CLINICAL STUDY PROTOCOL

NCT Number: NCT02761187

Study Title: A Global, Prospective, Non-interventional, Observational Study of Presentation, Treatment Patterns, and Outcomes in Multiple Myeloma Patients - the INSIGHT - MM Study

Study Number: NSMM-5001

Protocol Version and Date:
Version 3.0: 11-APRIL-2018

PROSPECTIVE OBSERVATIONAL STUDY PROTOCOL

A global, prospective, non-interventional, observational study of presentation, treatment patterns, and outcomes in multiple myeloma patients - the INSIGHT MM study

Sponsor:	Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. 40 Landsdowne Street, Cambridge, MA 02139, USA
Study Number	NSMM-5001
Compound:	This is a non-interventional, observational study. Multiple myeloma will be treated as per standard therapy and/or with medicinal product prescribed by the treating healthcare provider based upon his/her clinical judgment.
Version of Protocol:	Version 3.0
Date of Protocol:	11 April 2018
Previous Protocol Date and Version:	Version 2.0 (12 October 2016)

CONFIDENTIAL

This non-interventional, observational study will be conducted according to Guidelines for Good Pharmacoepidemiology Practices (GPP).

Protocol Approval – Sponsor Signatory

Study Title A global, prospective, non-interventional, observational study of presentation, treatment patterns, and outcomes in multiple myeloma patients - the INSIGHT MM study

Protocol Number NSMM-5001
Protocol Date 11 April 2018

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Declaration by Treating Healthcare Provider

Study Title	A global, prospective, non-interventional, observational study of presentation, treatment patterns, and outcomes in multiple myeloma patients – the INSIGHT MM study
Protocol Number	NSMM-5001
Protocol Date	11 April 2018

I confirm that I have read and understand this protocol entitled "A global, prospective, non-interventional, observational study of presentation, treatment patterns, and outcomes in multiple myeloma patients – the INSIGHT MM study". I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study patients.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence, Country)

Table of Contents

Contents

List of Tables

Summary of Changes

Table 1-1 Protocol Amendment History and Summary of Changes

Version	Date	Summary of Changes
Version 1.0	12 February 2016	Original protocol
Version 2.0	12 October 2016	Editorial and administrative changes were made throughout the document for clarity. Redactions were made to Section 6.3 to avoid redundancy and improve clarity. The summary of significant changes includes the following: **Changes to Inclusion/Exclusion Criteria:** • For newly diagnosed multiple myeloma (ND MM), patients will be enrolled within 3 months from initiation of treatment. • For relapsed/refractory multiple myeloma (R/R MM), only those patients who have received 1 to 3 prior lines of therapy will be enrolled. Data to be collected for R/R patients will include month and year of diagnosis and the regimens used in 1st, 2nd, and 3rd line as applicable, whether stem cell transplant was part of 1st, 2nd, and 3rd line of therapy, whether consolidation/maintenance was part of 1st, 2nd, and 3rd line of therapy, also whether investigational therapy/treated on a clinical trial was part of any of these regimens. • Patients willing and able to complete Patient Reported Outcomes (PROs) in accordance with local regulatory and data protection requirements will be enrolled. **Changes to Study Objectives, Outcomes and Analysis:** • The primary and secondary analysis descriptions were modified. **Changes to Study Sites:** • Australia and Africa were removed from the list of study sites. **Changes to Adverse Event Reporting:** • Serious adverse events (SAEs), regardless of causality, in patients taking any Takeda drug must be reported to Cognizant within 24 hours of PPD learning about the event. When an SAE is reported in the electronic case report form (eCRF) for a patient that is on a Takeda product, the investigators will be asked to complete a standard SAE reporting form. The criteria used to define "serious" are outlined in the protocol. • Serious adverse events occurring more than 30 days after the last dose of a Takeda drug generally do not need to be reported to Cognizant except for the circumstances outlined as follows: o New primary malignancies (i.e., all malignancies other

		than the disease of indication) and progressive multifocal leukoencephalopathy need to be reported indefinitely. o Pregnancy in a female patient, or female partner of a male patient, must be reported if the event occurs within 90 days of the patient's last dose of a Takeda drug. o Serious adverse events and non-serious adverse events (AEs) that are determined to be related to a Takeda product need to be reported indefinitely. Relatedness is determined by the healthcare provider. • Serious adverse events in patients who have never taken a Takeda product will be recorded in the eCRF but do not need to be reported to Cognizant/Takeda. For SAEs in patients not taking Takeda drugs, if there is a reasonable possibility that the non-Takeda drug caused the event, local reporting requirements should be followed. • Non-serious AEs resulting in drug discontinuation or dose modification must be recorded in the eCRF. o If non-serious AEs resulting in drug discontinuation or dose modifications are related to a Takeda product, the adverse event form should be completed and the AE reported to Cognizant/Takeda. o Other non-serious AEs do not need to be reported to Cognizant/Takeda, but will be captured in the eCRF. **Additional Enrollment Criteria:** • Enrollment will include approximately 50% ND MM and 50% R/R MM patients. Patient numbers will be capped at the site level. **Changes in the Informed Consent Process:** • Reference to the "Legal guardian" was removed. • Information regarding pregnant partner informed consent form (ICF) was added. **Changes to Data Collection Schedule:** • The data collection schedule was updated to include additional detail on study assessments and associated frequencies. **Changes to Baseline Assessments:** • Baseline assessments for ND and R/R MM patients were modified.

		Changes to Multiple Myeloma Management: • Assessments for Multiple Myeloma Management were modified. **Changes to Patient Reported Outcomes (PROs)/electronic PROs and Questionnaires to Include:** • Frequency of completion of PROs will be quarterly. PROs will not be collected at multiple myeloma-directed treatment change. • The Work Productivity and Activity Impairment Questionnaire for General Health (WPAI–GH) was removed. • The resource utilization questionnaire has been modified by excluding questions related to multiple myeloma treatment change. • The Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) questionnaires will be completed annually by the treating healthcare provider (physician, physician's assistant, nurse practitioner, etc.) in eCRFs. • PROs will be completed on an electronic device at home, an electronic device during on-site routine office visits or on paper during on-site routine office visits. No device will be given to the patient. Patient self-reported outcomes cannot be interviewer-administered by anyone, including a caregiver or site staff. **Changes to Vital Status:** • Patients withdrawing consent will be followed-up only for vital status until the end of the study or the patient's death, whichever occurs earlier. • Patients withdrawing consent could be re-screened for the study based on their willingness and consent. • If the patient does not visit the site or complete PROs at the end of the quarterly visit the site will attempt to contact the patient via telephone. If the attempt is unsuccessful, and the patient remains inactive during the next quarter, the site will again attempt to contact the patient. A final attempt will be made to contact the patient, relative, close friend, or other physician via telephone if the patient has been inactive for a period of 9 months. If this final attempt is unsuccessful, a certified letter will be sent to the patient's last known address. If the patient fails to respond to the certified letter, that patient will be considered lost to follow-up. • The healthcare provider and/or caregiver will be contacted if the patient is lost to follow-up. The ICF will have the provision of a checkbox to be checked off so that the site can contact the

		patient's caregiver when needed. • The healthcare provider may search regional death indexes/registries for vital health statistics of lost to follow-up patients as per routine practice. The date of follow-up will be noted for censoring purposes.
Version 3.0	11 April 2018	Editorial and administrative changes were made throughout the document for clarity. The summary of significant changes includes the following: **Change to Sample Size:** • To account for the reduction of total study sites, the total sample size for this study was reduced to 4200 patients from 5000 patients. The defined accrual period of three years will remain the same, ensuring timely data delivery to the larger multiple myeloma community. **Changes to PROs/electronic PROs and Questionnaires to Include:** To reduce patient and site burden, yet still allow for collection of critical PRO items, the following changes were made: • Electronic PRO (ePRO) collection will be discontinued. Patients will now be asked to complete paper PROs during routine on-site office visits. • The EuroQol, 5-dimension, 5-level questionnaire (EQ-5D-5L) was removed. • Items collected from the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC QLQ-C30) tool was reduced. The Global Health Status/QoL subscale (items 29 and 30) will continue to be collected. • Items collected from the EORTC Quality of Life Questionnaire - 20-item Multiple Myeloma Module (EORTC QLQ-MY-20) tool was reduced. Item 43 measuring peripheral neuropathy will continue to be collected. **Changes to Data Collection Schedule:** • Site assessments were removed as these are not being collected. • The data collection schedule was updated to include additional detail on study assessments and associated frequencies. • Patients who are lost to follow-up will be followed-up only for vital status until the end of the study or the patient's death, whichever occurs earlier.

Protocol Synopsis

This is a non-interventional, observational study; therefore, no study drug or medication will be provided. No change in the patients' management (routine clinical care or treatments) will be required because of this study. However, patients will be asked to complete patient self-reported outcomes (PROs) during on-site routine office visits.

