Title: A Prospective, Multicenter, Observational Study in Relapsed and/or Refractory Multiple Myeloma Patients Treated with Ixazomib plus Lenalidomide and Dexamethasone

NCT Number: NCT03433001

Protocol Approve Date: 24-AUG-2021

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.

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- Patient identifiers within the text, tables, or figures or in by-patient data listings.
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Note; This document was translated into English as the language on original version was Japanese.

CLINICAL STUDY PROTOCOL

A Prospective, Multicenter, Observational Study in Relapsed and/or Refractory Multiple Myeloma Patients Treated with Ixazomib plus Lenalidomide and Dexamethasone

Sponsor:	Takeda Pharmaceutical Company Limited
Study number:	C16042
Study phase:	Medical Affairs, Post-Approval Company Sponsored (Observational)

IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Study Drug:	Ixazomib		
Date:	24 August 2021	**Amendment Number:**	Version 3

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1.0 THE PRINCIPLES OF CLINICAL STUDIES AND ADMINISTRATIVE INFORMATION

1.1 Principles of Clinical Studies

This study will be conducted with consideration for the individual participants in accordance with this clinical study protocol and the following:

- The ethical principles based on the Declaration of Helsinki.
- The Ethical Guidelines for Medical and Health Research Involving Human Subjects ((Ministry of Education, Culture, Sports, Science and Technology, and Ministry of Health, Labor and Welfare).
- All applicable laws and regulations, including data privacy laws, and guidelines and regulations on conflicts of interest).

1.2 Research Implementation Structure

This clinical study will be conducted in accordance with the clinical study protocol planned and drafted by the sponsor according to the following implementation system: Other implementation systems are described in a separate document.

Sponsor

Takeda Pharmaceutical Company, Ltd.
Japan Oncology Division
Medical Affairs Department

The sponsor is responsible for the planning, drafting, conducting, and managing this clinical study, obtaining results, and reporting. The method of supervision of subcontractors concerning this clinical study will be included in the supplementary documents to be prepared separately.

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

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

Study Steering Committee

Study Steering Committee Chair:

PPD

Study Steering Committee Members:

PPD

PPD

Director of Statistical Analysis:

PPD

Clinical Genetics Specialists:

PPD

1.3 Contact for Inquiries Concerning Study Protocol

Refer to Supplement 1 of Clinical Study Protocol

1.4 Contact for Inquiries Concerning Registration Procedures

Refer to Supplement 1 of Clinical Study Protocol

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2.0 STUDY SUMMARY

Sponsor:
Takeda Pharmaceutical Co., Ltd.

Title of Clinical Study:
A Prospective, Multicenter, Observational Study in Relapsed and/or Refractory Multiple Myeloma Patients Treated with Ixazomib plus Lenalidomide and Dexamethasone

Study Number: C16042	**Phase**: 4

Study Design:
This clinical study is a non-interventional, domestic, multicenter, prospective, observational study in patients with relapsed and/or refractory multiple myeloma (RRMM). The patient population will consist of adult men and women who have a confirmed diagnosis of multiple myeloma (MM), who are scheduled to begin treatment with ixazomib, lenalidomide, and dexamethasone (IRd) due to relapsed and/or refractory disease, and who meet other eligibility criteria. Approximately 300 patients are planned for enrollment in this study.

As this is a non-interventional study, the dosage and administration of ixazomib, lenalidomide, and dexamethasone will not be defined by the protocol but by the package insert of each drug. The IRd therapy administration period will be determined by the principal investigator or investigator(s), and patients are required to visit the hospital or contact the principal investigator or investigator(s) during the study (including the follow-up period).

No restrictions will be placed on treatments received by, or management of, patients as part of routine medical care. However, study subjects will be asked to visit or contact the hospital periodically during the observational period (also including the follow-up period).

The principal investigator or investigator(s) will conduct the clinical examinations and laboratory testing required for standard-of-care treatment, and conduct follow-up on the primary outcome of progression free survival (PFS) and secondary outcomes. Study subjects will be asked to complete the EORTC-QLQ-30 and MY-20 questionnaires at home or during hospital visits in order to assess their quality of life (QOL).

After the patients start receiving IRd therapy, the principal investigator or investigator(s) will conduct follow-up investigations according to the clinical study schedule (Appendix A). The observation period for each patient will be from the start of IRd therapy until either 24 months after the enrollment date of the final patient to enrol, or until death or withdrawal of consent, whichever is earlier. The collection of safety data will begin at the start of IRd therapy and continue until 30 days after termination of IRd therapy or the start of the next treatment, whichever is earlier.

Objective:
To investigate the efficacy and safety of IRd therapy in patients with RRMM, under conditions of standard medical care. CCI [redacted] CCI [redacted]

<table>
<tr><td colspan="2">Subjects:
Patients with RRMM who are scheduled to begin IRd therapy</td></tr>
<tr><td>Planned number of subjects:
300</td><td>Number of study sites:
Approximately 100</td></tr>
<tr><td>Dosage and administration:
As this is a non-interventional study, the dosage and administration of ixazomib, lenalidomide, and dexamethasone will not be defined by the protocol but according to the package insert of each drug.</td><td>Administration route:
All of the drugs are taken orally.</td></tr>
<tr><td>Duration of Treatment:
At the discretion of the principal investigator or investigator(s).</td><td>Period of Evaluation:
Planned period for implementation of the clinical study (registration period and observation period): 36 months
• Registration period: 12 months
• Observation period: 24 months from the registration date of the last registered patient</td></tr>
<tr><td colspan="2">Inclusion criteria:
Patients satisfying all of the following criteria are eligible to participate in this clinical study:
1. Male or female patients 20 years of age or older at the time of enrollment
2. Patients with RRMM
3. Patients who are scheduled to start IRd therapy
4. Patients who can provide written informed consent of their own free will before the start of study treatment
5. Patients who are judged by the principal investigator or investigator(s) to have the faculty to understand and comply with the requirements of the study</td></tr>
<tr><td colspan="2">Exclusion criteria:
Patients meeting any of the following criteria are not to be enrolled in this clinical study:
1. Female patients who are nursing or pregnant
2. Patients who have been treated with ixazomib
3. Patients with hypersensitivity to any of the components of IRd therapy, their analogs or excipients
4. 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
5. Patients who are not registered with, or comply with, the guidelines of the lenalidomide management program (RevMate®)</td></tr>
</table>

6. Patients who, in the judgment of the principal investigator or investigator(s), are considered to be unsuitable for enrollment into the study

Criteria for Evaluation and Analyses:

Primary outcome

Progression-free survival (PFS)

Secondary outcomes

- PFS rate at 12 months and 24 months after the start of treatment
- Overall survival (OS)
- Best response
- Time to next treatment (TTNT)
- Duration of therapy (DOT)
- Proportion of patients who continue to receive treatment at 12 months and 24 months after start of treatment
- Overall response rate (ORR)
- Complete response (CR) plus very good partial response (VGPR) rate (CR+VGPR rate)
- Patient-reported outcomes: health-related quality of life (HRQoL), as evaluated by the EORTC QLQ-C30 and MY-20 instruments
- Rate of minimal residual disease (MRD) negativity in bone marrow in patients who achieved CR
- Relative dose intensity (RDI) for ixazomib, lenalidomide and dexamethasone
- Bone evaluation
- Adverse events (AEs)

CCI [redacted]

CCI [redacted]

Statistical methods:

Population for Analyses:

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

The 'Full Analysis Set' is defined as all patients who enroll into the study and who receive at least one dose of ixazomib. The 'Efficacy Analysis Set' are defined as all patients included in the FAS who have measurable lesions prior to the start of IRd therapy and who have at least one response evaluation after the start of IRd therapy. The 'Safety Analysis Set' is defined as all patients who enroll into the study who receive at least one dose of any drug used in IRd therapy (i.e. ixazomib, lenalidomide, or dexamethasone).

In addition to the analysis of all enrolled patients, analyses will be conducted in patient subgroups defined according to the following characteristics;

- Frailty-adjusted subgroups
- Cytogenetic risk subgroups
- Renal function subgroups

Analysis of effectiveness:

Primary outcome

PFS will be analyzed using disease progression data from the disease evaluations conducted by the principal investigator or investigator(s).

