are subject to follow-up surveillance to determine OS. Follow-up is conducted every 6 months until death or the patient is lost to follow-up. Follow-up for OS is conducted by way of telephone, e-mail, mail, etc.; a hospital visit may not be necessary. Investigators will record the following information

- Date of follow-up
- Date of death or final known survival date.

9.1.20 Next-line Treatment

If the patients received treatment after discontinuing IRd in Treatment Period II, for the first therapy after discontinuation the investigator collects the following contents.

- Names of regimens used
- Start date

9.1.21 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent to the end of the study, female patients of childbearing potential (i.e., nonsterilized, premenopausal female patients) who are sexually active must comply with RevMate® and use appropriate methods of contraception.

9.1.22 Pregnancy

If any female patient is found to be pregnant during the study period or within 90 days after the end of the study, the pregnancy should be reported immediately.

If the patient agrees to the primary care physician (obstetrics and gynecology specialist) being informed, the investigator or sub-investigator should notify the primary care physician that the

patient was participating in a clinical study at the time she became pregnant and provide details of treatment the patient received.

For all reported pregnancies, the outcome until the delivery, including premature birth, will be followed up and reported to the representative investigator and Takeda using the pregnancy form under the agreement from the patient. Evaluations after the birth of the child will also be conducted.

For male patients, if a patient's female partner becomes pregnant during study treatment or within 90 days of termination of study, the outcome until the delivery, including premature birth, will be followed up and reported to the representative investigator and Takeda using the pregnancy form under the agreement from the patient. Evaluations after the birth of the child will also be conducted.

9.1.23 Study Participation Discontinued Before Administration of Study Medication

In the event that a patient signs a consent form and the investigator prepares a case report form, for those patients who then discontinue before the administration of the study medication, the case report will contain the following items:

- Date of consent acquisition
- Date of birth (If a date cannot be provided, then the age at registration)
- Sex
- Eligibility
- Reason for cancellation
  Investigators to collect the main reasons for the patients who discontinued before starting treatment medication administration in the following categories:
    - Does not meet selection criteria or violates exclusion criteria
    - Critical deviation from study protocol
    - Unable to follow-up
    - Voluntary discontinuation; describe the reason
    - Cancellation of the clinical study as a whole
    - Other; describe the reason

The investigator must not use the identification code of the patient who discontinued before the start of study drug administration.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Event Definition

AE is defined as any untoward medical occurrence in a patient or subject administered a pharmaceutical product (including the study drug); 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.

Adverse event is a disease or the like in the clinical research method

10.1.2 Adverse Event Definition

Generally, undesirable AEs include:

- Newly diagnosed disease or deterioration of an existing condition
  (Intermittent events of existing disease are not considered as AEs)
- Any event requiring treatment or medical treatment
- AEs requiring invasive diagnostic procedures
- AEs requiring discontinuation of study drug or dose change
- AEs that the principal investigators or investigators regarded as undesirable

Diagnosis name and signs/symptoms:

- AEs are recorded by diagnosis name. Any accompanying signs (including abnormal laboratory test values or abnormal ECG) or symptoms are not considered AEs. In case of an AE without a diagnosis, signs and symptoms are considered AEs.

Laboratory test values and ECG findings:

- For clinical laboratory test values or ECG, it is considered as an AE only when the responsible the principal investigator or investigator determines that there is a clinical problem from the transition (i.e., when a treatment or medical treatment is required, or if the principal investigator or the investigator deems a change beyond the normal physiological variation range for the patient). Reexamination and/or ongoing monitoring of abnormal values are not considered as medical treatment. In addition, repeated or additional noninvasive examination for verification, evaluation or monitoring is not considered to be a medical treatment.
  However, if the clinical laboratory test value or ECG is accompanied by a diagnosis of an AE (e.g. creatinine increase due to impaired renal function), its diagnosis name is regarded as an AE.

Existing diseases (diseases and symptoms existing before the start of study drug administration):

- Diseases and symptoms existing before the start of study drug administration are recognized as complications and are not recognized as AEs. If the complication worsens, the deterioration is recognized as an AE, and the principal investigator or investigator records the name of AE name as a worsening of complications (e.g. 'worsening hypertension') in the case report
- If the patient has a temporary existing disease (e.g., asthma, epilepsy), if the frequency of its symptoms increases, or an increase in severity or advancement of disease is observed, the existing disease is recorded as an AE. If the patient has a chronic disease (e.g. cataract, rheumatoid arthritis), the chronic disease is recorded as an AE if the symptoms worsen more than expected. The principal investigator or investigator should record the reported AE name as a change in existing chronic disease symptoms (e.g. worsening of...) from the start of the study treatment.
- Deterioration of AE:
  If the AE worsens after a change in the study medication, or if secondary signs and symptoms of the adverse event are observed, these secondary changes are regarded as new AEs, and recorded in the case report. The principal investigator or investigator should record the reported AE name to clearly show that the symptom change (e.g. worsening of …).

Changes in the severity of AE:

- If there is a change in the severity of the AE, the principal investigator or investigator records only the instance when the maximum severity is observed.

Pre-planned surgery or treatment:

- The surgery or treatment planned before the start of study drug administration is not considered an AE. However, if the patient's existing symptoms deteriorate markedly and surgery or treatment needs to be performed urgently, that condition or event is considered an AE. Complications due to pre-planned surgical procedures are recorded as AEs.

Surgery or treatment requiring no urgency:

- Surgery or treatment which does not suddenly affect the patient's symptoms, such as cosmetic surgery, is not considered an AE. However, the investigator records this case in the case report. Complications due to surgery that require no urgency are reported as AEs.

Progressive disease:

- PD is not regarded as an AE as it is a result of lack of efficacy of pharmaceuticals. Also, symptoms that are merely for PD need not be considered serious AEs. However, if the progress of existing cancers (including the development of new metastases) is confirmed clinically or by examination, and if the degree of progression of the cancer falls under the

serious criterion of as per section 10.1.3, progression of the cancer is considered a serious AE.

Overdose of study drug:

- Overdose of drugs without any event expression is not considered an AE. However, investigators record overdose in the case report. When an event occurs due to overdose of the drug, the investigator records the symptom as an AE in the case report.