Protocol Number:	NSMM-5001
Title:	A global, prospective, non-interventional, observational study of presentation, treatment patterns, and outcomes in multiple myeloma patients - the INSIGHT MM study
Sponsor:	Millennium Pharmaceuticals, Inc. a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. 40 Landsdowne Street, Cambridge, MA 02139, USA
Indication:	Multiple Myeloma
Rationale:	Although advances in chemotherapy and novel agents have improved the prognosis and increased disease-free survival for patients with multiple myeloma (MM), currently available data on presentation, treatment patterns, and outcomes for MM at the global level are limited. By establishing an international, non-interventional, observational study with multi-year inclusion and follow-up, contemporary demographics and patterns of care for MM patients can be tracked longitudinally in a large, more generalizable population. The main goals of this study include conducting prospective, non-interventional, observational research to gain a better understanding of the disease presentation and patient characteristics, treatment patterns, and clinical outcomes associated with MM and the impact of treatment on safety, effectiveness, and health-related quality of life (HRQoL), on both a country-specific and global basis. With this purpose, this study will collect data on patterns of clinical presentation, management, and outcomes.
Objectives:	**Primary objective**: • Describe contemporary, real-world patterns of patient characteristics, clinical disease presentation, therapeutic regimen chosen, and clinical outcomes in patients with newly diagnosed [ND] MM and patients with relapsed/refractory [R/R] MM. **Secondary objectives**: • Describe patient characteristics, clinical disease presentation,

	therapeutic regimen chosen, and clinical outcomes in ND and R/R MM patients by type of treatment facility and country. • Describe patterns and durations of treatment combinations, sequencing, retreatment, and continuous versus fixed duration treatment strategies; and the clinical outcomes associated with different treatment regimens. • Describe factors associated with treatment initiation, treatment modification, or treatment change over time, including whether treatment at relapse was initiated due to biochemical progression versus symptomatic progression. • Describe HRQoL and healthcare resource utilization (HRU). • Explore associations between patient characteristics, clinical disease presentation, therapeutic regimen chosen, and clinical outcomes.
Patient Population:	Adult (18 years of age or older) patients with ND MM, or adult patients with R/R MM.
Study Design:	This is a prospective, global, non-interventional, observational study. This is a non-interventional study as defined in the Directive 2001/20/EC and will follow the Good Pharmacoepidemiology Practices guidelines. No study drug or medications will be provided. No modification of standard care will be assigned per protocol. The assignment of an eligible patient to a therapy shall be decided by the treating healthcare provider and not by the study protocol, and the prescription of such therapy or medicinal product shall be wholly separate from the decision to include the patient in the study. No change in the patients' management (routine clinical care or treatments) will be required because of this study. However, patients will be asked to complete paper PROs during on-site routine office visits. Eligible patients will be identified and followed prospectively. Information regarding patient characteristics, diagnosis, and previous treatments will be recorded based on review of hospital or clinic records. Multiple myeloma management data and safety data will be obtained as part of routine office visits. If the patient does not visit the site per the defined data collection schedule, the site will attempt to contact the patient via telephone. If the attempt is unsuccessful, and the patient remains inactive throughout the next evaluation period, the site will again attempt to contact the patient. A final attempt will be made to contact the patient, relative, close friend, or other physician via telephone if the patient has been inactive for a period of 9 months. If this final attempt is unsuccessful, a certified letter will be sent to the patient's last known

	address. If the patient fails to respond to the certified letter, that patient will be considered lost to follow-up. Attempts to collect the vital health status of patients who are not available for data collection for more than 9 months and therefore considered lost to follow-up, will occur. The healthcare provider and/or caregiver will be contacted if the patient is lost to follow-up and healthcare provider may search regional death indexes/registries for vital health statistics. PROs will be completed in paper format while the patient is on-site for routine office visits. Patients will complete PROs at study entry and then quarterly while the patient remains on the study. Patient self-reported outcomes cannot be interviewer-administered by anyone, including a caregiver or site staff.
Estimated Study Duration:	Patients will be enrolled over a period of 3 years, and each included patient will be evaluated and followed-up for a period of at least 5 years, until death, or the end of the study, whichever comes first. It is expected that the study will end after all patients in the study have completed at least 5 years of follow-up, are lost to follow-up, or have died during the study period. Patients withdrawing consent will be followed-up only for vital status until death or the end of the study. The date of follow-up will be noted for censoring purposes. The healthcare provider and/or caregiver will be contacted if the patient is lost to follow-up and healthcare provider may search regional death indexes/registries for vital health statistics.
Assessments:	Demographic and biometric data; general medical history; and MM history, baseline data at inclusion, and disease presentation, will be recorded. Multiple myeloma management will be assessed based on previous and current treatments and changes to treatment and reason(s). Effectiveness will be assessed based on response to each regimen; progression status on each regimen; time to next therapy; and vital status, date of death, and cause of death. Safety will be assessed based on the serious adverse events (SAEs) and non-serious adverse events (AEs) leading to treatment discontinuation (temporary and permanent) or drug modification, and second primary malignancies collected during the study. Patient self-reported outcomes will be collected using the following tools: Items 29 and 30 measuring global QoL and health status from the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC QLQ-C30), item 43 measuring peripheral neuropathy from the EORTC Quality of Life Questionnaire - 20-item Multiple Myeloma Module (EORTC

	QLQ-MY-20), and the 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9). A patient survey will be conducted at baseline and a healthcare resource utilization survey will be completed by patients quarterly while the patient remains on the study. The frailty index is based on the Charlson Comorbidity Index, the Katz Index of Independence in Activities of Daily Living (ADL), and the Lawton Instrumental Activities of Daily Living (IADL) scales, all of which will be completed by the treating healthcare provider annually in electronic case report forms (eCRFs). Healthcare resource utilization will be assessed including, but not limited to, inpatient and intensive care unit admissions, length of stay, outpatient clinic visits, and emergency room visits.
Study Treatment:	This is a prospective, global, non-interventional, observational study. Treatment will not be determined or altered by participation in this study, with patients receiving usual therapy as determined by their treating healthcare provider. No additional treatments or procedures will be utilized for this study. However, patients will be asked to complete PROs. Patients can also be enrolled in an observational or interventional study while participating in this study.
Sample Size:	The study will attempt to enroll approximately 4200 patients globally. The planned sample size is intended to provide enough patients to characterize treatments in a broad population. A sample size of 268 patients in each of any 2 comparison subgroups will have at least 80% power to detect a difference between two proportions given that the true difference is at least 12%. Enrollment will include approximately 50% ND MM and 50% R/R MM patients. Patient numbers may be capped at the site level.
Statistical Methods:	Statistical analysis will be performed using SAS® software Version 9.2 or later. Population characteristics and all relevant primary and secondary outcomes will be summarized as mean, standard deviation, minimum, maximum, median, 25th and 75th percentile, and 95% confidence interval (CI) of the mean for continuous variables; and count and proportion with 95% CI of the proportion for categorical data. Counts of non-missing observations will be included. Event rates and 95% CIs for selected outcomes will also be summarized. Descriptive statistics will be used to describe patient characteristics, disease presentations, treatment patterns, safety assessments, clinical outcomes, economic outcomes, and HRQoL outcomes observed during the study period. Treatment patterns will be summarized according to subgroups based on clinically relevant factors.

	Multivariable analysis of economic outcomes and PROs will be conducted using appropriate regression models. HRQoL outcomes will be summarized using descriptive statistics and longitudinal analysis. All data collected for SAEs and non-serious AEs leading to treatment discontinuation (temporary and permanent) or drug modification, and second primary malignancies will be summarized. Since this is a disease-focused non-interventional, observational study with potential complicated confounding between treatment assignments and outcomes, all comparative effectiveness analyses will be considered exploratory.
Date of Protocol:	11 April 2018

List of Abbreviations

Abbreviation	Definition
ADL	Activities of daily living
AE	Adverse event
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence interval
CRAB	Calcium, renal failure, anemia, and bone damage
CT	Computed tomography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
FLC	Free light chain
GEP	Gene expression profiling
GPP	Good Pharmacoepidemiology Practices
HRQoL	Health-related quality of life
HRU	Healthcare resource utilization
IADL	Instrumental activities of daily living
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IMWG	International Myeloma Working Group
IRB	Independent review board
ISS	International Staging System
LDH	Lactate dehydrogenase
MGUS	Monoclonal gammopathy of unknown significance
MM	Multiple myeloma
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network

Abbreviation	Definition
ND	Newly diagnosed
NGS	Next-generation sequencing
OS	Overall survival
PET	Positron emission tomography
PFS	Progression-free survival
PRO	Patient self-reported outcomes
QALY	Quality adjusted life year
QLQ-C30	Quality of Life Questionnaire – 30 item Cancer
QLQ-MY-20	Quality of Life Questionnaire - 20-item Multiple Myeloma Module
R-ISS	Revised International Staging System
R/R	Relapsed/refractory
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Steering Committee
SMM	Smoldering multiple myeloma
SPEP	Serum protein electrophoresis
TSQM	Treatment Satisfaction Questionnaire for Medication
TSQM-9	9-Item Treatment Satisfaction Questionnaire for Medication
UPEP	Urine protein electrophoresis
US	United States

Schedule of Assessments

The Data Collection Schedule is provided in Table 1-2. The schedule of data collection will not interfere with the standard schedule of routine office visits for MM patients.

No information will be collected until the patient has provided consent to participate in the study.