PFS for the FAS will be estimated using the Kaplan-Meier method, and the quartiles and two-sided 95% confidence intervals will be calculated.

Secondary outcomes

For the 'Full analysis Set' and the 'Efficacy 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 'Safety Analysis Set', 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 IRd therapy in RRMM patients in Japan.

Recent pivotal clinical trials in patients with RRMM, including ASPIRE, ELOQUENT-2, TOURMALINE-MM1, and POLLUX, were all designed with Rd therapy as a comparator; the values of median PFS with Rd in these studies were 17.6, 14.9, 14.7, and 18.4 months, respectively. The only report of a complete set of data on patients receiving Rd therapy in Japan is from a prospective observational study by KMF, with a reported median PFS of 17.0 months. Although direct comparison between studies is difficult due to differences in patient populations and disease characteristics, the median PFS for patients receiving Rd therapy in Japan is estimated to be 15–18 months, based on currently available data.

In TOURMALINE-MM1, a pivotal clinical trial investigating IRd triplet combination therapy, the hazard ratio for PFS in favor of the IRd therapy arm versus the control arm (placebo-Rd arm) was 0.74 (0.59–0.94). Based on the assumption that no differences exist in the relative efficacy of IRd and placebo-Rd between Japanese patients and the TOURMALINE-MM1 study population, we used a conservative HR estimate of 0.80 for our calculations. Assuming a constant exponential survival distribution, and utilizing a median PFS of 15–18 months for Rd therapy and a HR in favor of IRd versus Rd of 0.74–0.80, the following table shows the expected median PFS values for IRd therapy:

Median PFS of Rd therapy	Estimated median PFS with IRd therapy		
	HR=0.74	HR=0.77	HR=0.80
15 months	20.3 months	19.5 months	18.8 months
16 months	21.6 months	20.8 months	20.0 months
17 months	23.0 months	22.1 months	21.3 months
18 months	24.3 months	23.4 months	22.5 months

The sample size for this study was determined using a precision-based method, based on the expected median PFS with IRd therapy, the primary outcome. The following equation based on the median PFS may be used for precision-based sample size calculation:

$$Z = \frac{\hat{\varphi} - \varphi}{I_1(\hat{\varphi})^{-\frac{1}{2}}} \sim N(0,1)$$

$$I_1(\hat{\varphi}) = \frac{9r}{\hat{\varphi}^2}$$

φ: cube root transformed hazard under the null hypothesis

φ^: cube root transformed hazard under the alternative hypothesis

I: observed Fisher information

r: expected number of events

If the expected median PFS values with IRd therapy were as shown in the above table, then to estimate the two-sided 95% confidence interval with an accuracy of ± 3 months, the required sample sizes in the present study of IRd are shown in the corresponding locations in the table below (assuming a registration period of 12 months, and follow-up of 24 months from the time when the last patient enrolled into the study):

Median PFS with Rd therapy	Sample size required for study of IRd		
	HR=0.74	HR=0.77	HR=0.80
15 months	224	200	180
16 months	266	239	214
17 months	317	283	256
18 months	370	333	298

Based on the considerations above, the number of patients planned for enrollment in this study is 300.

3.0 ABBREVIATIONS

ADL	activity of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BIRC2/3	baculoviral IAP repeat containing gene2/3
BRD	Bromodomain
CCI	charlson comorbidity index
Ccr	creatinine clearance
CCND	cyclin D
CD40	cluster of differentiation 40
Cdk	cyclin-dependent kinase
CI	confidence interval
CR	complete response
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CVA	cerebrovascular attack
CYLD	Cylindromatosis
DLT	dose limiting toxity
DNA	deoxyribonucleic acid
DOT	duration of therapy
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 module
FGFR	fibroblast growth factor receptor
FLC	free light chain
G-CSF	granulocyte-colony stimulating factor
GM-CSF	granulocyte macrophage colony stimulating factor
GTP	guanosine triphosphate

HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	Health-related quality of life
IADL	instrumental activity of daily living
IL	Interleukin
IMiDs	immunomodulatory drugs
IMWG	International Myeloma Working Group
IRd	ixazomib plus lenalidomide and dexamethasone
IRF	interferon regulatory factor
ISS	International Staging System
ITT	intent-to-treat
JCOG	Japan Clinical Oncology Group
KMF	Kansai Myeloma Forum
LDH	lactate dehydrogenase
LIF	leukemia inhibitory factor
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MMSET	multiple myeloma SET domain
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging
NDMM	newly diagnosed multiple myeloma
NFκB	nuclear factor-kappa B
NIK	NF-κB inducing kinase
NGS	next generation sequencing
ORR	overall response rate
OS	overall survival
OSM	oncostatin M
PD	progressive disease
PFS	progression-free survival
PI	proteasome inhibitor
QOL	quality of life
RAS	rat sarcoma oncogene
RDI	relative dose intensity

Rd	lenalidomide and dexamethasone
RRMM	relapsed and/or refractory multiple myeloma
SAE	serious adverse event
sCR	stringent complete response
SOC	system organ class
SPEP	serum protein electrophoresis
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
Tmax	time to first occurrence of maximum concentration
TRAF	TNF receptor-associated factor
TTNT	time to next treatment
UPEP	urine protein electrophoresis
VGPR	very good partial response
X-p	x-ray photograph

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

Study site:

Refers to corporations, administrative bodies, and sole proprietors who will conduct the clinical study. This excludes parties that are entrusted with only part of the tasks related to specimen and/or information storage, statistical analyses, and other study-related activities.

Collaborative study sites:

Refers to a study site where the study is conducted jointly based on the clinical study protocol. This includes institutions that acquire new samples and/or information from subjects for the study and supply it to other study sites.

Investigator(s):

Refers to the principal investigator and other relevant parties involved with the implementation of the study (including performing tasks at that site for the collection and distribution of samples and/or information). This excludes parties who only supply existing samples and/or information at locations other than the study sites, and parties involved with only a portion of the work associated with the study.

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.

Director of study site:

Refers to the representative of the corporation, the director of the administrative body, or the sole proprietor of the study site conducting the study.

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].

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. hree drug combination 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 dexamethazon, are recommended [8][9]. MM is predominantly a disease of the elderly, and it is estimated that the median age at the time of diagnosis is 72 years [10]. MM is generally considered incurable with current therapy.

In recent years, the overall survival (OS) of patients with MM has been extended with the introduction of novel therapeutic agents [11] [12]. In a retrospective analysis by the Japanese Society of Myeloma, 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 Society of Myeloma and the European Myeloma Network showed that the use of new drugs was an independent prognostic factor improving OS in both 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 Japanese Society of Hematology. The number of treatment options using new therapeutic agents is increasing, and research into prognostic factors is 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 proteasomes, which are 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 effective 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, 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 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 outcome 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 (HR) for progression or death was 0.74 (95% confidence interval [CI], 0.59–0.94, stratified log rank p=0.012), representing a statistically significant improvement in PFS in the ixazomib group compared with the placebo group [18]. OS was a secondary outcome; 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), with a HR of 0.87 (95% CI, 0.64–1.18). 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 4.2% (15/361) in the ixazomib group and 6.4% (23/359) in the placebo group. The incidence of all adverse events (AEs) was 98.3% (355/361) and 99.4% (357/359) in the ixazomib and placebo groups, respectively, and the incidence of Grade ≥3 AEs was 74.0% (267/361) and 68.8% (247/359), respectively. AEs for which the incidence in the ixazomib group was 10 percentage points higher than in the placebo group were thrombocytopenia (23.8% and 11.4%, respectively) and vomiting (23.3% and 11.7%, 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 phase 3 C16010 trial (TOURMALINE-MM1), a statistically significant and clinically significant PFS extension was observed in the ixazomib group compared to the placebo group, in the primary efficacy analysis of the ITT population. However, it was determined that further study in a Japanese population was required as TOURMALINE-MM1 included only 41 Japanese RRMM patients (20 in the ixazomib group and 21 in the placebo group). The C16010 trial is ongoing in a double-blinded fashion, per protocol, to follow up for OS. Additionally, a domestic phase 2 trial of IRd – the C16028 trial – has started. The C16010 and C16028 trials are ongoing as post-marketing trials. In both trials, patients who were refractory to PI-based or lenalidomide treatment were excluded, and eligible patients were restricted to 1 to 3 prior therapies; in the C16010 trial, 90% of patients had 1 or 2 prior treatments [18]. Furthermore, lenalidomide was administered at a dose of 25 mg in C16010 and C16028, whereas the median dose of lenalidomide in a Japanese, post-marketing, all-case surveillance study was 15 mg [19]. Considering the restricted RRMM patient population for C16010 and C16028, the real-world dosing reported with lenalidomide, and the need to manage side effects with the IRd regimen, it was determined that investigation of IRd was required in a patient population that more closely reflected the real-world RRMM patient population in Japan.