10.1.3 Serious Adverse Event Definition

Serious AE means any untoward medical occurrence that at any dose:

1. Results in death.
2. 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).
3. Requires inpatient hospitalization or prolongation of an existing hospitalization (see below on hospitalizations that are not considered serious AEs).
    a. Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the study
    b. Hospital admissions or surgical procedures for an illness or disease that are not related to AEs.
4. 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).
5. Results in a congenital anomaly/birth defect.
6. Is a medically serious 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 one 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 (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent. Any terms included in the Takeda Medically Significant AE List (**Table 10.a**) are defined as a Serious AE.

Table 10.a Takeda Medically Significant AE List

Acute respiratory failure, or acute respiratory distress syndrome (ARDS)	Hepatic necrosis
Torsarde de pointes, ventricular fibrillation, or ventricular tachycardia	Acute liver failure
Malignant hypertension	Anaphylactic shock
Convulsive seizures (including convulsions, epilepsy)	Acute renal failure
Agranulocytosis	Pulmonary hypertension
Aplastic anemia	Pulmonary fibrosis (including interstitial pneumonia)
Toxic epidermal necrolysis, or Stevens-Johnson syndrome	Malignant syndrome or malignant hyperthermia
	Spontaneous abortion, stillbirth or fetal death
	Transmission or suspected transmission of drug-mediated infection
	Endotoxin shock or suspect thereof

10.1.4 Clinically Important AEs (Intensively Investigated Events)

Among the important identified risks, the important potential risks or the related events described in the drug risk management plan of the study drugs, the following events are intensively investigated events.

The principal investigator or the investigator continuously monitors these events and promptly notifies the representative investigator and Takeda when they request the information.

- Thrombocytopenia
- Severe gastrointestinal disorders
- Skin disorders
- Peripheral neuropathy
- Infection

These events may require further investigation to establish an evaluation. For the reporting method and the reporting time from the principal investigator or investigator to the representative investigator and Takeda, see Section 10.4.

10.1.5 Severity of AEs

Severity (toxicity grade) for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE Japanese Version 4.03, and defined as below (**Table 10.b**)

Table 10.b AE Grade Defined in CTCAE Japanese Version 4.03

Grade	Definition

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

A semi-colon indicates 'or' within the description of the grade.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

10.1.6 Causal Relationship of Adverse Events

Causal relationship between test medication (study drug at Treatment Period I, study drug at Treatment Period II) and AE, and causal relationship with study drug (only in case of 'related') Is classified and defined as follows.

Related	There is an obvious temporal correlation (including the course of symptoms after discontinuation of administration). Or, other factors such as original disease, complications, concomitant medications, and combined treatment, may be responsible for the AE but it may also be caused by study drug or study treatment.
Not related	There is no clear temporal correlation with study drugs or treatments. Or an AE that is considered to be related to other factors such as original disease, complications, concomitant medications, concomitant treatment or the like

10.1.7 Date of onset

Judge the date of onset of adverse event according to the following criteria:

Adverse event	**Date of onset**
Signs, symptoms, diseases (diagnosis name)	Record the date when the subject or the principal investigator or investigator noticed the first signs and symptoms of adverse event.
Asymptomatic disease	Record the date of obtaining a definite diagnosis after conducting a test for diagnosis. Record the date of obtaining a definite diagnosis even when the test findings show old findings or suggest approximate timing of onset.
Aggravation of complications	Record the date when the subject or the principal investigator or investigator noticed the signs and symptoms of adverse event for the first time.

Abnormal laboratory findings after initiation of protocol treatment	Record the date of test where abnormal laboratory values considered clinically problematic were observed.
Abnormality was observed on the test at initiation of protocol treatment, and aggravation was shown on subsequent tests.	Record the date of tests when values were medically judged to be obviously increased and decreased based on the changes in test values.

10.1.8 Date of resolution

The date when the adverse event resolved (or resolved with sequelae). Date of death when a subject died of the concerned adverse event. When recovery cannot be confirmed at study completion, it is considered ongoing.

10.1.9 Treatment Regarding Study Medication

As a treatment for the AE, the time at which the study treatment is discontinued is defined as 'discontinuation of administration'.

10.1.10Outcome

The outcomes of AEs are classified as follows.

Classification	Evaluation
Recovered	• Disappearance of symptoms and findings, or recovery • Normalization of laboratory values, or recovery to baseline
Lightly recovered	• Severity reduced by ≥1 Grade • Disappearance of symptoms and findings • Improvement of laboratory values, but not recovered to baseline • In cases of death, the AE was not a direct cause of death, and the AEs had lightly recovered before death
Unresolved	• No change in symptoms, findings and laboratory values • Symptoms, findings and laboratory values on the last day of the observable period was worse than at the time of observation • Irreversible congenital anomalies • In cases of death, if the adverse event is not a direct cause of death and the AE remains unrecovered

Recovered but with sequelae	Dysfunction that interferes with daily living occurred
Died	• There was a direct association between death and the AE; 'direct relevance was recognized' is defined as the AE causing the death or the AE contributed to the death • Any AEs that were judged or estimated not to be the direct cause of death, shall not be recorded as death due to AE
Unknown	• Not able to follow-up after the date of observation as described in the study protocol, due to e.g. hospital transfer or patient relocation

10.2 Procedures for Recording and Reporting AEs and Serious AEs

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. 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.

10.2.1 Collection and Reporting of AEs

10.2.1.1 Collection Period of AEs

Investigators will start collection of AEs from the start of the study Treatment Period I, and continue until discontinuation of the Treatment Period I, or 30 days after the discontinuation of Treatment Period II, or until the start of the next treatment, whichever comes first.

In addition, new primary malignancies that occur during the follow-up periods after the discontinuation of the Treatment Period II must be reported, irrespective of causality to study regimen, to the representative investigator and Takeda for a minimum of 3 years after the discontinuation of study treatment through death or termination of the study by them.

10.2.1.2 Reporting AEs

When the patient visits, the principal investigator or investigator confirms the presence or absence of symptoms of AEs with patients. The investigator inquires with the patient, e.g. 'How is your physical condition since the last visit?' to the patient, and listens to the patient's description AEs that occurred during the study.