Table 1-2 Data Collection Schedule

Frequency	**Inclusion**	**Quarterly from Inclusion**	**Annually from Inclusion**
Visit Window		**+1 month**	**±1 month**
Obtaining informed consent	X		
Inclusion/Exclusion criteria	X		
Demographic information[1]	X		
Medical evaluation: Height	X		X
Medical evaluation: Weight	X		X
Vital status		X	
Insurance information	X		X
Relevant past medical history[2]	X		
Multiple myeloma medical history, disease characteristics and staging, diagnostic and presenting symptoms for MM[3]	X		
Frailty status[4]: Charlson Comorbidity Index, Katz Index of Independence in ADL, Lawton IADL scale	X		X
ECOG performance status	X		X
Follow-up medical evaluation		X	
Vaccinations	X		X
Bone marrow evaluations, Cytogenetics, FISH, MRD, GEP, NGS and investigational analysis, if available in clinical records	X	X	
Laboratory results (hematology and chemistry)[5]	X	X	
Laboratory test results (paraprotein evaluation/SPEP)[6]	X	X	

Frequency	**Inclusion**	**Quarterly from Inclusion**	**Annually from Inclusion**
Visit Window		**+1 month**	**±1 month**
Laboratory results HevyLite (if available)	X	X	
Laboratory results (UPEP) (if available)[7]	X	X	
Imaging results (if available)[8]	X	X	
Multiple myeloma related radiation therapy		X	
Multiple myeloma related surgeries and other procedures		X	
Multiple myeloma therapy prior to study entry (ND MM)[9]	X		
Multiple myeloma therapy prior to study entry (R/R MM)[10]	X		
Multiple myeloma therapy status (ND MM and R/R) (includes reason for not receiving therapy)	X	X	
Administered/prescribed MM therapy drugs for regimen (current regimen)[11]	X	X	
Multiple myeloma regimen therapy plan[12]	X	X	
Response assessment for a regimen, MRD (if available)[13]	X	X	
Patient Baseline Survey	X		
Patient self-reported outcomes[14] (Note: PRO completion can occur any time during a visit quarter. See footnote for details)	X	X[14]	
Stem cell transplants	X	X	
Multiple myeloma supportive care	X	X	
Healthcare resource utilization[15] (Note: HRU is completed by both the HCP and the patient quarterly. See footnote for details)		X	

Frequency	**Inclusion**	**Quarterly from Inclusion**	**Annually from Inclusion**
Visit Window		**+1 month**	**±1 month**
Study Discontinuation[16]		X	
Safety assessments (AE/SAE)[17]	X	X	
Pregnancy reporting	X	X	

Abbreviations: ADL, activities of daily living; AE, adverse event; BUN, blood urea nitrogen; CRAB, calcium, renal failure, anemia, and bone damage; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; FISH, fluorescence in situ hybridization; FLC, free light chain; GEP, gene expression profiling; HCP, healthcare provider; HRU, healthcare resource utilization; IADL, instrumental activities of daily living; LDH, lactate dehydrogenase; MGUS, monoclonal gammopathy of unknown significance; MM, multiple myeloma; MRD, minimal residual disease; MRI, magnetic resonance imaging; ND, newly diagnosed; NGS, next-generation sequencing; PET, positron emission tomography; PRO, patient self-reported outcomes; R/R, relapsed/refractory; SAE, serious adverse event; SMM, smoldering multiple myeloma; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis.

1 Including age, sex, race, ethnicity (optional based on country requirements), from PRO and height, weight, and geographic region.

2 Relevant medical history includes peripheral neuropathy, hypertension, thromboembolism, osteopenia/osteoporosis, cataracts, arrhythmias, assessments if available: Echocardiogram, multigated acquisition scan (MUGA), Myelodysplastic Syndromes (MDS), MM-related radiation therapy, MM-related procedures/surgeries, myeloma/skeletal-related procedures, other surgeries/procedures, and vaccinations.

3 Multiple myeloma medical history at initial diagnosis, if available, will include: disease stage at initial diagnosis, serum Beta-2 microglobulin, serum albumin, LDH, cytogenetics/FISH risk, bone lesions, calcium, BUN, creatinine, hemoglobin, MGUS/SMM, CRAB symptoms; and medical history prior to study inclusion, if available: bone marrow, FLC, MRI, M-component, immunofixation, PET/CT, GEP, amyloidosis, plasmacytoma, central nervous system involvement, and stem cell transplant.

4 The frailty index will be based on the Charlson Comorbidity Index (Charlson et al. 1987), the Katz Index of Independence in ADL (Katz 1983), and the Lawton IADL scales (Lawton and Brody 1969), all of which will be completed by the treating healthcare provider annually in eCRFs.

5 Hematology and Chemistry laboratory test results of known prognostic, predictive markers. Baseline Hematology: white blood cell count, absolute neutrophil count, hemoglobin, and platelet count. Baseline Chemistry: calcium, creatinine, alkaline phosphatase, total bilirubin, aspartate aminotransferase, alanine aminotransferase, LDH. Albumin, and serum Beta-2 microglobulin, if available in clinical records. Quarterly Hematology: white blood cell count, absolute neutrophil count, hemoglobin, and platelet count; Quarterly Chemistry: calcium, creatinine, total bilirubin, albumin, and serum Beta-2 microglobulin, if available in clinical records.

6 Paraprotein laboratory test results, if available: serum protein electrophoresis (SPEP) (serum total protein, m-spike level, serum immunofixation, serum quantitative immunoglobulins), Serum FLCs.

7 UPEP (24-hour urine, urine M-spike/BJP, urine immunofixation), or spot urine (protein, urine immunofixation). If both 24-hour and spot urine were tested, provide only the 24-hour urine results.

8 Imaging tests include skeletal survey, standard CT, MRI, PET/CT, bone mineral density, whole body assessments (low dose CT and MRI, if done for

myeloma evaluation).

9 For patients with ND MM only. Regimen, treatment durations and reasons for initiation of regimen.

10 For patients with R/R MM only. Therapy prior to study entry including 1st, 2nd, and 3rd relapses and details for number of previous lines of therapy, regimens used in 1st, 2nd, and 3rd line as applicable; whether stem cell transplant was part of 1st, 2nd, and 3rd line of therapy, and whether consolidation/maintenance was part of 1st, 2nd, and 3rd line of therapy; also, whether investigational therapy/treated on a clinical trial was part of any of these regimens.

11 Administered/prescribed MM therapy drugs for regimen for current treatment (including treatment received at study entry), including individual drug, dose, route, schedule, duration and dose modification and reasons for medication changes.

12 MM regimen therapy plan includes current (including regimen at study entry) regimen, line of therapy, phase of regimen, reason for initiation of this regimen (includes relapse), treatment intent of the regimen, duration, part of interventional clinical trial.

13 Response assessment for a regimen includes MRD, if assessed, best response achieved during the evaluation period, progression, and time to next therapy.

14 Global Health Status/QOL scale (2 items) from the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - C30 (EORTC QLQ-C30), a single item on peripheral neuropathy from the EORTC Quality of Life Questionnaire - 20-item Multiple Myeloma Module (EORTC QLQ-MY-20), and the 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9). A patient baseline survey will be conducted at study entry. The + 1 month visit window does not apply to PRO collection; PROs may be collected from the patient at any time within the defined quarterly visit schedule.

15 Including but not limited to inpatient and intensive care unit admissions, reasons for admission, length of stay, outpatient clinic visits, and emergency room visits. The healthcare resource utilization questionnaire is completed by the investigator in the eCRF; in this case, the frequency will be +1 month. Hospice details will also be collected on eCRFs. A healthcare resource utilization questionnaire will also be completed by the patient in the paper PRO packet.

16 Study discontinuation includes date and cause of death. After withdrawal or loss to follow-up, the patient's vital status will be assessed. The healthcare provider may search regional death indexes/registries for vital health statistics of lost to follow-up patients as per routine practice.

17 All serious AEs and non-serious AEs regardless of causality leading to treatment discontinuation (temporary or permanent) or drug modification, and second primary malignancies will be recorded on the eCRFs. All SAEs and non-serious AEs regardless of causality leading to treatment discontinuation (temporary or permanent) or drug modification of Takeda products will be reported following Section 6.5.3.

1. Introduction

Multiple myeloma (MM) is a clonal plasma cell disorder that accounts for 1% of all cancers and 10% of hematologic malignancies (National Comprehensive Cancer Network [NCCN] 2015). It is the second most common hematologic malignancy, with an estimated worldwide incidence of 114,000 new cases and 80,000 deaths in 2012 (Ferlay et al. 2013). In the United States (US), the estimated annual incidence in 2015 was 26,850 new cases and 11,240 deaths (National Cancer Institute 2015). In Europe, the estimated annual incidence in 2012 was 38,900 new cases and 24,300 deaths (Ferlay et al. 2013).

Multiple myeloma is largely a disease of older people. The median age at diagnosis is 69 years, and approximately 2/3 of people are over age of 65 at the time of diagnosis (Ailawadhi 2012, NCCN 2015). Also, MM is more common in men than women, and in black people compared to other races (Alexander 2007). Although the reasons for these differences are not clearly understood, risk factors such as obesity, socioeconomic status, and workplace environment and exposures may have a role. The incidence of MM is increasing slowly; this may be related to an aging population, as well as to increasing obesity rates. However, deaths from MM are decreasing year-on-year: the 5-year survival rate in the US was 27% in 1975 compared to 53% from 2008 to 2010 (National Cancer Institute 2015, Pulte 2015), and in Europe was approximately 40% between 2006 and 2008 (Sant 2014).