Therefore, this prospective, observational clinical study was planned to investigate the efficacy and safety of IRd therapy in Japanese patients with RRMM receiving standard medical care. As part of the study, subgroup analysis for identification of prognostic and predictive factors, investigation into risk-related factors, and evaluation of new patient stratification factors using an exploratory analysis are also planned. Furthermore, assessment of patients' QOL during IRd treatment will be conducted to investigate the influence on physical, social, and emotional functioning by the continued administration of IRd under the daily medical practice.

5.0 STUDY OBJECTIVE

5.1 Objectives

To examine the efficacy and safety of ixazomib in combination with lenalidomide and dexamethasone in Japanese patients with RRMM receiving standard medical care. CCI [redacted]

5.2 Outcomes

5.2.1 Primary Outcome

- Progression-free survival (PFS)

5.2.2 Secondary Outcomes

- PFS rate at 12 months and 24 months
- Overall survival (OS)
- Best response
- Time to next treatment (TTNT)
- Duration of therapy (DOT)
- Proportion of patients who continue to receive treatment at 12 months and 24 months after start of treatment
- Overall response rate (ORR)
- Complete response (CR) plus very good partial response (VGPR) rate (CR+VGPR rate)
- Patient-reported outcomes: health-related quality of life (HRQoL), as evaluated by the EORTC QLQ-C30 and MY-20 instruments
- Rate of minimal residual disease (MRD) negativity in the bone marrow of patients who achieve CR
- Relative dose intensity (RDI) for ixazomib, lenalidomide and dexamethasone
- Bone evaluation
- AEs

5.2.3 CCI [redacted]

CCI [redacted]

6.0 STUDY DESIGN

6.1 Overall Study Design and Plan: Description

This clinical study is a non-interventional, domestic, multicenter, prospective, observational study in patients with RRMM. Adult men and women who have a confirmed diagnosis of MM, who are scheduled to begin IRd therapy due to relapsed and/or refractory disease, and who meet other eligibility criteria, will be enrolled. Approximately 300 patients will be enrolled in the study.

As this is a non-interventional study, the dosage and administration of the ixazomib, lenalidomide, and dexamethasone will not be defined by the protocol but by the package insert of each drug. The IRd therapy administration period will be determined by the principal investigator or investigator(s), and patients are required to visit the hospital or contact the principal investigator or investigator(s) during the study (including the follow-up period). Assuming a registration period of 12 months, and follow-up of 24 months from the time when the last patient enrolled into the study.

No restrictions will be placed on treatments received by, or management of, patients as part of routine medical care. However, study subjects will be asked to visit or contact the hospital periodically during the observational period (also including the follow-up period).

The principal investigator or investigator(s) will conduct the clinical examinations and laboratory testing required for standard-or-care treatment, and conduct follow-up on the primary outcome of PFS and secondary outcomes. Study subjects will be asked to complete the EORTC QLQ-30 and MY-20 questionnaires at home or during hospital visits in order to assess their QOL.

After the patients start IRd therapy, the principal investigator or investigator(s) will conduct follow-up investigations according to the clinical study schedule (Appendix A). The observation period for each patient will be from the start of IRd therapy until either 24 months after the enrollment date of the final patient to enroll, or until death or withdrawal of consent, whichever is earlier. The collection of safety data will begin at the start of IRd therapy and continue until 30 days after termination of IRd therapy or the start of the next treatment, whichever is earlier.

For the testing, observation, and follow-up schedule, refer to Appendix A.

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 Ethical Guidelines for Medical and Health Research Involving Human Subjects that compromises the safety of the study participants.

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 Ethical Guidelines for Medical and Health Research Involving Human Subjects, clinical 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 sponsor, an institutional review board (IRB), or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; 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 sponsor 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. In addition, principal investigators shall confirm the content of the revision of the protocol and submit a letter of agreement to the sponsor as evidence of agreement with the 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 sponsor and the research steering committee chairperson.

Following notification regarding such a protocol revision, the principal investigator of each study site must obtain the approval from the head of the study site after undergoing review by the site's internal ethics committee as necessary, 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.

7.1 Inclusion Criteria

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

1. Men and women aged 20 years or older at the time of enrollment
2. Patients with RRMM
3. Patients who are scheduled to start IRd therapy
4. Patients who can provide written informed consent of their own free will before the start of study treatment
5. Patients who are judged by the principal investigator or investigator(s) to have the faculty to understand and comply with the requirements of the study

7.2 Exclusion Criteria

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

1. Female patients who are nursing or pregnant
2. Patients who have been treated with ixazomib
3. Patients with hypersensitivity to any of the components of IRd therapy, their analogs or excipients
4. 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
5. Patients who are not registered with, or comply with, the guidelines of the lenalidomide management program (RevMate®)
6. Patients who, in the judgement of the principal investigator or investigator(s), are considered to be unsuitable for enrolment into the study

7.3 Study Registration

Patients are to be enrolled into the study after providing consent and all patients who provide consent are to be registered on the web-based registration site at the start of treatment.

For procedures to document study subjects who withdraw before the start of IRd therapy, refer to section 9.1.21.

Subjects should be included in the study only once.

Data erroneously collected from subjects for which written consent is not available, will not be included in or will be deleted from the database.

8.0 TREATMENTS

Non-interventional/observational – no treatments/pharmacotherapy are instructed by the study protocol.

All treatments employed in this study are prescription medicines and will be administered or monitored from study sites. For details and handling of medications, refer to the latest package inserts.

8.1 IRd Therapy

8.1.1 Definition of IRd Therapy

IRd therapy used in this clinical study is a combination of three drugs: ixazomib, lenalidomide, and dexamethasone. IRd therapy will be considered to be ongoing even during periods in which any of the three drugs are not administered due to e.g. AEs.

The start date of a cycle of IRd therapy will be defined as the earliest date of the three start dates for ixazomib, lenalidomide, and dexamethasone. One cycle is defined as 28 days.

8.1.2 Dosage and Administration Method in IRd Therapy

As this clinical study is a non-interventional study, the dosage and administration of ixazomib, lenalidomide, and dexamethasone will not be defined by the protocol but by the latest package insert of each drug.

8.1.3 Overdose of Ixazomib

An overdose is defined as a known, deliberate, or accidental administration of ixazomib, to or by a patient, at a dose above that which is specified in the package insert.

All cases of overdose of ixazomib should be documented in the appropriate section in the case report form (CRF), in order to record any data on ixazomib overdose into a database. Any AEs due to overdose of ixazomib are to be documented according to section 11.0.

Any serious adverse events (SAEs) associated with overdose of ixazomib are to be reported according to section 11.2.2.

8.2 Excluded Concomitant Medications and Procedures

As this is a non-interventional observational study, there will be no provisions on excluded concomitant medications, or procedures; however, the precautions for concomitant medications for each drug must be followed as described in the latest package insert.

If any drugs or procedures other than IRd therapy are administered during the clinical study for the treatment of MM, information on these drugs or treatments will be gathered as described in the protocol.

8.3 Discontinuation of IRd Treatment

The number of cycles of IRd therapy is not prespecified and is determined according to the judgement of the principal investigator or investigator(s) until a patient wishes to stop participating in the clinical study or dies. The principal investigator or investigator(s) must record the main reason for discontinuation of study treatment in the CRF, according to the following classifications. For cases in which the patient discontinues before commencing IRd therapy, see section 9.1.21.

1. Lack of efficacy (or exacerbation of disease)

   Defined as PD according to IMWG criteria (Appendix F).