Regarding AEs, irrespective of the symptoms of the patients being related to the study drug, the principal investigator or investigator examines the symptoms of the patient until the symptoms disappear. The investigator examines the symptoms of the patient until the abnormality of the clinically relevant laboratory test value recovers to the value at the start of the test treatment. The investigator tracks all the patients to be studied until a sufficient explanation can be given about the change in the patient's symptoms. Regardless of the patient's symptoms being related to the study treatment medicine, the principal investigator or investigator records all AEs on the AE page of the case report. Each event is described as follows.

1. Event name
2. Expression date and date of disappearance
3. Severity
4. Causality relationship with study drug
5. Clinical treatment for study drug
6. Outcome
7. Severity

The principal investigator or investigators should not use QOL questionnaires as the main method for collecting AEs. However, if, during the collection of QOL questionnaires the principal investigator or investigator recognizes the patient's symptoms are likely due to AEs, the principal investigator or investigator may follow-up and investigate the patient's symptoms. The principal investigator or investigator then performs a medical evaluation on the symptoms of the patient. As a result of the follow-up study, if the symptom of the patient is judged to be an AE not previously reported, the investigator will report according to the usual reporting procedure.

10.2.2 Collection and Reporting of Serious AEs

The principal investigator or investigator immediately reports to the director of study site when the principal investigator or investigator judges that a serious adverse event has occurred. And the principal investigator or investigator should also report to the CRO within 24 hours of recognition of the onset of an event. In addition, the principal investigator will submit a serious AE report detailed in 10 calendar days to Takeda through the CRO. The principal investigator shall describe all information as much as possible, and the description of the following contents is mandatory.

- Name of the adverse event (including known/unknown events*)
- Brief description of the event and reasons for judging it to be serious
- Research patient identification code
- Name of the principal investigator or investigator
- Name of study medication
- Determination of causality

*: The principal investigator or the investigator will determine whether adverse events are known or unknown according to the latest package insert of the drug used in the protocol treatment.

The representative investigator receiving a report from the CRO will hear the opinions of the Certified Review Board, and also provide information to the principal investigator at each study site through the CRO according to the Clinical Research Act. The principal investigator will report to the director of the study site as necessary.

After the AE collection period, the principal investigator or investigator must report to the representative investigator and Takeda about any AEs voluntarily reported by the patient and may be due to the patient participation in the clinical study.

10.3 Follow-up of Serious AEs

If the principal investigator or investigator obtained at a later date any information that was not initially reported, the principal investigator or investigator shall fill out a report of serious AEs for follow-up or create another document and promptly report it to Takeda through the CRO. If requested, the investigator copies relevant data (e.g. electrocardiogram, clinical laboratory value, summary of discharge report, necropsy outcome and so on) from the medical record of the study site and reports it to the representative investigator and Takeda. The principal investigator or investigator will track the patient's symptoms until the event disappears or the final outcome is confirmed. The deadline and procedure concerning the report of the follow-up survey are done in the same way as the initial report.

10.3.1 Reporting Serious AEs to Regulatory Authorities

Takeda should report according to regulations, unexpected serious adverse drug reactions and other serious adverse events that are subject to emergency reporting to regulatory authorities.

From the time point of first acknowledging the event or receiving additional information, Takeda or CRO should comply with regulatory required time frame for reporting, and make emergency report concerning unexpected serious adverse drug reactions and expected serious adverse drug reactions to regulatory authorities. Also, Takeda should in the same way make an emergency report of other critical safety information that may have a major effect on the study drug risk-benefit, continuation of study drug administration, and continuation of this clinical study .

A report to CRB in the event that an adverse event suspected to be attributable to this study is reported comply with the following report deadline.

Severity	Predictability	deadline
death	Does not matter	Within 15 days
Hospitalization or extension of hospitalization Handicap	cannot predict Predictable but there are concerns about expansion	Within 15 days
Fear of death or handicap Serious adverse events similar to the above Congenital disease in the later generations	predictable	Within 30 days
Adverse events due to infection	cannot predict	Within 15 days

Death from infectious diseases Hospitalization or extension of hospitalization Handicap Fear of death or failure Serious adverse events similar to the above Congenital disease in the later generations	Does not matter	Within 15 days

10.4 Reporting of additional information on AEs

When the representative investigator and Takeda request the principal investigator or investigator to provide additional information on an AE, the principal investigator or investigator must enter it in the eCRF system or submit a written report.

11.0 STUDY-SPECIFIC COMMITTEES

No data safety monitoring committee or central assessment committee will be used in this study.

11.1 Study Steering Committee

The study steering committee consists of medical professionals involved in this clinical study, Takeda, and independent statistical experts. The study steering committee and the representative investigator oversee the implementation and reporting of the study, ensures highly specialized medical guidance, ensures a high level of scientific quality, and makes appropriate revision of the study protocol. The responsibilities of the committee are stipulated in the procedure manual of the clinical research steering committee.

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 will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the database of medical drug name.

12.1 Case Report

The principal investigator or investigator prepares a case report for all patients who have given consent.

Takeda or its designee provides the study site with access rights to the electronic case report form (eCRF). Takeda or its designee provides training for site managers, investigators and research collaborators when using the eCRF. The case report will be used to report the information gathered during clinical research implementation to Takeda. The case report is prepared in Japanese. The principal investigator or investigator inputs the data directly when preparing the case report.

Any change of, modification of, or addition to the data in the case report are recorded. These corrections are recoded as audit trails that capture the information before and after the change or modification, the personnel who made these change or correction, and the date of change or modification.

The principal investigator must review the eCRF for completeness and accuracy and digitally sign the corresponding page of the case report. The principal investigator is fully responsible for the accuracy and authenticity of all data entered in the case report.

The following are data recorded directly in the case report.

- The severity and seriousness of AEs, causal relationships with study drugs and study drugs, outcome
- Reason for discontinuation before administration of study medication
- Reason for discontinuation of clinical study end status

In cases where the principal investigator or investigator changes or corrects the data inputs in the case report after the database is fixed, the principal investigator or investigator must obtain and use the Data Clarification From. The principal investigator must confirm that the change and correction record of the case report is described accurately and completely, then signs or stamps and record the date.