The improvement in overall survival (OS) is likely due to the introduction of more effective treatments, both in general as well as through individualization and sequencing of therapies based on identification of important patient sub-groups with the use of advanced diagnostics (e.g., fluorescence in situ hybridization [FISH] and high-throughput gene expression profiling [GEP]). The introduction of novel classes of agents with increased efficacy, including proteasome inhibitors (bortezomib, carfilzomib, and ixazomib) and immunomodulatory agents (thalidomide, lenalidomide, and pomalidomide), has played a role in increasing both the progression-free survival (PFS) and the OS of these patients, and has changed the natural history of the disease. In addition, agents with new mechanisms of action such as panobinostat (histone deacetylase inhibitor) and daratumumab and elotuzumab (monoclonal antibodies) have recently been approved in the US and the submission of these agents for approval globally is underway. The investigation continues with these agents, other agents with the same or similar mechanisms of action as well as agents with novel mechanisms of action. Treatment landscape for patients with MM is rapidly changing and it is anticipated that treatment changes will continue for the foreseeable future.

Although advances in chemotherapy and novel agents have improved the prognosis and disease-free survival for patients with MM, currently available data on presentation, treatment patterns, and outcomes for MM at global level are limited. By establishing an international non-interventional, observational study with multi-year inclusion and follow-up, contemporary demographics and patterns of care for MM patients can be tracked longitudinally in a large, more generalizable population.

The main goals of this study include conducting prospective, non-interventional, observational research to gain a better understanding of the disease presentation and patient characteristics, treatment patterns, and clinical and economic outcomes associated with MM and the impact of treatment on safety, effectiveness, health-related quality of life (HRQoL), and healthcare resource utilization (HRU), on both a country-specific and global basis. With this purpose, this study will collect data on patterns of clinical presentation, management, and outcomes.

2. Study Objectives

2.1. Primary Objective

The primary objective of this study is to describe contemporary, real-world patterns of patient characteristics, clinical disease presentation, therapeutic regimen chosen, and clinical outcomes in patients with newly diagnosed [ND] MM, and patients with relapsed/refractory [R/R] MM.

2.2. Secondary Objectives

The secondary objectives of this study are to:

- Describe patient characteristics, clinical disease presentation, therapeutic regimen chosen, and clinical outcomes in ND and R/R MM patients by type of treatment facility and country.
- Describe patterns and durations of treatment combinations, sequencing, retreatment, and continuous versus fixed duration treatment strategies; and the clinical outcomes associated with different treatment regimens.
- Describe factors associated with treatment initiation, treatment modification, or treatment change over time; including whether treatment at relapse was initiated due to biochemical progression versus symptomatic progression.
- Describe HRQoL and HRU.
- Explore associations between patient characteristics, clinical disease presentation, therapeutic regimen chosen, and clinical outcomes.

3. Investigational Plan

3.1. Study Design

This is a prospective, global, non-interventional, observational study. The purpose of this study is to describe contemporary, real-world presentation, therapies, and clinical outcomes in patients with MM. Therefore, no modification of standard care is assigned per protocol. This is a non-interventional, observational study; therefore, no study drug or medications will be provided. No change in the patients' management (routine clinical care or treatments) will be required because of this study. However, patient self-reported outcomes (PROs) will be completed during on-site routine office visits.

This is a non-interventional study as defined in the Directive 2001/20/EC (The European Parliament and the Council of the European Union 2001) and will follow the Good Pharmacoepidemiology Practices (GPP) guidelines (Epstein 2005).

Eligible patients will be identified and followed prospectively. Information regarding patient characteristics, diagnosis, and previous treatments will be recorded based on review of hospital or clinic records. Multiple myeloma management data and safety data will be obtained as part of routine office visits. Patients who are not available for data collection for more than 9 months will have a follow-up for survival. The site will have made 3 possible attempts to contact the patient by the time this 9-month period is reached. The healthcare provider and/or caregiver will be contacted if the patient is lost to follow-up. The healthcare provider may search regional death indexes/registries for vital health statistics of lost to follow-up patients as per routine practice. Patient self-reported outcomes will be collected during on-site routine office visits. Patients will complete PROs at study entry and then quarterly thereafter while the patient remains on the study. The HRU will also be assessed quarterly while the patient remains on the study.

This study will attempt to enroll approximately 4200 patients globally. Patients will be enrolled over a period of approximately 3 years, and each included patient will be evaluated and followed-up for a period of at least 5 years, until death, withdrawal of consent to participate, or the end of the study, whichever comes first. It is expected that the study will end after all patients in the study have completed at least 5 years of follow-up, are lost to follow-up, or have died prior to study end.

Patients lost to follow-up will be followed-up only for vital status until the end of the study or the patient's death, whichever occurs earlier. The date of follow-up will be noted for censoring

purposes. Patients will not be asked to travel to the site only for this study. Multiple myeloma management data and safety data will be obtained as part of selected routine office visits.

The data collected for this study are detailed in Section 6 and the Data Collection Schedule is provided in Table 1-2.

3.1.1 Rationale of Study Design

An observational design is used as it will not interfere with patient's treatment as prescribed and directed by the healthcare provider. The schedule of data collection is also in agreement, and will not interfere with the standard schedule of routine office visits for MM patients. No additional treatments or diagnostic or monitoring procedures will be utilized for this study. However, patients will be asked to complete PROs in paper format during on-site routine office visits.

The need for HRQoL endpoints in MM studies to better inform treatment decisions in cancer has been increasingly recognized (Kvam et al. 2009). Furthermore, regulatory agencies and health technology assessment bodies are increasingly considering PROs, such as physical functioning and symptoms, in their deliberations. The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) instrument has been recommended for use in oncology trials (Basch et al. 2012) and is widely utilized in clinical trials and in global registries. The psychometric properties of the measure have been established (Aaronson et al. 1993) and the clinically meaningful difference in scores of the global quality of life health status scale, which will be assessed as a standalone scale in this study, has been determined in MM populations (Wisløff et al. 1996; Kvam et al. 2011). In addition to EORTC QLQ-C30, the common symptom of peripheral neuropathy will be assessed by a single item of the EORTC Quality of Life Questionnaire - 20-item Multiple Myeloma Module (QLQ-MY-20) (Stead et al. 1999). Additional information on these questionnaires is provided in Section 6.4.

To capture patient satisfaction with MM-directed therapy, including the important dimension of convenience, the Treatment Satisfaction Questionnaire for Medication (TSQM) will be administered to patients in its 9-item version (TSQM-9) (Bharmal et al. 2009). The TSQM is also a widely-used questionnaire in the context of oncology (Escudier et al. 2009). Additional information on the TSQM-9 is provided in Section 6.4.3.

To incorporate data from a wide range of countries, initial recruitment will start in the US with other countries included as soon as sites are identified, selected for submission, approved as per

local regulatory requirements, and ready for patient recruitment.

The study has been designed as a non-interventional, observational study, with a specified target sample size of approximately 4200 patients globally, tied to achievable rates of patient inclusion during 3 years, and with a follow-up of a minimum of 5 years, until death, withdrawal of consent to participate, or the end of the study, whichever comes first. Enrollment will include approximately 50% ND MM and 50% R/R MM patients. Patient numbers will be capped at the site level. This target is sufficient to achieve a satisfactory degree of precision and to provide valuable data on the study objectives (see Section 7.2). Patients withdrawing consent could be re-screened for the study based on their willingness and consent. Patients lost to follow-up will be followed-up only for vital status until the end of the study or the patient's death, whichever occurs earlier. The healthcare provider and/or caregiver will be contacted if the patient is lost to follow-up. The healthcare provider may search regional death indexes/registries for vital health statistics of lost to follow-up patients as per routine practice. The date of follow-up will be noted for censoring purposes.

3.1.2 Potential Risk and Benefits

Patients included in the study will undergo routine clinical assessment; treatment will not be determined or altered by participation in this study, with patients receiving usual therapy as determined by their treating healthcare provider during their care. No additional treatments or procedures will be utilized for this study, although patients will be asked to complete PROs. Therefore, no specific risks have been identified other than the potential for loss of confidentiality. Every effort will be made to protect patient confidentiality: the data analysis will be performed using only masked data (see Section 7.6.1). Informed consent containing detailed information about potential benefits and risks for the patient will be required from all patients.

Although patients included in this study might not receive any benefit from the study, the study will promote better understanding of contemporary demographics, patterns of care, and outcomes for MM patients in a large, more generalizable population. This new information will be shared with the medical community.

3.1.3 Potential Selection Bias

Due to the nature of the study design and because the patients are being selected by the healthcare providers, the possibility of sample selection bias due to "convenience" sampling must be considered. Reasonable efforts will be made to include a sample of MM patients who represent the general population of MM patients in any specific country. This may include

regular monitoring of included and screened patients, periodic adjustments in inclusion caps and other such efforts. During the analysis phase, statistical adjustments may also be implemented to further address bias and/or confounding that persist despite best efforts to capture representative sample. The statistical analysis plan (SAP) will describe these approaches in detail.

4. Patient and Site Selection and Withdrawal Criteria

4.1 Selection of Study Population

Patients cared for at participating clinics who meet study eligibility criteria will be approached for formal consent to participate in the study.