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

3. Voluntary withdrawal by patient

   Defined as when a patient wishes to stop participating in study treatment. If the reason for discontinuation is known, the investigator is to record the reason(s) in the CRF

   Investigators should attempt to make the reasons for voluntary discontinuation as clear as possible

4. Significant deviation from study protocol

   Defined as occurring if, after the start of IRd therapy, it becomes known that the patient did not meet the inclusion criteria of the study protocol; or, 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

5. Lost to follow-up

   Defined as if a patient does not visit the hospital and the investigator can not contact the patient. In this case, the investigator should record that an attempt has been made to contact the patient in the source document.

6. Termination of study

   For example, if the sponsor, ethics review committee, or regulatory authority decide to terminate the clinical study. See section 6.2.1 for details.

7. Patient Death during study treatment

   Defined as if a patient dies before a decision is reached to discontinue IRd therapy. The investigator to record the date of death in the CRF.

8. Pregnancy

When a female patient's pregnancy becomes known.

9. Other

   If the principal investigator or investigator(s) decide that it is necessary to discontinue treatment for any other reasons, the investigator will describe the details in the CRF.

8.4 Procedure for Discontinuation of Clinical Study by the Enrolled Patient

A patient may discontinue their participation in the study at any time without explanation.

If a patient discontinues from the study, the principal investigator or investigator(s) will record the main reason in the CRF.

9.0 STUDY PLAN

9.1 Study Procedures

The following section describes the study procedures and data to be collected by the principal investigator or investigator(s). For each procedure, the same principal investigator or investigator(s) will perform the testing, observation, and follow-up of the subjects whenever possible. For the study schedule, refer to Appendix A.

9.1.1 Informed Consent Procedure

The protocol for obtaining informed consent is described in Section 16.3. Each patient must provide written informed consent before any study-related procedures are conducted, including collection of any study data (but excluding data collected as part of standard clinical care).

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.

A separate informed consent will be requested from the patient for the exploratory biomarker study.

9.1.2 Patient Demographics and Baseline Disease Characteristics

Demographic information and disease characteristics at baseline to be obtained will include:

- Date of birth (if not provided, age at registration will be used)
- Sex
- Initial diagnosis of MM: initial date of diagnosis of MM
- M-protein isotype:

  IgG κ or λ, IgA κ or λ, IgD κ or λ, IgE κ or λ, IgM κ or λ, Bence Jones type κ or λ, non-secretory type, other
- Clonal bone marrow plasma cell percentage:

  Clonal bone marrow plasma cell percentage will be collected if it is measured just before starting of IRd therapy.
- Immunophenotyping: CD20, CD56 (positive, negative, not conducted)
- Clinical stage according to ISS (Appendix C)
- Cytogenetic abnormalities at initial diagnosis: t(4;14), t(14;16), t (11;14), del(17p), 1q gain
- Frailty score:

  Patients will be investigated the frailty score according to the IMWG frailty scale (Appendix E) [21]. Patients will record the activities of daily living (ADL) and the

instrumental activities of daily living (IADL) and investigators will record the charlson comrbidity index (CCI) as described in Section 9.1.3 at the start of IRd therapy.

- Evaluation of bone lesions and extramedullary masses:

  If imaging is conducted at the start of the IRd therapy, it will be assessed for the presence of bone lesions and extramedullary masses (bone-delivered, or soft tissue-delivered or others). Alternatively, the most recent imaging assessments from prior to obtaining consent may instead be used.

- Determination of prior treatment efficacy:

  The clinical efficacy of prior treatment received immediately before commencing IRd therapy will be determined based on the IMWG criteria (2014 version) (Appendix F ,**Table 9.a**) [9].

  The treatment effect is determined by comparing the best response of prior treatment with the laboratory result at relapse.

Table 9.a Criteria for determination of relapse

Clinical relapse	• Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, magnetic resonance imaging, or other imaging • Definite increase in the size of existing plasmacytomas or bone lesions, defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion • Hypercalcemia (serum calcium > 0.25mmol/L of ULN; pH-corrected serum calcium > 11.5 mg/dL) • Decrease in hemoglobin of more than 2 g/dL (1.25mM) or to less than 10 g/dL • Rise in serum creatinine by more than or equal to 2 mg/dL • Hyperviscosity requiring treatment
Paraprotein relapse	In patients who do not have clinical relapse, a significant paraprotein relapse is defined as patients fulfilling at least one of the below criteria for two consecutive measurements separated by ≤ 2 months

	• Doubling or more of serum M-protein when M-protein is ≥ 0.5 g/dL • Increase in the absolute level of serum M-protein by ≥ 1 g/dL • Increase in urine M-protein by ≥ 500 mg/24h • Increase in the FLC level by ≥ 200 mg/L

9.1.3 Comorbidity

Investigators will record patient comorbidities at the start of IRd treatment using the Charlson comorbidity index (CCI) [20] (Appendix B).

In addition, investigators will evaluate the presence or absence, and Grade, of peripheral neuropathy and rash at the start of IRd treatment.

9.1.4 Medical History

The investigator will record whether a patient has received antineoplastic therapy, prior radiation therapy, or hematopoietic stem cell transplantation for the treatment of MM.

- Prior antineoplastic therapies: drug name, date of start of treatment, date of termination of treatment, reason for termination (i.e. PD, reason other than PD), best response
- Prior radiation therapy
- Prior hematopoietic stem cell transplant; if yes, the date of start of treatment.

9.1.5 Physical Examination

A complete physical examination and symptom-directed physical exam of relevant organ systems will be undertaken by the investigator prior to the start of IRd treatment.

Regarding physical examinations after the start of IRd treatment, the investigator will evaluate the presence or absence of clinically significant differences compared with the examination undertaken prior to start of IRd treatment.

9.1.6 Performance Status

Performance Status will be assessed according to the ECOG PS (Appendix D).

9.1.7 Body Weight, Height

Weight and height will be measured at the study site prior to the start of IRd treatment.

Height will be recorded in centimeters to the nearest whole number, and weight will be measured in kilograms to one decimal place.

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

9.1.8 Status of IRd Therapy

The principal investigator or investigator(s) will record the following information related to IRd therapy in the CRF:

- Dosing of each drug used in IRd therapy, including the start date of a treatment cycle, and the dose administered of each drug.

  Note: the start date of a treatment cycle is defined as the earliest of the three start dates of the drugs used in IRd therapy. One cycle is defined as 28 days.

9.1.9 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed at each study site. For clinical chemistry and hematology parameters measured, see **Table 9.b**.

Table 9.b Laboratory tests

Hematology	Serum biochemistry
White blood cell count	Albumin
Hemoglobin	Total bilirubin
Platelet count	AST
Neutrophil count	ALT
	ALP
	LDH (only at the start of IRd therapy)
	Creatinine
	Ccr (measured value)
	Calcium
	β2-microglobulin (only at the start of IRd therapy)

Creatinine clearance (Ccr) (estimated value) and the glomerular filtration rate (eGFR) will be estimated using the serum creatinine value and, for Ccr, the Cockcroft-Gault equation.

Calculation for the estimation of eGFR, published by the Japanese Society of Nephrology (2008):

For men:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 194 * \text{serum creatinine [mg/dL]}^{-1.094} * \text{age [years]}^{-0.287}$$

For Women:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 194 * \text{serum creatinine [mg/dL]}^{-1.094} * \text{age [years]}^{-0.287} \times 0.789$$

Cockcroft-Gault equation for the estimation of Ccr:
For men:

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

For women:

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

9.1.10 Evaluation of QOL

Patient-reported outcomes (QOL) will be collected by the investigators using the EORTC-QLQ-C30 (Appendix G) [22] and MY-20 (Appendix H) [23] instruments.

Patient-reported outcomes will be collected before administration of IRd therapy. During treatment with IRd, patient-reported outcomes will be collected every 6 cycles (i.e. before administration of therapy in cycle 1, before administration of therapy in cycle 7, etc.).

9.1.11 Quantification of M-protein

M-protein levels in blood samples and urine samples will be measured at the study sites. If it is not possible to measure serum and urine M-protein levels, the serum FLC level may be measured instead. The reference value of FLC will be taken from the standards used in the FREELITE® assay, developed by Binding Site.

9.1.12 Response Assessment

The principal investigator or investigator(s) will determine the clinical response of the patient according to the IMWG criteria (2014 version) (Appendix F) using data on serum M-protein, urine M-protein, and serum FLC.