Takeda or its designee confirms that the case report is properly prepared according to the procedure prescribed for each study. The representative investigator or its designee will view medical records and hospital records of patients participating in the study as necessary to ensure the accuracy of the case report. The completed case reports are the sole property of Takeda and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without the written permission of Takeda.

12.2 Electronic Case Report Input System Deadline

Takeda and its designee must request the principal investigator or investigator to input the electronic case report system at an early stage in the period from the registration of the research patient to the end of the follow-up period. After obtaining the data to be recorded in the case report, the principal investigator or investigator must input the electronic case report system within 14 days as a general rule.

12.3 Record Retention

The principal investigator or the director of study site shall keep the following documents, including records and study-specific documents as specified in section 12.1, for investigation or audit by regulatory authorities and the representative investigator and its designee. The documentation, research patient identification code list, medical records, signed and dated original informed consent form, including the audit trail, copies of case report forms of changes and modifications record, and the like. In addition, the principal investigator and the director of study site must retain these documents until the day 5 years after the early termination or completion of the study, or the day 3 years after which the study results are presented in public.

However, if the representative investigator and Takeda request a longer period for retention, the director of the study site should discuss how long and hot retain those documents with them.

13.0 STATISTICAL METHODS

Statistical analysis will be undertaken by persons who are appointed by the statistical analysis manager and statistical analysis supervisor (analysts who belong to the contract research organization [CRO] independent from Takeda).

13.1 Statistics and Analysis Plan

An initial version of the statistical analysis plan (SAP) will be prepared prior to acquisition of consent from the first patient. The SAP will be finalized prior to database lock. The SAP will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1.1 Analysis Sets

In this clinical study, the following two analysis sets are defined:

- Full Analysis Set (FAS): all patients who enroll in Treatment Period I and who receive at least one dose of any therapy during the Treatment Period
- Safety Analysis Set for Treatment Period II: all patients who enroll into Treatment Period II and who receive at least one dose of the study drug

13.1.2 Analysis of Demographics and Other Baseline Characteristics

The key demographics and other baseline characteristics will be summarized for the FAS.

13.1.3 Efficacy Analysis

(1) Primary Endpoint and Analytical Methods

[Primary endpoint]

PFS rate at 12 months from the start of study Treatment Period I.

The primary endpoint of PFS rate at 12 months from the start of study Treatment Period I is defined as the proportion of patients who are alive and have not had disease progression at 12 months after the start date. The start date is defined as the date of first dose of treatment in Treatment Period I. Patients without 12-month imaging data for determining PD, or patients lost to follow-up, are included in the denominator; however, they are not treated as patients who have not had disease progression.

[Primary analysis]

For the primary endpoint analysis, the null hypothesis will be that the proportion of patients in the FAS who are alive and progression-free at 12 months after the start of Treatment Period I is ≤36%.The one-sided significance level will be 5%. Two-sided 90% confidence intervals will be calculated via exact binomial distribution.

(2) Secondary Endpoints and Analytical Methods

[Secondary Endpoints]

- OS from the start of study Treatment Period I

OS is defined as the period from the first dose of treatment in Treatment Period I to the time when death (regardless of the cause of death) is confirmed. Patients who are still alive will be censored at the last confirmed date of survival or the date of data cut-off, whichever is earlier.

[Analysis Method]

OS for the FAS will be estimated using the Kaplan-Meier method, and the quartiles and two-sided 95% confidence intervals will be calculated using the double logarithmic transformation method of Brookmeyer and Crowley [29].

- PFS from the start of study Treatment Period I

PFS is defined as the period from the first dose of treatment in Treatment Period I to the time of confirmed PD or confirmed death (regardless of the cause of death), whichever is earlier. Patients who are still alive and progression-free will be censored at the last confirmed date at which they are progression-free.

[Analysis Method]

PFS for the FAS will be estimated using similar methodology to that used for analysis of OS.

- Very Good Partial Response (VGPR) or more

This secondary endpoint is defined as the proportion of patients achieving a VGPR or better, according to the IMWG criteria (2014 version) (Appendix E), after the start of the study.

[Analysis Method]

The percentage of patients achieving VGPR or better and 95% confidence intervals on both sides will be calculated for the FAS. Confidence intervals will be accurately calculated based on a binomial distribution.

- Proportion of patients with CR who achieve minimal residual disease (MRD) negativity in bone marrow

This secondary endpoint is defined as the proportion of patients achieving CR who are MRD-negative. If a patient is MRD-positive at their first evaluation and MRD-negative after re-examination, the patient will be considered to be MRD-negative.

[Analysis Method]

For patients in the FAS who enrolled in Treatment Period II and also achieved VGPR or above as best response in Treatment Period II,, the proportion of patients who are MRD-negative and two-sided 95% confidence intervals will be calculated. Confidence intervals will be accurately calculated based on a binomial distribution.

- Best Response

The secondary endpoint of best response is defined as the cumulative numbers of patients who achieve each level of best response, as defined by the IMWG criteria (2014 version) (Appendix E), after each cycle of treatment.

[Analysis Method]

A histogram (or similar) showing the numbers of patients in the FAS achieving different levels of best response will be created after each cycle of treatment.

- Overall Response Rate (ORR)

The ORR is defined as the proportion of patients who achieve a best response of PR or better according to the IMWG criteria (2014 version) (Appendix E) after the start of the study treatment.

[Analysis Method]

The ORR and 2-sided 95% confidence intervals will be calculated in the FAS. Confidence intervals will be accurately calculated based on a binomial distribution.

- Proportion of patients continuing treatment with ixazomib at 12 months from the start of study Treatment Period I.

[Analysis Method]

For the FAS, the proportion of patients who are continuing to receive study drug at 12 months after the start of Treatment Period I, and the two-sided 95% confidence intervals, will be calculated. The confidence intervals will be calculated via exact binomial distribution.

- Duration of Response (DOR)

DOR is defined as the time from the date of first documentation of response ≥PR according to the IMWG criteria (2014 version) (Appendix E) to the date of first documentation of PD or death due to any cause.