4.1.1 Inclusion Criteria

Each patient must meet all of the following criteria to be included in this study:

1. Is 18 years of age or older.

2. Is experiencing one of the following:

    a. Newly diagnosed MM within 3 months from initiation of treatment with documented month and year of diagnosis, criteria met for diagnosis, stage, and MM-directed treatment history, including duration.

    b. Relapsed/refractory MM who have received 1 to 3 prior lines of therapy with documented data in the medical record regarding diagnosis (month and year), the regimens used in 1st, 2nd, and 3rd line as applicable, whether stem cell transplant was part of 1st, 2nd, and 3rd line of therapy, whether consolidation/maintenance was part of 1st, 2nd, and 3rd line of therapy, also whether investigational therapy/treated on a clinical trial was part of any of these regimens.

3. Patients willing and able to complete PROs in accordance with local regulatory and data protection requirements will be enrolled.

4. Is willing and able to sign informed consent to participate.

4.1.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Patients reporting to a site in this study for a second opinion (consultation only) or patients whose frequency of consult and follow-up are not adequate for quarterly electronic case report form (eCRF) completion.

2. Participation in another study (observational or interventional) that prohibits participation in this study.

4.2 Selection of Study Sites

Patients will be recruited to this study from sites across the world that may include North America, Europe, Asia, and South America. In addition, this study has the potential to partner with MM registries or other observational MM studies, with the goal to build a global MM observational study.

The healthcare providers in each participating country will be recruited to reach an adequate sample of sites based on the following selection criteria:

- All participating healthcare providers and sites must provide care for MM patients.
- Each site must be represented by a healthcare provider who is a full-time member of the hospital or clinic staff, who agrees to serve as the principal MM healthcare provider or oversee MM healthcare for patients who may be included at their respective hospital or clinic under the care of a Sub-Investigator, and who agrees to ensure that the scientific and ethical requirements in this protocol are followed.

4.3 Withdrawal of Patients from the Study

The duration of the study is defined for each patient as the date that signed written informed consent is provided through the end of the follow-up period, death, or the end of the study. Patients may withdraw their consent at any time and for any reason without prejudice to their future medical care by the healthcare provider or at the study site. In case of withdrawal, patients will have the right to be remembered and the right to be forgotten in accordance with local regulatory and data protection rules. These rights will be included in the informed consent form (ICF).

Patients withdrawing consent can be re-screened for the study based on their willingness and consent. They will be followed-up only for vital status until the end of the study or the patient's death, whichever occurs earlier. The ICF will have the provision of a checkbox to be checked off so that the site can contact the patient's caregiver when needed.

4.3.1 Reasons for Withdrawal

Treatment will not be determined or altered by participation in this study, with patients receiving usual therapy as determined by their treating healthcare provider during their care. Patients can also be enrolled in another observational or interventional study while participating in this study.

The reasons for patients not completing the study will be recorded. A patient may be withdrawn

from the study for any of the following reasons:

- The patient withdraws consent.
- If the patient enrolls in another observational or interventional study that requires withdrawal from this study, the patient may be re-included into this study when the patient's participation in the other study is completed.

Patient participation in this study may be discontinued without patient consent at any time at the discretion of the healthcare provider, Takeda, or a regulatory authority. The healthcare provider will also withdraw a patient if Takeda terminates the study.

4.3.1 Handling of Withdrawals

When a patient withdraws from the study, the reason(s) for withdrawal shall be recorded by the treating healthcare provider on the relevant page in the eCRF, including reasons for "lost to follow-up" if necessary. Every attempt will be made by the site to document the reason of study withdrawal.

If the patient does not visit the site at the end of the quarterly visit, the site will attempt to contact the patient via telephone. If the attempt is unsuccessful, and the patient remains inactive during the next quarter, the site will again attempt to contact the patient. A final attempt will be made to contact the patient, relative, close friend, or other physician via telephone if the patient has been inactive for a period of 9 months. If this final attempt is unsuccessful, a certified letter will be sent to the patient's last known address.

If the patient fails to respond to the certified letter, that patient will be considered lost to follow-up. The primary healthcare provider and/or caregiver will be contacted if the patient is lost to follow-up for vital status. The healthcare provider may search regional death indexes/registries for vital health statistics of lost to follow-up patients as per routine practice. The date of follow-up will be noted for censoring purposes.

5 Study Treatments

This is a prospective, global, non-interventional, observational study where patients included will undergo routine clinical care under the supervision of an authorized healthcare provider. Treatment will not be determined or altered by participation in this study, with patients receiving usual therapy as determined by their treating healthcare provider during their care. Patients can also be enrolled in an observational or interventional study while participating in this study. No additional treatments or procedures will be utilized for this study. However, patients will be asked to complete PROs and questionnaires including healthcare utilization.

6 Study Assessments and Collection of Data

Before collecting any data, all potential patients will sign an ICF. Patients will have the opportunity to have any questions answered before signing the ICF. The healthcare provider must address all questions raised by the patient. Refer to Section 8.3 for additional details on patient's consent.

Refer to data collection schedule provided in Table 1-2 for more information.

6.1 Baseline Assessment

Baseline data will include, but will not be limited to, the following questions related to medical history prior study inclusion and status at study inclusion.

For ND and R/R:

- Demographic and biometric information including age, sex, race, ethnicity (optional, based on country requirements), height, weight, insurance information and geographic region.
- Date of initial diagnosis (including month and year for R/R and day, month and year for ND) and criteria used International staging system (ISS)/revised ISS (R-ISS).
- Medical history at initial diagnosis, if available, will include: disease characteristics, stage by ISS or R-ISS, presence of bone lesions, relevant baseline laboratory values, history of monoclonal gammopathy of unknown significance/smoldering multiple myeloma (MGUS/SMM).
- Frailty status, including Charlson Comorbidity Index, Katz Index of Independence in activities of daily living (ADL), and Lawton instrumental activities of daily living (IADL) scale, as well as Eastern Cooperative Oncology Group (ECOG) performance status.
- Medical history data prior to study inclusion, if available: relevant medical history to be captured as detailed in the eCRF, including vaccination history and stem cell transplants.
- Medical evaluation (collected at baseline and quarterly) as detailed in the eCRF.

Therapy prior to study entry:

- For ND: phase of treatment, regimen, treatment durations and reasons for initiation of regimen, response evaluation and assessment, and minimal residual disease (MRD) (if done).

- For R/R: including 1st, 2nd, and 3rd relapses and number of previous lines of therapy, regimens used in 1st, 2nd, and 3rd line as applicable; whether stem cell transplant was part of 1st, 2nd, and 3rd line of therapy, whether consolidation/maintenance was part of 1st, 2nd, and 3rd line of therapy; also, whether investigational therapy/treated on a clinical trial was part of any of these regimens; and response evaluation, MRD (if done).

6.2 Multiple Myeloma Management

The following information will be collected to assess MM management:

Therapy at inclusion:

- For ND and R/R: current therapy, including regimens and drugs; and reasons for not receiving a therapy, if any.

Quarterly assessment:

- Changes to treatment from previous evaluation period including line of therapy, regimen, drug, schedule and duration, dose modifications, and reason(s) for medication changes at inclusion and quarterly during the study.

- Hematology/chemistry form will be completed based on laboratory values obtained closest to the beginning of the most recent cycle of therapy (if available) or the laboratory values closest to the quarterly eCRF completion date.

- History of radiation therapy.

- History of MM-related surgeries and/or other procedures.

- Stem cell transplant, if done.

- MM-supportive care, if received.

- HRU, overnight hospital admissions, emergency room visits (see Section 6.3).

- Safety assessment (see Section 6.5).
- Pregnancy assessment (see Section 6.6).
- Frailty status will be measured yearly.

Study status for patient continuation to the next evaluation period will be assessed.

6.3 Effectiveness

The following information will be collected quarterly during the study to assess effectiveness of MM management:

- Bone marrow evaluation, FISH, cytogenetics, MRD, positron emission tomography (PET)/computed tomography (CT), next-generation sequencing (NGS), GEP, serum para-protein evaluation (SPEP), HevyLite (if available), urine protein electrophoresis (UPEP) laboratory results. HevyLite and UPEP will also be collected at inclusion, if available.
- Imaging results for all assessment performed within an evaluation period, if done for MM assessment.
- Response to each regimen (per the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma) (Durie BG, et al. 2006)
- Progression status on each regimen.
- Time to next therapy.
- Vital status, date of death, and cause of death.

6.4 Patient Self-Reported Outcomes

Patient self-reported outcomes; including the Global Health Status/QoL subscale from the EORTC QLQ-C30, a single item on peripheral neuropathy from the EORTC QLQ-MY-20, and TSQM-9, will be assessed at study inclusion and quarterly thereafter. A baseline questionnaire will be completed at inclusion and HRU will be assessed quarterly. Patient self-reported outcomes will be collected on paper forms during on-site routine office visits. Patient self-reported outcomes cannot be interviewer-administered by anyone, including a caregiver or site staff.

6.4.1 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Global Health Status/QoL Subscale

The EORTC QLQ-C30 (Aaronson et al. 1993) was designated to assess HRQoL in a wide range of cancer patient populations. The Global Health Status scale/QoL scale includes 2 questions measured with a 7-point numeric rating scale (very poor to excellent). Raw scores are converted into scale scores ranging from 0 to 100. A higher score represents better HRQoL.