9.1.13 Bone Marrow Aspiration

Bone marrow samples will be collected at the start of IRd therapy and at suspected CR (response better than VGPR). Bone marrow aspiration must take place on Monday through Friday, and must not take place on Saturday, Sunday or the holiday. The samples collected at the start of IRd therapy will be used for cytogenetic testing, measurement of MRD, and biomarker research (see section 9.1.14). The samples collected at initial assessment of CR will be used for MRD

measurement; re-assessment for MRD is possible on one occasion, from 6 months after bone marrow aspiration for evaluation of MRD until completion of this clinical study. For patients from whom bone marrow samples were collected at discontinuation of IRd therapy (i.e. sample taken between the date of discontinuation of IRd and the date of initiation of next treatment), if possible, these samples should also be submitted for biomarker research. Clinically unnecessary intervention (i.e. bone marrow aspiration) to collect a sample at discontinuation of IRd therapy is prohibited. The time and date of sample collection will be noted on the analysis request form.

- Cytogenetic testing

  Cytogenetic testing will be conducted using the bone marrow aspirate sample collected at the start of IRd therapy. After isolation of CD138-positive cells, the proportion of cells positive for t(4;14), t(11;14), t(14;16), 1q gain, and del(17p) will be measured

- MRD measurement:

  MRD evaluation will be conducted by the NGS method using the bone marrow aspirate samples from the start of the IRd treatment, and MRD measurement will be conducted by both the NGS method and PPD -flow method using bone marrow aspirate samples from CR assessment.

9.1.14 Biomarker Study

Samples of bone marrow aspirate (see section 9.1.13) and blood will be collected from patients who provide additional consent for participation in the biomarker study and evaluated for a range of biomarkers. See section 10.0 for more information on the biomarker study.

9.1.15 Image Examination

When the investigator(s) performs an imaging test on the patient, the presence or absence of new bone lesions and extramedullary plasmacytomas (bone-delivered, or soft tissue-delivered or others) will be evaluated.

9.1.16 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 IRd therapy until discontinuation of IRd therapy.

9.1.17 Adverse Events

AEs (serious and non-serious) will be monitored throughout the study period. For details regarding defining, recording, and reporting of AEs and serious AEs, see section 11.0.

9.1.18 Follow-up Assessments

Patients who discontinue administration of IRd therapy before disease progression will be subject to follow-up surveillance to determine PFS. Follow-up assessment for PFS will be

conducted by hospital visits every 3 months until confirmed PD or death, or until the patient is lost to follow-up.

All patients who discontinue IRd therapy will be subject to follow-up surveillance to determine OS. Follow-up assessment for OS will be conducted every 6 months until death or until the patient is lost to follow-up. OS follow-up will be done by methods including telephone calls, e-mails, or mail, and a hospital visit may not be necessary. Investigators will collect the following information

- Survival date
- Date of death or last known survival date

9.1.19 Next-line Treatment

If a patient receives treatment after discontinuing IRd therapy, the investigator will collect the following information for the subsequent therapy after discontinuation.

- Name of drugs
- Start date

9.1.20 Pregnancy

If any female patient is found to be pregnant during treatment with IRd therapy 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 principal investigator or investigator(s) 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 the treatment the patient received.

For all reported pregnancies, the outcome until the delivery, including premature birth, will be followed up and reported to the sponsor using the pregnancy form, with the patient's consent. Evaluations after birth will also be conducted.

For male patients, if a patient's female partner becomes pregnant during treatment with IRd therapy or within 90 days of termination of study, the outcome until the delivery, including premature birth, will be followed up and reported to the sponsor using the pregnancy form, with the patient's consent. Evaluations after birth will also be conducted.

9.1.21 Study Participation Discontinued Before Administration of Study Medication

In the event that a patient signs a consent form and the investigator prepares a CRF, but the patient then discontinues before the administration of the study medication, the CRF will contain the following items:

- Date of consent acquisition
- Consent to biomarker study

- Date of birth (If a date cannot be provided, then the age at registration)
- Sex
- Eligibility
- Reason for cancellation
  Investigators will collect the main reasons for discontinuation before administration of IRd therapy medication according to the following categories:
    - Did not meet selection criteria or violated 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 reuse the identification code of the patient who discontinued before administration of IRd therapy, for another patient in the study.

10.0 BIOMARKER STUDY

10.1 Objective

The objective of this exploratory study is to investigate:

CCI [redacted]

10.2 Planned Biomarker Study

10.2.1 Relationship between outcomes and biomarkers

The study will evaluate whether myeloma-associated gene mutations in myeloma cells collected from bone marrow are predictive for PFS, the primary outcome. The correlation between PFS and tumor-associated gene mutations, CCI [redacted], will be investigated using myeloma cells collected from bone marrow aspirate samples obtained before the initiation of IRd therapy.

To evaluate whether myeloma-associated gene mutations in myeloma cells collected from bone marrow are predictive for secondary efficacy outcomes, the correlation between secondary efficacy outcomes and myeloma-related gene mutations will be investigated using myeloma cells collected from bone marrow aspirate samples obtained before the initiation of IRd therapy.

An analyst will prepare a statistical analysis plan for the biomarker analyses prior to the start of biomarker analyses. The statistical analysis plan will describe the definitions of the biomarker analysis population and outcomes, and will include details of the analysis methods.

10.2.2 Other

1) To evaluate the correlation between various biomarkers in bone-marrow myeloma cells and circulating free tumor DNA in plasma, biomarkers in DNA from bone marrow myeloma cells collected before IRd therapy and circulating free tumor DNA in plasma will be studied.
2) The relationship between predictors of efficacy and changes in biomarkers found in circulating free DNA in plasma, and its association with IRd therapy, will be investigated. These biomarkers can be used to further understand the mechanism of ixazomib resistance and to obtain knowledge to contribute to future personalized medical treatment. The relationship between efficacy and changes in biomarkers found in circulating free DNA samples taken before treatment and at termination of IRd therapy will also be examined.
3) Measurement Items
   Biomarkers to investigate genetic mutations, amplifications, and gene rearrangements etc. of myeloma-associated genes CCI [redacted]

[redacted] relevant to IRd therapy. For biomarkers in this study, the appropriate myeloma-associated genes will be selected by the time of evaluation. The study protocol will be revised prior to evaluation to define the selected myeloma-associated genes.

10.3 Rationale for selecting biomarkers

The following section describes the rationale for selecting each biomarker. With regards to genomic biomarker and measurement technology, new biomarkers may be added as new findings are obtained every day. Additional criteria using new measurement methods may be included.

10.3.1 [redacted]

[redacted]

10.3.2 [redacted]

[redacted]

10.3.3 [redacted]

[redacted]

10.3.4 [redacted]

[redacted]

CCI

[redacted]

10.3.5 CCI

CCI

[redacted]

10.4 Bone Marrow Aspiration

10.4.1 Samples for Analysis

For patients who provide consent at initiation of IRd therapy, bone marrow aspirate collected at initiation of IRd therapy will be used (see section 9.1.13).

10.4.2 Collection of Bone Marrow Aspirate

The principal investigator or investigator(s) will collect bone marrow aspirate samples according to section 9.1.13.

10.4.3 Delivery of Bone Marrow Aspirate

The principal investigator or investigator(s) will send the sample to PPD using materials prepared by PPD. In advance of the study starting, PPD will send the necessary materials for transporting bone marrow aspirate samples to all participating study sites.

10.5 Blood samples

10.5.1 Samples for analysis

For patients who provide consent at initiation of IRd therapy, blood will be drawn at two timepoints: at initiation of IRd therapy and at termination of IRd therapy (i.e. between 4 weeks from the day of termination of IRd therapy and the start of next treatment).

For cases in which consent is obtained after initiation of IRd therapy, a blood sample will be collected at termination of IRd therapy.

10.5.2 Collection of Blood Samples

The principal investigator or investigator(s) will send the samples to PPD using the materials prepared by PPD. Two EDTA tubes (8 ml) of blood will be collected at each sample collection.

The blood sample may be collected at any time after the patient has provided consent and until immediately before the initiation of IRd therapy. On termination of IRd therapy, a blood sample should be collected at 4 weeks from the date of treatment termination or before the start of the next treatment.