[Analysis Method]

DOR for patients in the FAS who achieve PR or better at any time during the study will be estimated using the Kaplan-Meier method, and the quartiles and 95% confidence intervals will be calculated by the double logarithmic transformation method of Brookmeyer and Crowley [29]. Patients who achieve PR or better and have not experienced PD will be censored from the date when their response was confirmed as not being worse than PR.

- Patient-reported outcome: HRQoL, determined using EORTC-QLQ-C30 and MY-20

EORTC-QLQ-C30 comparises five functional scales (physical, role, emotional, cognitive, social), a global health/quality of life scale, three symptom scales (tiredness, nausea and vomiting, pain) and six single items (dyspnea, insomnia, anorexia, constipation, diarrhea, economic difficulty).

MY-20 consists of four independent subscales, two functional subscales (body image, future perspective) and two symptom subscales (multiple myeloma symptoms, treatment adverse effects).

[Analysis Method]

Scores will be calculated for each subscale according to the EORTC Scoring Manual, and summary statistics (number of cases, average value, median, standard deviation, minimum value, maximum value, quartile value) and 2-sided 95% confidence intervals will be determined for each treatment cycle, and mean values will be calculated and presented graphically as plots over time. Summary statistics for change from cycle 1, Treatment Period I, plus the mean and 95% confidence intervals, will be calculated. For patients in the FAS who enroll in Treatment Period II, summary statistics for change from cycle 1, Treatment Period II, plus the mean and 95% confidence intervals, will also be calculated. Changes over time for each subscale will be evaluated in an exploratory fashion by utilizing a statistical model such as a linear mixture model. In addition, data from patients enrolled in Treatment Period I will be used for exploratory analyses of the trends in subscale scores over time.

- Quality-Adjusted Life Years (QALY)

The global health/quality of life scale score from the EORTC-QLQ-C30 instrument will be converted into a utility value ranging from 0 to 1, and used to adjust the value of survival years; this value is defined as the modified QALY.

[Analysis Method]

Summary statistics regarding modified QALYs will be calculated for the FAS.

- Healthcare Resource Utilization

[Analysis Method]

For the FAS, the exposure-adjusted rate of hospitalization events (per patient-months) and the duration of hospitalization among patients in Treatment Period I and Treatment Period II will be calculated.

- Relative Dose Intensity (RDI)

[Analysis Method]

Summary statistics for RDI for ixazomib, lenalidomide and dexamethasone, will be calculated for the FAS. Also, the time plot is outputted.

- Bone Evaluation

[Analysis Method]

For the FAS, the proportion of patients with bone lesions and the two-sided 95% confidence intervals will be calculated. The confidence interval will be calculated via exact binomial distribution.

13.1.4 Analysis of Safety

Treatment-emergent Adverse Events

A treatment-emergent adverse event (TEAE) is defined as either:

- For patients who discontinued after Treatment Period I, an AE that occurred from the start of study until the end of Treatment Period I
- For patients who enrolled into Treatment Period II, an AE that occurred from the start of treatment in Treatment Period I until 30 days after the end of Treatment Period II or the start of next treatment, whichever occurs first

TEAE will be coded using MedDRA and will be summarized by Preferred Term (PT) and System Organ Class (SOC).

In Treatment Period II, TEAEs will be regarded as any AEs that occur after the first dose of study drug.

The following data will be collected in the Full Safety Analysis Set.

- Frequency of all TEAEs
- Frequency of Grade 3 or higher TEAEs
- Frequency by Grade for all TEAEs
- Frequency of serious TEAEs
- Frequency of TEAEs that result in death

In addition, the following data reported during Treatment Period II will be analyzed in the Safety Analysis Set:

- Frequency of all TEAEs observed during Treatment Period II
- Frequency of study drug-related TEAEs observed during Treatment Period II
- Frequency of Grade 3 or higher TEAEs observed during Treatment Period II
- Frequency of Grade 3 or higher, drug-related TEAEs observed during Treatment Period II
- Frequency by Grade of all TEAEs observed during Treatment Period II
- Frequency by Grade of study drug-related TEAEs observed during Treatment Period II
- Frequency of TEAEs resulting in discontinuation of treatment* during Treatment Period II
- Frequency of TEAEs resulting in dose delay* during Treatment Period II
- Frequency of TEAEs resulting in dose reduction* during Treatment Period II

- Frequency of serious TEAEs observed during Treatment Period II
- Frequency of TEAEs resulting in death, observed during Treatment Period II

* One or more of the following: study drug, lenalidomide, dexamethasone

13.2 Interim Analysis and Criteria for Early Termination

An interim analysis is not planned.

13.3 Determination of Sample Size

The purpose of this clinical study is to investigate the efficacy and safety of long-term administration of PI-based therapy with IRd in RRMM patients who are unable to continue treatment with injectable PI-based therapy. The primary efficacy endpoint of this study is the 12-month PFS rate. The sample size was estimated using the results of a preceding overseas (i.e. non-Japanese) clinical trial, and was set so the expected 12-month PFS rate exceeds the threshold 12-month PFS rate.

In a clinical trial of patients with RRMM treated with VRd therapy, the 12-month PFS rate was 36%; this value was set as the threshold PFS rate. Assuming that the hazard rate follows a constant exponential distribution, the hazard rate was estimated to be 0.085[30].

To calculate the expected PFS rate at 12 months, it is assumed that injectable PI-based therapy will be continued up to 3 cycles, and that the PFS rate 9 months after switching to IRd therapy can be based on the PFS distribution in the IRd arm of the C16010 study, an international, double-blind, randomized, placebo-controlled phase 3 study conducted in patients with RRMM with 1-3 prior therapies. In the C16010 study, the median PFS of the IRd group was 20.6 months; assuming that the hazard rate for PFS in the IRd group has a constant exponential distribution, the hazard rate with IRd was 0.034. For the present study, assuming that the hazard rate for the first 3 months is 0.085, and assuming that from month 4 – after switching treatment to IRd therapy – the hazard rate is 0.034, the PFS rate at 9 months after switching to IRd therapy is estimated to be 57%, and this is therefore the expected 12-month PFS rate.