6.4.2 Quality of Life Questionnaire - 20-item Multiple Myeloma Module-Item 43 on Peripheral Neuropathy

The EORTC QLQ-MY-20 (Stead et al. 1999) was designed in collaboration with the EORTC Quality-of-Life Study Group as a MM-specific module to be administered with the EORTC QLQ-C30. Item 43 of the measure assesses the symptom of peripheral neuropathy, or tingling in the hands and feet, using a 4-point Likert scale ranging from "Not at all" to "Very much". A high score represents a high level of the symptom.

The EORTC QLQ-MY-20 item will be administered following the EORTC QLQ-C30 items.

6.4.3 Treatment Satisfaction Questionnaire for Medication

The TSQM-9 (Bharmal et al. 2009) will be administered at enrolment and quarterly thereafter to capture patient satisfaction with MM-directed therapy, including the important dimension of convenience. The TSQM-9 includes 9 items on a 5-point or 7-point Likert type scale and covers 3 domains, corresponding to distinct aspects related to the satisfaction of patients with their treatment (effectiveness, convenience, and global satisfaction). The TSQM-9 is a reduced version of the 14-item TSQM which includes 9 of the original questions but excludes the 5 TSQM questions related to side effects of medication. Higher scores on the TSQM-9 indicate higher satisfaction, better perceived effectiveness, and better convenience.

6.4.4 Healthcare Resource Utilization

Healthcare resource utilization for routine MM treatment will be assessed quarterly including, but not limited to, inpatient and intensive care unit admissions, reasons for admission, length of stay, outpatient clinic visits, and emergency room visits. Healthcare resource utilization will be assessed first, before the standard PRO questionnaires.

6.5 Safety Assessments

Safety will be assessed by the documentation and collection of serious adverse events (SAEs) and non-serious AEs leading to treatment discontinuation (temporary and permanent) or drug modification, and second primary malignancies.

6.5.1 Definitions of Adverse Events

Adverse Events

Adverse event means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal product. This includes any new event, or worsening of a previous condition.

Adverse Drug Reaction

For the purposes of this study, an adverse drug reaction is an AE that is considered related to MM treatments, or to other treatments according to the definition above.

Serious Adverse Event

An SAE is an AE that meets any of the following criteria:

- Is fatal or life threatening, i.e., in the view of the healthcare provider, places the patient at immediate risk of death from the reaction as it occurred. An event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening, even though drug-induced hepatitis can be fatal.

- 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.

- Requires inpatient hospitalization or prolongation of an existing hospitalization. Symptoms or conditions led to the hospitalization (e.g., dehydration, and shortness of breath) will be documented. Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient used the drug are not to be considered AEs unless the condition deteriorated in an unexpected manner during treatment (e.g.,

surgery was performed earlier or later than planned).

- Is a congenital anomaly/birth defect.
- Is a malignancy.
- Is a medically important event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

Seriousness serves as a guide for defining regulatory reporting obligations.

6.5.2 Collecting and Recording of Adverse Events

All SAEs, regardless of causality or expectedness, and non-serious AEs resulting in drug discontinuation (temporary or permanent) or dose modification will be collected from the patient medical records and captured in the eCRF. Multiple myeloma is a disease with high morbidity and high mortality, therefore this study will only collect SAEs and non-serious AEs resulting in drug discontinuation (temporary or permanent) or dose modification.

When an SAE is reported in the eCRF for a patient that is on a Takeda Oncology product the investigators will be asked to complete a standard SAE reporting form. All secondary primary malignancies must be collected, regardless of causality, upon awareness of the new primary malignancy for a minimum of 3 years after the last dose of ixazomib or other MM therapies.

Sufficient information should be recorded to enable the AE to be fully described and collected in the eCRF. If an SAE is present, the following information should be collected in the eCRF:

- A description of the AE.

- Start and stop dates of the AE.
- Outcome of AE.
- Actions taken by the health-care provider (especially if the actions involved stopping a drug or dose modification).
- Causal relationship to treatment, to concurrent medical conditions, to medical or surgical procedures, or to other unknown or suspected causes, or to concomitant drug(s).
- Severity of the SAE.
- Seriousness criteria met.

6.5.3 Reporting of Adverse Events

All SAEs, regardless of casualty or expectedness, and non-serious AEs leading to treatment discontinuation (temporary and permanent) or drug modification, and second primary malignancies will be recorded on the appropriate page in the eCRF on a quarterly basis.

In patients taking any Takeda Oncology drug, SAEs and non-serious AEs leading to treatment discontinuation (temporary and permanent) or dose modification, and secondary primary malignancies will be captured in eCRFs, and the investigators will be asked to complete a standard SAE reporting form. The event will then be reported automatically via email to Takeda Case processing (Cognizant) or designee within 24 hours after entry into the clinical database.

Serious adverse events occurring more than 30 days after the last dose of a Takeda drug generally do not need to be reported. There are some exceptions with longer reporting periods, as follows:

- New primary malignancies (i.e., all malignancies other than the disease of indication) and progressive multifocal leukoencephalopathy need to be reported indefinitely.
- Pregnancy in a female patient, or female partner of a male patient, must be reported if the event occurs within 90 days of the patient's last dose of a Takeda drug.
- Serious adverse events and non-serious AEs that are determined to be related to a Takeda product must be reported indefinitely. Relatedness is determined by the healthcare provider.

Serious adverse events in patients who have never taken a Takeda product will be recorded in the eCRF but do not need to be reported to Cognizant/Takeda. For SAEs in patients not taking Takeda drugs, if there is a reasonable possibility that the non-Takeda drug caused the event, local reporting requirements should be followed.

The Takeda Department of Pharmacovigilance or designee will be provided access to the database to view the information.

All SAEs and non-serious AEs collected during the study will be included in the study report and all SAEs and AEs, as required, will be reported by the sponsor to the regulatory agencies in accordance with reporting requirements.

6.5.4 Assessment of Severity

The healthcare provider will use the most recent version of the National Cancer Institute the Common Terminology Criteria for Adverse Events in the evaluation of AEs.

Severity grades will be collected on the AE/SAE form for patients taking Takeda Oncology products:

- **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 IADL*.
- **Grade 3 Severe or medically significant but not immediately life-threatening**: hospitalization indicated; disabling; limiting self-care ADL**.
- **Grade 4:** Life-threatening consequences; urgent intervention indicated.
- **Grade 5:** Death related to AE

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

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

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than 5 options for Grade selection. Grade 5 (death) is not appropriate for some AEs and therefore is not an option.

Note that "severe" is not synonymous with "serious." An AE may be assessed as severe without meeting the criteria for an SAE.

6.5.5 Relationship to Treatment

The following definitions of relationship should be used to characterize the suspected causality of each SAE as either related or not related to any MM treatment including ixazomib or bortezomib. This assessment should be based on the healthcare provider's consideration of all available information about the event, including temporal relationship to drug administration, recognized association with drug product/class, pharmacological plausibility, and alternative etiology (e.g., underlying illness, concurrent conditions, concomitant treatments):

- **Related**: There is a reasonable possibility that the drug caused the event.
- **Not related**: There is not a reasonable possibility that the drug caused the event.

6.5.6 Other Safety Information

Other Safety Information

The following events, whether or not they are associated with an AE, should be reported to Takeda within 24 hours of a Takeda employee or representative (e.g., contract research organization) learning about it:

Special situation reports:

- **Pregnancy** in a female patient, or female partner of a male patient, within 90 days of the patient's last dose of a Takeda drug.
- **Infant exposure due to breastfeeding**
- **Overdose:** Accidental or intentional overdose. Clinical judgement should always be applied.
- **Drug Abuse, misuse or medication error:** Intentional excessive use of a drug, which is accompanied by harmful physical or psychological effects. Any unintentional error in

the prescribing, dispensing, or administration of a drug while in the control of the healthcare professional or patient.

- **Suspected transmission of an infectious agent** by a Takeda product.
- **Lack of efficacy** of Takeda product.
- **Accidental occupational exposure:** This refers to exposure to a drug, as a result of one's professional or non-professional occupation.
- **Medication error:** This refers to any unintentional error in the prescribing, dispensing, or administration of a drug while in the control of the healthcare professional or patient.
- **Use of falsified** medicinal product

Product Quality Issues (Product defects related to):

- **Safety**
- **Identity**
- **Strength**
- **Quality, purity, or physical characteristics**
- **Packaging or design of the product**
- **Labelling**

6.5.7 Takeda Product Complaints or Product Quality Issues

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, physical characteristics or stability of a drug product. Individuals who identify a potential Takeda product complaint situation should immediately contact Takeda and report the event. Product quality issues may be reported with or without an associated AE. Whenever possible, the associated Takeda product should be maintained in accordance with the label instructions pending further guidance from a Takeda Quality representative.

For Takeda Product Complaints

Phone: 1-844-ONC-TKDA (1-844-662-8532)
E-mail: GlobalOncologyMedinfo@takeda.com
Fax: 1-800-881-6092
Hours: Mon-Fri, 9 a.m. – 7 p.m. ET

Product complaints in and of themselves are not AEs. If a product complaint results into an SAE, an SAE form should be completed and sent to Millennium Pharmacovigilance as indicated in Section 6.5.3.

6.6 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

Pregnancy in a female patient, or female partner of a male patient, must be reported if the event occurs within 90 days of the patient's last dose of a Takeda drug.

If a woman becomes pregnant while taking any Takeda product, this must be captured in the eCRF. The outcome of the pregnancy should be reported once known.