The collected blood sample will be centrifuged and the plasma stored in a ≤ -20°C freezer until PPD collects the sample.

The date of blood collection should be noted on the analysis request form.

10.5.3 Submission of Blood Samples

PPD must send in advance any materials necessary for collecting and submitting blood samples to the registered study sites.

The principal investigator or investigator(s) must request PPD to collect the sample before drawing blood.

Details concerning the collection and submission of blood or plasma samples are described in the supplementary documents to be prepared separately.

10.6 Analysis of Bone Marrow Aspirate and Blood Samples

Genetic material extracted from bone marrow aspirates and plasma samples will be analyzed for genetic mutations.

The method of analysis is described, and details of the analytical laboratory are shown in Supplement 1 of the study protocol.

Table 10.a Method of Genetic Analysis

Sample type	Measurement Method
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]

10.7 Storage and Disposal of Samples

The collected samples shall be stored by PPD and the gene analysis laboratory as described in Supplement 1 of the study protocol. Bone marrow aspirate samples and plasma samples, prior to DNA extraction, and extracted genomic samples, will be stored in a -80°C deep freezer.

Submitted bone marrow aspirate and plasma samples, as well as extracted genomic samples, may be used in future for a secondary study of biomarkers. In this clinical study, therefore, the study subjects shall be asked to consent to the use of samples for secondary studies. The use of samples from consenting study subjects will not be limited to the current exploratory biomarker study. As these valuable samples may benefit future medical research, samples shall be kept for a maximum of 20 years after the completion of this clinical study. When these specimens are determined to not be used for further study, or when the preservation period expires, the subject ID shall be deleted, the specimens appropriately discarded as medical waste, and discard records shall be noted. In addition, if the study subjects withdraw consent, when the subject ID cannot be recognized e.g. due to label or computer abnormality, or when the principal investigator or investigator(s) determines that disposal is necessary, samples may be discarded. If the samples to

be discarded e.g. due to withdrawal of consent, are stored at the study site, the principal investigator or investigator(s) will discard them at the study site. If the stored sample is to be used for secondary medical research in the future, a new research plan will be prepared and approval obtained from the ethics review committee as necessary.

10.7.1 Clinical Geneticist

The main purpose of the clinical geneticist is to advise on the analytical results, and to consider the results obtained. Details of the role of the clinical geneticist are specified in a separate procedures manual.

For the clinical geneticist, refer to section 1.2.

10.7.2 Reporting of Analysis Results

The analysis results shall be disclosed if there is a request from the study subject. However, when disclosing the analysis results to study subjects, it must be considered that the study of biomarkers in this clinical study is exploratory, and the results obtained need to be proved by further studies. The accuracy and precision of the analytical methods used may be immature and there may be uncertainties in analysis results. However, even if these considerations are taken into account, if it is considered to be better to disclose secondary findings to the study subject from an ethical point of view, the ethics review committee will deliberate on the issue as necessary.

11.0 SAFETY REPORTING

11.1 Definitions

11.1.1 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a study subject administered a pharmaceutical product (including IRd therapy); the untoward medical occurrence does not necessarily have a causal relationship with the treatment (including IRd therapy.)

An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical product (including IRd therapy), whether or not it is related to the medical product (including IRd therapy).

11.1.2 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 IRd therapy or dose change
- AEs that the principal investigator or investigator(s) regarded as undesirable

Diagnosis name and signs/symptoms:

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

Laboratory test values and ECG findings:

- Changes in clinical laboratory test values or ECGs will be considered as AEs only when the responsible principal investigator or investigator(s) determines that there is a clinical problem arising from the changes (i.e., when a treatment or medical treatment is required, or if the principal investigator or the investigator(s) regards the change as 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 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 will be 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 administration of IRd therapy will be recognized as complications and not as AEs. If the complication worsens, the deterioration will be recognized as an AE, and the principal investigator or investigator(s) will record the name of AE name as a worsening of complications (e.g. 'worsening hypertension') in the CRF
- If a patient has a temporary existing disease (e.g., asthma, epilepsy), if the frequency of its symptoms increases, or if an increase in severity or advancement of disease is observed, the existing disease will be recorded as an AE. If a patient has a chronic disease (e.g. cataract, rheumatoid arthritis), the chronic disease will be recorded as an AE if the symptoms worsen more than expected. The principal investigator or investigator(s) 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

Changes in the severity of AE:

- If there is a change in the severity of the AE, the investigator will record only the instance when the maximum severity is observed.

Pre-planned surgery or treatment:

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

Surgery or treatment requiring no urgency:

- Surgery or treatment that does not suddenly affect the patient's symptoms, such as cosmetic surgery, will not be considered an AE. However, the investigator will record this in the CRF. Complications due to surgery that require no urgency will be reported as AEs.

Progressive disease:

- PD will not be regarded as an AE as it is a result of lack of efficacy of pharmaceuticals. Also, symptoms that corresponds to a diagnosis of PD do not need to be considered as a serious AE. However, if the progression of an existing cancer (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 11.1.3, progression of the cancer will be considered a serious AE.

Overdose of ixazomib:

Overdose of ixazomib without any event will not be considered an AE. However, investigators shall record the overdose in the CRF. When an event occurs due to overdose of the drug, the investigator will record the symptom as an AE in the CRF.

- 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 from which the patient was at risk of death at the time of the event. It does not refer to an event that 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, or require medical or surgical intervention to prevent one of the outcomes listed above. Any terms included in the Takeda Medically Significant AE List (**Table 11.a**) are defined as a Serious AE.

Table 11.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 suspicion thereof

11.1.3 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 11.b**)

Table 11.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.

11.1.4 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 sponsor when the sponsor requests 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 the investigator to the sponsor, see Section 11.4.

11.1.5 Causal Relationship of Adverse Events

A causal relationship between IRd therapy and an AE, and a causal relationship with ixazomib (only in the case of AEs deemed 'related' to IRd therapy) 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 IRd therapy or ixazomib.
Not related	There is no clear temporal correlation with IRd therapy or ixazomib. Or an AE that is considered to be related to other factors such as original disease, complications, concomitant medications, concomitant treatment or the like

11.1.6 Treatment Discontinuation due to AEs

Discontinuation of IRd therapy due to an AE will be defined as 'discontinuation of administration'. Treatment is not regarded as discontinued if administration of any of the three drugs is continued.

11.1.7 Outcome

The outcome of AEs will be 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 AE 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 were worse than at the time of observation • Irreversible congenital anomalies • In cases of death, if the AE is not a direct cause of death and the AE remains unresolved
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

11.2 Procedures for Recording and Reporting AEs and Serious AEs

11.2.1 Collection of and Reporting of AEs and Product Quality Issues

11.2.1.1 Collection Period of AEs

The collection of safety data will begin at the start of IRd therapy and continue until 30 days after termination of IRd therapy or the start of the next treatment, whichever is earlier.

In addition, new primary malignancies that occur during the follow-up periods must be reported, irrespective of causality to study regimen, to the sponsor for a minimum of 3 years after the discontinuation of IRd therapy through death or termination of the study by the sponsor.

11.2.1.2 Reporting AEs

When a study subject visits the site, the principal investigator or investigator(s) will confirm the presence or absence of symptoms of AEs with patients. At each study visit, the principal investigator or investigator(s) will interview the subject to determine whether any AEs had occurred. A neutral question, such as, 'How have you been feeling since your last visit?' will be asked to capture any AEs occurring between the visits.

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, will be followed until the symptoms resolve, or any clinically significant abnormal laboratory values return to baseline (screening values), or there was a satisfactory explanation for the change (for permanent or irreversible AEs).

Regardless of the patient's symptoms being related to IRd therapy, the principal investigator or investigator(s) will record all AEs on the appropriate pages of the CRF. Each event will be described as follows:

1. AE term
2. Date of onset and resolution
3. Severity
4. Causal relationship with IRd therapy or ixazomib
5. Action taken for the IRd therapy

6. Outcome of event
7. Seriousness

The principal investigator or investigator(s) 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(s) recognizes that the patient's symptoms are likely due to AEs, the principal investigator or investigator(s) may follow-up and clinically evaluate the patient's symptoms. If, as a result of the follow-up study, the symptom of the patient is determined to be an AE not previously reported, the investigator shall report according to the usual reporting procedure.