With a threshold 12-month PFS rate of 36%, an expected 12-month PFS rate of 57%, a one-sided significance level of 5%, and 80% power, the number of study subjects required is 39.

Based on the considerations above, the minimum number of patients required to be administered IRd in this clinical study is 39. However, estimating that approximately 20% of patients may not meet the inclusion criteria or may discontinue the trial, the number of patients enrolled in Treatment Period I will be 47.

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 in the case reports. The principal investigator and the director of study site guarantee access to the source documents by the monitor.

All aspects of the study and its documentation will be subject to review by the monitor, including the patient identification code list, patient medical records, original informed consent documentation which includes the signature and date. Then, the monitor confirms that study is carried out in compliance with the study protocol. In addition, the monitor confirms the consistency between the case report and the relevant source material. The principal investigator or investigator and others involved in clinical research will make efforts to respond by allocating sufficient time for each worker to proceed with the work when making a visit to a research institution for monitoring.

For details on the frequency of monitoring to research institutes and the procedure, follow the procedure written separately.

14.2 Deviations from the Clinical Research Act and Study Protocol

The principal investigator or investigator should record all deviations from the Clinical Research Act and protocol.

When acknowledging that the Clinical Research Act, ICH-GCP and protocol are not met (hereinafter referred to as "non-compliance"), the principal investigator or investigator should immediately report it to the director at the study site and notify the principal investigator through the CRO. They should provide information on non-compliance to principal investigator and director at each study site through the CRO.

The representative investigator receiving a report from the CRO will hear the opinions of the Certified Review Board according to the Clinical Research Act when he/she determines it to be serious non-compliance.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance inspections by the auditor and the Certified Review Board. In this circumstance, the representative investigator and Takeda designated auditor will contact the site in advance to arrange an inspecting visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory body, the representative investigator and Takeda

should be notified immediately. The principal investigator and the director of the study site guarantee access for quality assurance auditors to all study documents.

15.0 ETHICAL IMPLEMENTATION OF CLINICAL STUDY

This study will be conducted with the highest respect for the individual participants (ie, patients) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki and the Clinical Research Act. Each principal 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 H and 'Responsibilities of the representative investigator and Investigator' that are listed in Appendix I.

15.1 Certified Review Board Approval

Through the conduct of this clinical study, approval by the Certified Review Board and permission for the conduct of the study by the director of study site should be obtained for the conduct of the study according to the clinical study protocol.

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15.2 Conflicts of Interest

This clinical trial is conducted with support of Takeda.

Prior to conduct of the study, the principal investigator should appropriately manage according to the Clinical Research Act, that this study has no conflict of interests (hereinafter referred to as COI) in companies involved in protocol treatment[31] [32].

The study site shall comply with all requirements prescribed by the Certified Review Board. This includes self-declaration of COI, study protocol, consent form and any explanatory documents.

15.3 Subject Information, Informed Consent, and Subject Authorization

Written consent documents and explanatory documentations will embody the elements of informed consent as described in the Declaration of Helsinki and the Clinical Research Act and will be in accordance with all applicable laws and regulations. The informed consent form describes the approval by the Certified Review Board and the director of study site, the implementation plan has been submitted to the Minister of Health, Labor and Welfare, how to disclose the study information, the compensation for health damage related to the study and what they consist, content of examination by the Certified Review Board, the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study, including to national or international third parties. The informed consent form further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date that informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The representative investigator is responsible for the preparation of the informed consent form, content, and Certified Review Board approval.

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

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

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

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

15.4 Subject Confidentiality

The person engaged in this clinical study or the person who has been engaged in this clinical study 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 Takeda's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with the Clinical Research Act and to verify compliance with this protocol, the principal investigator to permit its monitor, representatives from any regulatory authority (eg, the FDA, MHRA,PMDA), the auditors, and the appropriate Certified Review Board to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, electrocardiogram reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (refer to Section 15.3)

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

15.5 Consultation for Study Subjects or Stakeholders

The principal investigator establishes a consultation desk to respond to consultations on this clinical trial from patients or stakeholders. Details about the consultation desk are described in the consent form and explanation document.

15.6 Economic Burden or Reward for Research Patients

Of the expenses related to this clinical study, Takeda will provide finance which is not covered by national insurance. CCI

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15.7 Profit of Non-Profit for the Study Subject

15.7.1 Profit of the Research Patient

As this clinical study is conducted within the scope of medical treatment, there will be no specific profit for patients in participating in this study.

15.7.2 Disadvantages for Research Patients

As this clinical study is conducted within the scope of medical treatment, there will be no specific disadvantages for patients in participating in this study.

15.8 Attribution and Access Rights of Research Results

15.8.1 Attribution of Research Results

All data and information obtained through this clinical study are attributed to Takeda. The data obtained in this study may be used for secondary analyses e.g. for meta-analysis, and such data will not be linked to personal identification information.

15.8.2 Data Access Rights

Access rights to all data and information obtained from this clinical study will be given to the person(s) approved by Takeda.

15.9 Publication, Disclosure, and Clinical Trial Registration Policy

15.9.1 Publication

The principal investigator is obliged report a summary of results to the director of the study site, and to provide the representative investigator and Takeda with complete test results and all data derived by the principal investigator from the study. During and after the study, only representative investigator and/or its designee may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation.

During and after the study, the representative investigator and/or its designee must summarize the data and publish in a medical journal and/or present at e.g. a meeting of a professional association. The representative investigator and/or its designee may publish any data and information from the study (including data and information generated by the principal investigator) with the consent of the principal investigator.

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

When the final publication is completed, Takeda should notify the head of study site.

15.9.2 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, the representative investigator and Takeda will, at a minimum register interventional clinical trials Takeda conducted anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study. Takeda's contact information, along with investigator's institution name, city, country, and recruiting status will be registered and available for public viewing.

The representative investigator will perform registration in the database established by the Ministry of Health, Labour and Welfare (jRCT: Japan Registry of Clinical Trials) according to the Clinical Research Act after approval by the Certified Review Board.

15.9.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites and registries, as required by applicable laws and/or regulations.