If a female partner of a male patient becomes pregnant while the male patient is being treated with Takeda product, this must also be captured in the eCRF. Every effort should be made to determine the final pregnancy outcome. There will be a separate ICF for data collection of the pregnant partner and the newborn.

7 Statistical and Analytical Plan

A complete description of the statistical analyses and methods will be provided in the SAP, which will be finalized prior to database lock. The detailed analysis plan will be based on the GPP (Epstein 2005) and the Agency for Healthcare Research and Quality's Registries for Evaluating Patient Outcomes: A User's Guide (Agency for Healthcare Research and Quality 2014).

7.1 Outcome Measures

7.1.1 Primary Outcome Measures

The primary outcome measures for describing contemporary, real-world patterns of patient characteristics, clinical disease presentation, therapeutic regimen chosen, and clinical outcomes in patients with ND MM, and patients with R/R MM are:

- Patient demographics, co-morbidities;
- Diagnostic and presenting symptoms; ECOG performance status, frailty status, assessment of myeloma cytogenetic risk, and ISS/R-ISS stage.
- Myeloma-directed therapeutic regimens, duration of each line of therapy, stem cell transplant status.
- Overall survival, progression status and response to each regimen (per International Myeloma Working Group [IMWG]) criteria [Durie BG, et al. 2006]), and time to next therapy.

7.1.2 Secondary Outcome Measures

The secondary outcome measures of this study are:

- Patterns of treatment combinations, sequencing, and retreatment; and clinical outcomes for different strategies.
- Treatment duration and clinical outcomes between continuous treatment and fixed duration treatment strategy.
- Factors associated with treatment initiation, treatment modification, or treatment change over time, including whether treatment at relapse was initiated due to biochemical progression versus symptomatic progression.

- Health-related quality of life, treatment satisfaction, and HRU.
- Associations between patient characteristics, clinical disease presentation, therapeutic regimen chosen, and clinical outcomes.
- All SAEs and non-serious AEs leading to treatment discontinuation (temporary and permanent) or drug modification, and second primary malignancies.

7.2 Sample Size Calculations

The study will attempt to enroll approximately 4200 patients globally. The patients included will receive various treatment regimens as determined by their healthcare provider. The planned sample size is intended to provide a sufficient number of patients to characterize treatments in a broad population. Enrollment will include approximately 50% ND MM and 50% R/R MM patients. Patient numbers will be capped at the site level.

The planned sample size will maintain a reasonable level of estimation precision of statistics such as proportions and event rates, as well as some level of statistical power to detect differences in studies subgroups. The justifications are given below.

The Score method for a 95% confidence interval (CI) of a proportion (p) is given by [2np + z^2 ± z * SQRT (z^2 + 4npq)] / 2(n + z^2) (Newcombe 1998), where:

SQRT = square root n = group size

p = proportion estimate

z = standard normal with a 2-tailed probability alpha q = 1 – p

Table 7-1 provides CIs of estimated proportions for individual subgroups. According to the table, a sample size of 270 patients, for a proportion estimate of 0.5 the 95% CI is from 0.441 to 0.559, and for a proportion estimate of 0.9 the 95% CI is from 0.858 to 0.930.

Table 7-1 Confidence Intervals of Estimated Proportions Based on Sample Size for Individual Groups

Proportion	n	LCL	UCL		Proportion	n	LCL	UCL
0.5	100	0.404	0.596		0.5	1000	0.469	0.531
0.6	100	0.502	0.691		0.6	1000	0.569	0.630
0.7	100	0.604	0.781		0.7	1000	0.671	0.728
0.8	100	0.711	0.867		0.8	1000	0.774	0.824
0.9	100	0.826	0.945		0.9	1000	0.880	0.917
0.5	270	0.441	0.559		0.5	4200	0.485	0.515
0.6	270	0.541	0.657		0.6	4200	0.585	0.615
0.7	270	0.643	0.752		0.7	4200	0.686	0.714
0.8	270	0.748	0.843		0.8	4200	0.788	0.812
0.9	270	0.858	0.930		0.9	4200	0.891	0.909

Abbreviations: LCL, lower confidence limit; UCL, upper confidence limit.

Comparisons between proportions of 2 groups are based on the reference proportion (p0) and the effect size (i.e., the difference, delta) between the proportions. Table 7-2 provides sample sizes obtained from SAS® PROC POWER using Pearson's chi-squared test with a 2-sided critical level alpha of 0.05 and 80% power.

Table 7-2 Sample Size Needed to Detect Proportion Differences Between Sub-Groups

p0	delta	n per group		p0	delta	n per group		p0	delta	n per group
50%	2%	9806		50%	8%	609		50%	14%	196
60%	2%	9336		60%	8%	564		60%	14%	176
70%	2%	8080		70%	8%	471		70%	14%	141
80%	2%	6039		80%	8%	329		80%	14%	90
50%	4%	2448		50%	10%	388		50%	16%	149
60%	4%	2311		60%	10%	356		60%	16%	133
70%	4%	1977		70%	10%	294		70%	16%	105
80%	4%	1447		80%	10%	199		80%	16%	64
50%	6%	1086		50%	12%	268				
60%	6%	1016		60%	12%	244				
70%	6%	859		70%	12%	198				
80%	6%	615		80%	12%	131				

A formal hypothesis will not be tested in this study.

A sample size of 268 in each of any 2 comparison subgroups will have at least 80% power to detect a difference between 2 proportions given the true difference is at least 12%.

7.3 Analysis Sets

All patients included in the study will be considered for analysis. Disposition, demographic, baseline data at inclusion, treatment, and outcomes will be summarized by cohorts for all patients.

7.4 Subgroups of Interest

Subgroup analysis may be performed using baseline covariates of interest, including:

- Two distinct cohorts: 1) ND MM and 2) R/R MM
- Geographic region and country
- Type of treatment facility – academic versus community
- Patient attributes (demographics and clinical presentation), such as frail patients, elderly patients, and patients with baseline comorbidities of interest (e.g., renal and cardiac

function, peripheral neuropathy)

- Disease presentation – stage, risk category
- Treatment choices

Other subgroups may be defined in the SAP.

7.5 Statistical Analysis Methodology

Since this is a non-interventional, observational study, there can be potential complicated confounding between treatment assignments and outcomes, extensive missing data, and included patient samples which do not represent real world clinical practices. Therefore, all analyses from this study should be considered exploratory in nature.

Statistical analysis will be performed using SAS® software (SAS Institute, Inc, Cary, North Carolina) Version 9.2 or later.

Population characteristics (including demographics, medical conditions, duration of disease, and types of therapy used at study entry) and all relevant primary and secondary outcomes measures will be summarized as mean, standard deviation, minimum, maximum, median, 25th and 75th percentile, and 95% CI of the mean for continuous variables as appropriate; and count and proportion with 95% CI of the proportion for categorical data as appropriate. Counts of non- missing observations will be included. Event rates (e.g., per 1000 patient-years) and 95% CIs for selected outcomes will also be summarized. Descriptive statistics will be used to describe treatment patterns, safety assessments, clinical outcomes, economic outcomes, and HRQoL self-reported outcomes observed during the study period. Sample representativeness will be assessed based on published statistics, if available.

7.5.1 Primary Analysis

Disease presentation and patient characteristics, therapies, and clinical outcomes will be summarized descriptively, as explained above for the Primary Outcome Measures (Section 7.1.1). In addition, summaries will be performed within selected subgroups (Section 7.4), based on clinically relevant cohorts of interest.

7.5.2 Secondary Analyses

Healthcare resource utilization, treatment satisfaction, and patient self-reported HRQoL outcomes will be summarized using descriptive statistics. Associations between (a) MM therapy

regimens, disease attributes (e.g., stage and risk category), and patient attributes (e.g., age and frailty status); and (b) patient HRQoL and HRU will be assessed through confounding-adjusted regression. Changes in HRQoL will be assessed with longitudinal analysis.

Serious AEs and non-serious AEs leading to treatment discontinuation (temporary and permanent) or drug modification, and second primary malignancies will be summarized according to the treatment a patient receives at the time of onset, or to the last treatment a patient receives within a time interval (to be pre-specified in the SAP) number of days prior to the time of onset. Details will be provided in the SAP.

Patterns of treatment combinations, sequencing, repeated therapies, durations, and treatment strategies (e.g. continuous versus fixed duration) will be summarized using descriptive statistics and within some of the subgroups outlined in Section 7.4. Factors associated with treatment initiation, modification, or change at relapse will also be described with descriptive statistics.

To address potential confounding due to the observational nature of the study design, multivariable adjustment methods, such as the Cox Proportional Hazards regression models (Klein et al. 2003), propensity score based regressions, or propensity score matching techniques (Rosenbaum et al. 1983) will be used for the exploratory analyses (Sturmer et al. 2006) of clinical outcomes (e.g. OS, progression status and response to each regimen, and time to next therapy) and therapy regimens, disease presentation and patient characteristics. This will provide adjusted estimates for some of the comparisons of clinical outcomes. Important model covariates to minimize bias include number and type of prior therapies, age, sex, race, cytogenetic risk, ISS stage, frailty status, and other appropriate factors. Patterns of therapy regimens may be considered in the statistical models.

Contemporary practices and treatment dose relationships with outcomes will also be explored.

7.5.3 Interim Data Summaries

Data summaries will be generated while the study is on-going in order to summarize patient characteristics and to generate data for publication, as appropriate.