11.2.2 Collection and Reporting of Serious AEs

Any SAEs that developed during the period of AE collection will be reported by the principal investigator to the chief executive of the study site immediately, and to the Takeda PV Drug Safety immediately (within 24 hours) after obtaining knowledge of the event. The principal investigator is required to submit an official report to the sponsor detailing the event within 10 calendar days.

The following details will be included in the report, along with as much other information as possible.

- Brief description of the AE and why it was deemed to be serious
- Subject ID code
- Name of principal investigator or investigator(s)
- Name of study drug
- Determined causal relationship

The principal investigator or investigator(s) are required to spontaneously reported SAEs collected even after the AE collection period to the sponsor.

11.3 Follow-up of Serious AEs

The principal investigator or investigator(s) will follow up all SAEs until they resolve, or the final outcome of the event determined. If information for a SAE was not included in the detailed report and was obtained later, the principal investigator or investigator(s) must provide an addendum or submit an updated report within 1 day of the onset. Relevant data collected at the research site (e.g., ECG charts, laboratory test values, discharge summary, postmortem results) will be sent to the sponsor or IEC upon request.

11.3.1 Reporting Serious AEs to the Ethical Review Committee and Regulatory Authorities

On receiving a report of a serious AE from the principal investigator, the head of study site will consult with the ethics review committee etc., and will notify the outcome to the clinical study

sites through the sponsor or the clinical research organization (CRO) commissioned by the sponsor.

If the head of study site receives a report from the principal investigator or investigator(s) of an unexpected serious AE or a serious AE where the direct causal relationship with the study treatment (i.e. IRd therapy) cannot be determined, the head of study site will include additional information to the report from the principal investigator, and submit the report to the Minister of Health, Labor and Welfare, and notifies the other study sites. It is also possible to report to the Minister of Health, Labor and Welfare or to disseminate it to the study site through the sponsor.

Additional information to be added are:

- Actions taken for the serious AEs (e.g. discontinuation of new enrolment, revision of informed consent form and/or explanation document, re-consent obtained from other study subjects, etc.)
- Date of review, summary of review, result, necessary action, etc. related to the Ethics Review Committee, etc.
- Communication to collaborative study sites

The sponsor is required to report unpredictable serious AEs or any serious AE which are a target of the emergency report, to the heads of regulating authorities, principal investigators and study sites.

From the point of time when the sponsor or CRO commissioned by the sponsor initially learned of the event or of the additional information, the sponsor or CRO is required to make an emergency report containing unexpected serious AEs or predictable serious AEs, and must comply with the reporting deadline stipulated by the regulatory requirements. In addition, the sponsor will also urgently report on ixazomib's risk-benefit, continued administration of ixazomib, and other serious safety information which may have a significant impact on the continuation of the clinical study. The study site must submit a copy of the emergency report document to the Ethics Review Committee.

11.4 Reporting of additional information on AEs

When the sponsor requests the principal investigator or investigators to provide additional information on an AE, the principal investigator or investigators must enter it in the eCRF system or submit a written report.

12.0 STUDY-SPECIFIC COMMITTEES

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

12.1 Study Steering Committee

The study steering committee consists of medical professionals involved in this clinical study, sponsors, and independent statistical experts. The study steering committee oversees 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.

13.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. If selected for coding, AEs and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the database of medical drug name.

13.1 Case Report

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

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

Any change of, modification of, or addition to the data in the CRF 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 CRF. The principal investigator is fully responsible for the accuracy and authenticity of all data entered in the CRF.

The following are data recorded directly in the CRF.

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

In cases where the principal investigator or investigator changes or corrects the data inputs in the CRF 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 CRF is described accurately and completely, then signs or stamps and record the date.

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

13.2 Electronic Case Report Input System Deadline

The sponsor 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 CRF, the investigator must input the CRF within 14 days as a general rule.

13.3 Record Retention

The principal investigator or the head 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 sponsors 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 CRFs of changes and modifications record, and the like. In addition, the principal investigator and the head 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 sponsor requests a longer period for retention, the head of the study site should discuss how long and hot retain those documents with the sponsor.

14.0 STATISTICAL ANALYSIS

Statistical analysis will be undertaken by analysts who belong to the contract research organization [CRO] and who are independent from the sponsor; the analysts will be appointed by the statistical analysis manager and statistical analysis supervisor. The sponsor will not be involved in the statistical analysis.

14.1 Statistical 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 definitions of analysis variables and the analysis methodologies to be used to address all study objectives.

14.1.1 Analysis Sets

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

- Full Analysis Set (FAS): all patients who enroll into the study and who receive at least one dose of ixazomib
- Effectiveness Analysis Set: all patients included in the FAS who have measurable lesions prior to the start of IRd therapy and who have at least one response evaluation after the start of IRd therapy
- Safety Analysis Set: all patients who enroll into the study who receive at least one dose of any drug used in IRd therapy (i.e. ixazomib, lenalidomide, or dexamethasone)

In addition to the analysis of all enrolled patients, analyses will be conducted in patient subgroups defined according to the following characteristics; additions or changes to these subgroups may be made at a later date.

- Frailty-adjusted subgroups
- Cytogenetic risk subgroups
- Renal function subgroups

14.1.2 Analysis of Demographics and Other Baseline Characteristics

The key demographics and other baseline characteristics (e.g. number of previous treatments, duration of disease, etc.) will be summarized for the FAS.

14.1.3 Efficacy Analysis

(1) Primary Outcome and Analytical Methods

[Primary outcome]

- PFS

[Analysis Method]

PFS will be analyzed using disease progression data from the disease evaluations conducted by the principal investigator or investigator(s).

PFS for the FAS will be estimated using the Kaplan-Meier method, and the quartiles and two-sided 95% confidence intervals will be calculated. PFS is defined as the period from the first dose of treatment to the time of confirmed PD or confirmed death (regardless of the cause of death), whichever is earlier.

(2) Secondary Outcomes and Analytical Methods

[Secondary Outcomes]

- PFS rate at 12 months and at 24 months from the start of study.

[Analysis Method]

The secondary outcomes of PFS rate at 12 months and at 24 months from the start of study will be analyzed for patients in the FAS.

- OS

[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. OS is defined as the period from the first dose of treatment to the time when death is confirmed (regardless of the cause of death).

- Best Response

The secondary outcome 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 F), after each cycle of treatment.

[Analysis Method]

A histogram (or similar) showing the numbers of patients in the FAS and the Efficacy Analysis Set achieving different levels of best response will be created after each cycle of treatment, from cycle 1 onwards.

- Time to Next Treatment (TTNT)

[Analysis Method]

The secondary outcome of TTNT for the FAS will be estimated using the Kaplan-Meier method, and the quartiles and two-sided 95% confidence intervals will be calculated. TTNT is defined as the period from the first dose of treatment to the start of next treatment or time when death is confirmed (regardless of the cause of death), whichever is earlier.

- Duration of Therapy (DOT)

[Analysis Method]

Summary statistics for the secondary outcome of DOT in patients in the FAS will be collected, including the number of patients, mean, standard deviation, minimum value, maximum value, and the quartiles). DOT is defined as the treatment duration of IRd therapy.

- Proportion of patients who continue to receive treatment at 12 months and 24 months after start of treatment

[Analysis Method]

The secondary outcome of proportion of patients in the FAS who continue to receive treatment at 12 months and 24 months, and the two-sided 95% confidence intervals, will be calculated. Confidence intervals will be accurately calculated based on a binomial distribution.

- Overall Response Rate (ORR)

[Analysis Method]

The ORR and 2-sided 95% confidence intervals will be calculated in the Efficacy Analysis Set. Confidence intervals will be accurately calculated based on a binomial distribution. 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 F) after the start of IRd therapy.

- Rate of Complete Response (CR) and Very Good Partial Response (VGPR) (Rate of CR + VGPR)

The rate of CR + VGPR and 2-sided 95% confidence intervals will be calculated in the Efficacy Analysis Set. Confidence intervals will be accurately calculated based on a binomial distribution. The rate of CR + VGPR is defined as the proportion of patients who achieve a best response of VGPR or better according to the IMWG criteria (2014 version) (Appendix F) after the start of the IRd therapy.