The representative investigator will post the results of clinical trials on the database established by the Ministry of Health, Labour and Welfare (jRCT: Japan Registry of Clinical Trials) according to the Clinical Research Act after reporting to the Certified Review Board. The representative investigator and/or its designee will report director of the study site that the final post of this clinical study was done.

15.10 Insurance and Compensation for Injury

Regarding health damage caused by participating in this clinical study, the study subject is provided adequate treatment as insurance medical treatment according to the medical condition as well as ordinary medical treatment. At that time, the self-payment of medical expenses will be covered by the study subject and no compensation will be made with money.

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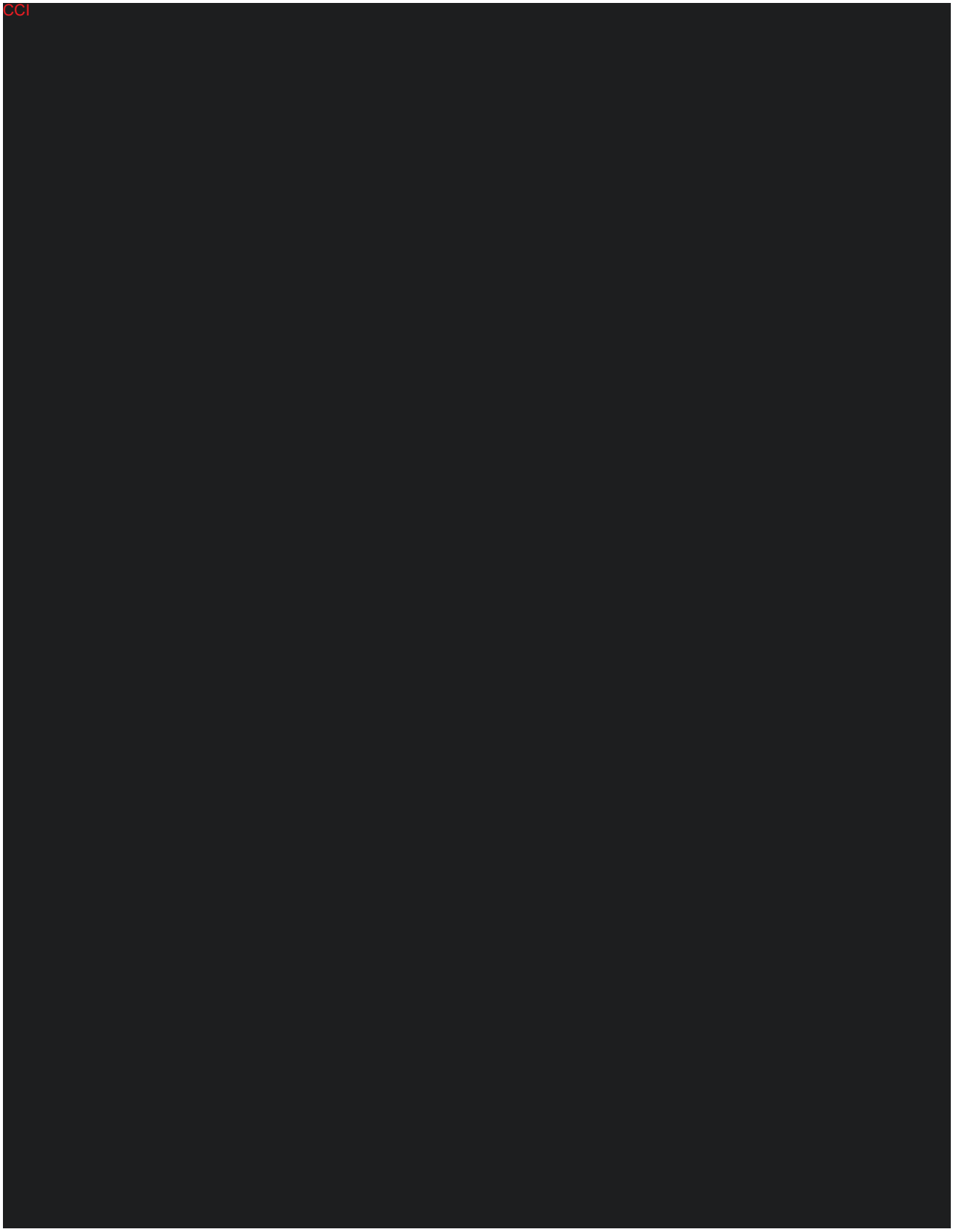