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

[Analysis Method]

For patients in the FAS, summary scores for all functional domains, subscales, and symptom scales of the EORTC and MY-20 instruments will be determined, and longitudinal changes for each subscale will be evaluated. Particular focus will be given to the physical function scale, the global health/quality of life scale, and the individual scales of tiredness, nausea and vomiting, pain, dyspnea, anorexia, constipation, and diarrhea. Analyses of these scores will be conducted using repeated measures analyses across all timepoints.

- Detection frequency of MRD in patients with CR

[Analysis Method]

The proportion of patients who are MRD-negative, and 95% confidence intervals on both sides, will be calculated for the Efficacy Analysis Set. Confidence intervals will be accurately calculated based on a binomial distribution. Patients will be considered MRD-negative if a first test is MRD-positive but a subsequent test is MRD-negative.

- Relative Dose Intensity (RDI)

[Analysis Method]

Summary statistics for RDI of ixazomib, lenalidomide, and dexamethasone will be calculated for the Safety Analysis Set. The outputs will include a plot of change over time.

14.1.4 Analysis of Safety

The following analysis will be evaluated in the Safety Analysis Set.

(1) Treatment-emergent Adverse Events (TEAEs)

A TEAE is defined as an AE that occurs at any time between the start of IRd therapy and 30 days after the end of IRd therapy or the start of next treatment, whichever occurs first. TEAEs will be coded using MedDRA and will be summarized by Preferred Term (PT) and System Organ Class (SOC).

The following data will be collected and analyzed:

- Frequency of all TEAEs
- Frequency of ixazomib-related TEAEs
- Frequency of Grade 3 or higher TEAEs
- Frequency of ixazomib-related Grade 3 or higher TEAEs
- Frequency by Grade for all TEAEs
- Frequency by Grade for ixazomib-related TEAEs
- Frequency of TEAEs resulting in discontinuation of treatment
- Frequency of serious TEAEs
- Frequency by time to onset of all TEAEs
- Frequency of TEAEs that result in death

(2) Laboratory values

Laboratory data values from before and after IRd therapy administration will be tabulated.

14.2 Interim Analysis and Criteria for Early Termination

An interim analysis is planned at 12 months from enrollment of the last patient, using data collected until that time. This interim analysis will evaluate the PFS rate at 12 months, the proportion of patients still on study treatment, and safety.

2.3 Determination of Sample Size

The purpose of this clinical study is to investigate the efficacy and safety of IRd therapy in RRMM patients in Japan.

Recent pivotal clinical trials in patients with RRMM, including ASPIRE, ELOQUENT-2, TOURMALINE-MM1, and POLLUX, were all designed with Rd therapy as a comparator; the values of median PFS with Rd in these studies were 17.6, 14.9, 14.7, and 18.4 months, respectively. The only report of a complete set of data on patients receiving Rd therapy in Japan is from a prospective observational study by KMF, with a reported median PFS of 17.0 months. Although direct comparison between studies is difficult due to differences in patient populations and disease characteristics, the median PFS for patients receiving Rd therapy in Japan is estimated to be 15–18 months, based on currently available data.

In TOURMALINE-MM1, a pivotal clinical trial investigating IRd triplet combination therapy, the hazard ratio for PFS in favor of the IRd therapy arm versus the control arm (placebo-Rd arm) was 0.74 (0.59–0.94). Based on the assumption that no differences exist in the relative efficacy of IRd and placebo-Rd between Japanese patients and the TOURMALINE-MM1 study population, we used a conservative HR estimate of 0.80 for our calculations. Assuming a constant exponential survival distribution, and utilizing a median PFS of 15–18 months for Rd therapy and a HR in favor of IRd versus Rd of 0.74–0.80, the following table shows the expected median PFS values for IRd therapy:

Median PFS of Rd therapy	Estimated median PFS with IRd therapy		
	HR=0.74	HR=0.77	HR=0.80
15 months	20.3 months	19.5 months	18.8 months
16 months	21.6 months	20.8 months	20.0 months
17 months	23.0 months	22.1 months	21.3 months
18 months	24.3 months	23.4 months	22.5 months

The sample size for this study was determined using a precision-based method, based on the expected median PFS with IRd therapy, the primary outcome. The following equation based on the median PFS may be used for precision-based sample size calculation:

$$Z = \frac{\hat{\varphi} - \varphi}{I_1(\hat{\varphi})^{-\frac{1}{2}}} \sim N(0,1)$$

$$I_1(\hat{\varphi}) = \frac{9r}{\hat{\varphi}^2}$$

φ: cube root transformed hazard under the null hypothesis

φ^: cube root transformed hazard under the alternative hypothesis

I: observed Fisher information

r: expected number of events

If the expected median PFS values with IRd therapy were as shown in the above table, then to estimate the two-sided 95% confidence interval with an accuracy of ± 3 months, the required sample sizes in the present study of IRd are shown in the corresponding locations in the table below (assuming a registration period of 12 months, and follow-up of 24 months from the time when the last patient enrolled into the study):

Median PFS with Rd therapy	Sample size required for study of IRd		
	HR=0.74	HR=0.77	HR=0.80
15 months	224	200	180
16 months	266	239	214
17 months	317	283	256
18 months	370	333	298

Based on the considerations above, the number of patients planned for enrollment in this study is 300.

15.0 QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Study-Site Monitoring Visits

The sponsor or its designee will conduct monitoring visits to the study sites periodically during the study to ensure that all aspects of the protocol are followed. Details on the frequency of monitoring to research institutes and the procedure, included in the supplementary documents to be prepared separately.

The principal investigator and the head of study site guarantee access to the source documents to the sponsor or its designee and the IRB.

15.2 Deviations from Ethical Guidelines and Study Protocol Concerning Medical Research for People

Principal investigator or investigator shall record all actions deviating from the ethical guidelines on medical research on human patients and the implementation plan of clinical trials.

The principal investigator shall promptly notify the head of the study site and the sponsor when a serious departure is found. In addition, the principal investigator consults with and agrees with the sponsor about the revision of the implementation plan of the clinical trial as necessary. When revising, the principal investigator or investigator submits the draft as soon as possible to the head of the research institution and obtains approval from the ethics review committee etc.

15.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or its designees to ensure that study procedures comply with the protocol and standard operating procedures, and that collected data is correct and complete.

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

16.0 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 ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the 'Responsibilities of the Investigator' that are listed in Appendix I.

16.1 IRB Approval

IRBs must be constituted according to the applicable local requirements of each participating region.

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

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

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

16.2 Conflicts of Interest

This clinical trial is conducted with support of the study sponsor.

Prior to conducting this clinical study, the investigators involved in this clinical study should appropriately manage their conflicts of interest (COI) so investigators involved in this clinical study will not violate the COI of their institutions [36] [37] [38] [39] [40].

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

16.3 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 ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study, 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 principal investigator is responsible for the preparation, content, and IRB approval of the informed consent form. The informed consent form must be approved by both the IRB and the sponsor prior to use.

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

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

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

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

16.4 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As

permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, the FDA, MHRA,PMDA), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, electrocardiogram reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (refer to Section 16.3)

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

16.5 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.

16.6 Economic Burden or Reward for Research Patients

Of the expenses related to this clinical study, the sponsor will provide finance which are not covered by national insurance. For any expenses which may arise due to normal clinic visits may be paid for by the study subject.

In addition, the sponsor will pay burden reduction costs to the study subjects in this clinical study for additional research (Frailty score survey, QOL survey) accompanying time extension of medical treatment performed. Details concerning the economic burden and rewards to the patients are described in the consent form and explanation document.

16.7 Profit of Non-Profit for the Study Subject

16.7.1 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.

16.7.2 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.

16.8 Attribution and Access Rights of Research Results

16.8.1 Attribution of Research Results

All data and information obtained through this clinical study are attributed to the sponsor. 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.

16.8.2 Data Access Rights

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

16.9 Publication, Disclosure, and Clinical Trial Registration Policy

16.9.1 Publication

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

During and after the study, the sponsor and designee must summarize the data and publish in a medical journal and/or present at e.g. a meeting of a professional association. The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

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

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

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

16.9.3 Clinical Trial Results Disclosure

The sponsor 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.

16.10 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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