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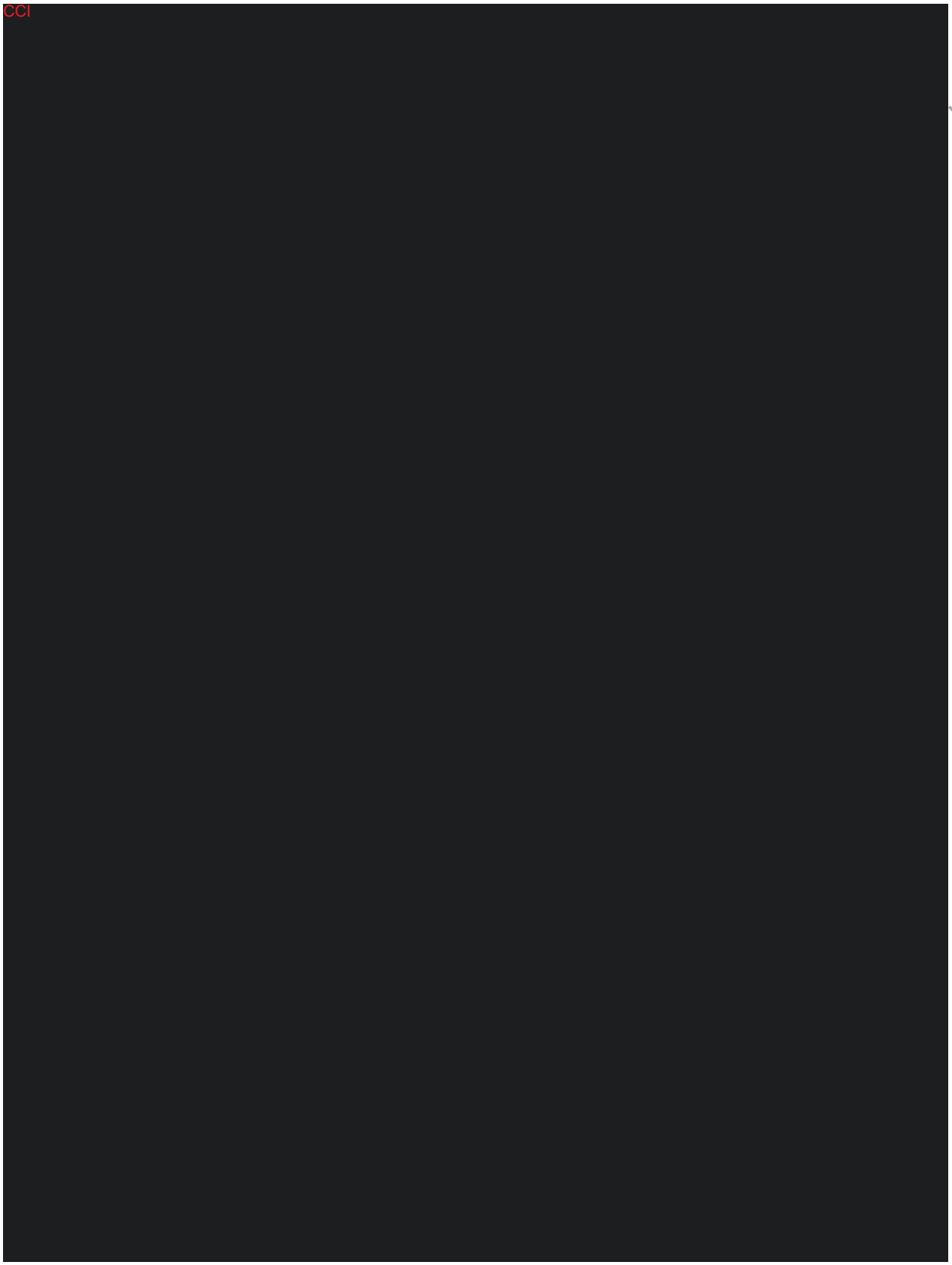

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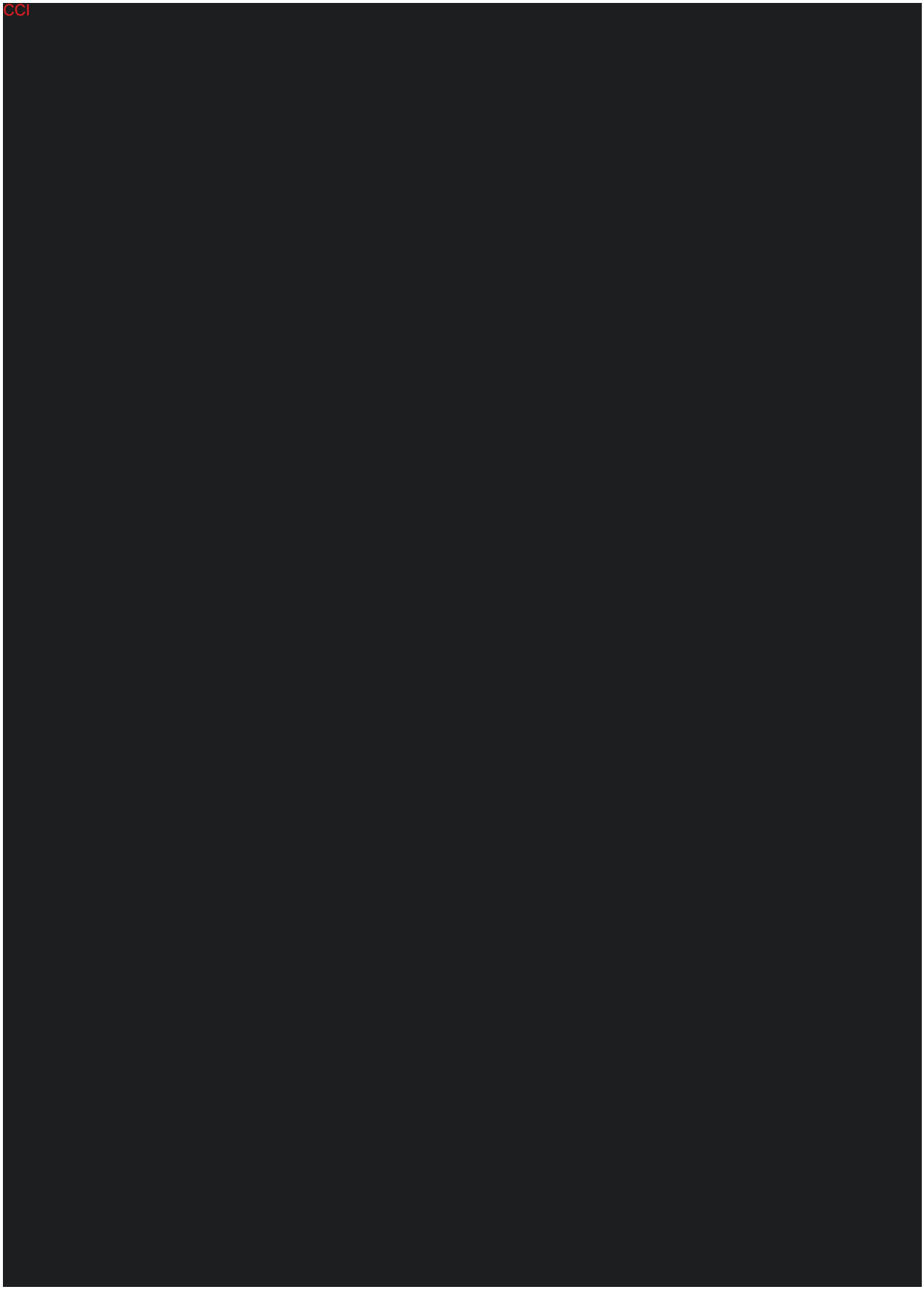

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