Interim data summaries and reports, as well as grouped reports for patient organizations and other healthcare providers, are planned to understand initial baseline characteristics at inclusion. Additional interim analyses will be performed on a biannual basis or as directed by the Steering Committee (SC). Details of the interim data summaries will be provided in the SAP.

7.5.4 Final Analysis

The final analysis will be conducted approximately 5 years after the last patient is enrolled. The final report will encompass all planned analyses, including a description of the complete study population, as described above and in the SAP.

7.5.5 Study Reports

At least 3 study reports are planned for this study. The initial report is planned after at least 1000 patients have been included. A second study report is planned to occur after 2000 patients are enrolled of which 200 patients have been dosed with ixazomib. Additional interim study report(s) may be generated as directed by the SC. The final analysis report will be conducted as described in Section 7.5.4. The planned analyses for each study report will be described in the SAP.

7.6 Data Quality Control

The handling of data, including data quality assurance, will comply with regulatory guidelines (e.g., GPP) and applicable Takeda standards.

To increase the quality and consistency of data in this study, training will be provided for the study coordinator and principal healthcare provider.

7.6.1 Data Management

The healthcare provider agrees to maintain accurate eCRFs and patient medical charts as part of the case histories.

The principal healthcare provider or study coordinator at each participating site will submit study data via a secure internet data capture system maintained by PPD and accessed by the PPD project staff.

Clinical data management will be performed in accordance with applicable Takeda standards and data cleaning procedures to ensure the integrity of the data, as outlined in the data management plan. The members of the SC will have access to summarized statistical data. Takeda, the study biostatisticians and epidemiologists, the data analysts, and the project coordinators assigned to the study by PPD will have access to individual hospital, clinic, or patient-level masked data.

All PPD staff involved in the handling of data has passed the collaborative institutional training initiative course on the protection of human research patients and are trained on Food and Drug

Administration (FDA) 21 Code of Federal Regulations (CFR), International Council for Harmonisation (ICH), GPP, and other guidelines and regulations as described in Section 8.2.

8 Ethics

8.1 Independent Ethics Committee or Institutional Review Board

Independent ethics committee (IEC)/Independent review board (IRB) must be constituted according to the applicable local law and requirements, and only when required. Each site will require documentation noting all names and titles of members who comprise the respective IEC/IRB. If any member of the IEC/IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

When IEC/IRB are required according to the applicable local law and requirements, the protocol, informed consent, advertisements to be used for the recruitment of study patients (if permitted), and any other written information regarding this study to be provided to the patient, including questionnaires, must be approved by the IEC/IRB before study onset.

Documentation of all IEC/IRB approvals will be maintained by the site and will be available for review by Takeda or its designee.

All IEC/IRB approvals should be signed by the IEC/IRB chairman or designee and must identify the IEC/IRB name and address, the study protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

Sites must adhere to the requirements stipulated by their respective IEC/IRB. This may include notification to the IEC/IRB regarding any amendments or updates to the documents initially submitted, materials intended for viewing by patients, local safety reporting requirements and reports, and updates regarding the ongoing review of the healthcare provider.

8.2 Ethical Conduct of the Study

This study will be conducted in accordance with the following guidance:

- Local ethical guidelines
- European directives on protection of human patients in research
- Declaration of Helsinki
- The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Guidelines

- Good Pharmacoepidemiology Practice Guidelines

- Other local, national-specific relevant guidelines, laws, or regulations

Each participating principal healthcare provider will be responsible for assuring Takeda or designee that this study is conducted in accordance with all regulations of their hospital.

8.3 Patient Information and Consent

A written informed consent in compliance with local regulatory authority regulations and FDA Title 21 CFR Part 50, ICH, GPP, and other local, national-specific relevant guidelines and regulations, including authorization to use the patient medical records, shall be obtained from each patient before entering the study. An informed consent template may be provided to study sites. If the ICF is revised during the course of the study, all active participating patients must sign the revised form. There will be a separate ICF for data collection of the pregnant partner and the newborn.

Before recruitment and inclusion in the study, each patient will be given a full explanation of the study and be allowed to read the approved ICF. The ICF will have the provision of a checkbox to be checked off so that the site can contact the patient's caregiver when needed. Once the healthcare provider is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent (and assent if applicable) to participate in the study by signing the ICF.

The healthcare provider shall retain the signed original ICF(s) and give a copy of the signed original form to the patient.

9 Healthcare Provider's Obligations

The following administrative items are meant to guide the healthcare provider in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IEC/IRB but may not result in protocol amendments.

9.1 Confidentiality

Patient data will not be released without the written permission of the patient, except as necessary for monitoring and auditing by Takeda, its designee, or regulatory authorities.

The healthcare provider and all employees and co-workers involved with this non-interventional, observational study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from Takeda or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2 Financial Disclosure and Obligations

Healthcare providers are required to provide financial disclosure information to allow Takeda to submit the complete and accurate certification or disclosure statements required under FDA 21 CFR 54, ICH, and local, national specific relevant guidelines. In addition, the healthcare provider must provide to Takeda a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither Takeda nor designee is financially responsible for testing or treatment of any medical condition that may be detected. In addition, in the absence of specific arrangements, neither Takeda nor designee is financially responsible for the treatment of the patient's disease.

9.3 Study Conduct and Adherence to Protocol

The healthcare provider agrees that the study will be conducted in accordance with the protocol, the principles of the declaration of Helsinki and GPP guidelines, and all national, state, and local, specific relevant guidelines, laws or regulations.

9.4 Adverse Events and Study Report Requirements

By participating in this non-interventional, observational study, the healthcare provider agrees

to submit reports of SAEs according to the timeline and method outlined in the protocol. In addition, the healthcare provider agrees to submit reports to the study site IEC/IRB as stipulated by his or her respective IEC/IRB.

9.5 Healthcare Provider's Final Report

Upon completion of the study, the healthcare provider, where applicable, should inform the institution; the healthcare provider/institution should provide the IEC/IRB with a summary of the study's outcome and Takeda and regulatory authorities with any reports required.

9.6 Records Retention

PPD will retain study data for a minimum of 3 years following the final publication of study findings or discontinuation of the study, or as per local legislation. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Takeda. It is the responsibility of Takeda to inform the healthcare provider/institution as to when these documents no longer need to be retained.

9.7 Publications

Takeda owns all data submitted, results, reports, findings, discoveries, and any other information collected during this study. Therefore, Takeda may use data from the present study, or in the form of a report, with or without comments and with or without analysis, in order to submit to government or health authorities where required by law.

PPD will retain masked data to perform analyses for use in scientific publications in support of the SC, which has full rights to publication based on data from this study and will have access to the data allowing for appropriate scientific review and reporting of study results.

Masked, grouped subsets of these data may be shared with qualified researchers for development of specific analyses that are approved by both the SC and Takeda.

The SC is committed to present and publish the results of this study, using only clean and quality-controlled data in order to ensure the accuracy of published results. Additional details on how publications will be coordinated will be presented in the SC charter.

10 Study Management

10.1 Monitoring

10.1.1 Steering Committee

Steering Committee of MM experts, selected by Takeda and representing the different participating countries, will provide support and advice for this study, and will oversee its scientific validity.

Details on the SC responsibilities, on the members of the SC, and on the Executive Committee to act on behalf of the SC between regular SC meetings, will be provided in the SC charter.

10.1.2 Monitoring of the Study

The monitor, as a representative of Takeda, has the obligation to follow the study closely. Takeda and/or designee will guarantee a sufficient study data monitoring level, as detailed in site management plan.

All aspects of the study will be monitored by Takeda, the SC, or their designee, for compliance with applicable government regulation with respect to current GPP guidelines and current standard operating procedures.

10.1.3 Inspection of Records

Takeda or designee may visit the study site to evaluate study conduct and compliance with protocols, standard operating procedures, GPP guidelines, and applicable regulatory requirements. The Takeda quality assurance unit, independent of the Clinical Research Department, is responsible for determining the need for (and timing of) a study site visit. Each healthcare provider must accept that regulatory authorities and Takeda or PPD representatives may conduct inspections to verify compliance of the study with GPP guidelines.

Healthcare providers and their relevant personnel must be available during the monitoring visits and possible audits or inspections and sufficient time must be devoted to the process.

10.2 Management of Protocol Amendments

10.2.1 Modifications of the Protocol

No changes or amendments to this protocol may be made by the participating healthcare providers or administrators or by the sponsor after the protocol has been agreed to and signed by both parties unless such change(s) or amendment(s) has/have been fully discussed and agreed upon by the participating healthcare providers or administrators and the sponsor.

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IEC/IRB, except when the change involves only logistics or administration. Amendments must be reviewed and approved by Takeda or its designee.

10.3 Study Termination

Takeda can decide at any time and for any reason to prematurely stop or to interrupt the study. This decision will be communicated in writing to the participating healthcare providers and the IRB/IECs.

The end of this non-interventional, observational study is defined as the date on which all patients in the study have completed at least 5 years of follow-up, are lost to follow-up, or have died.

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12 Appendices

Table 12-1 Modified IMWG Diagnosis Criteria for Active (Symptomatic) Myeloma

Diagnosis of Multiple Myeloma Requires:

Clonal bone marrow plasma cells ≥10 percent, or extramedullary plasmacytoma (the presence of a plasma cell tumor), plus at least one of the following two features:

1. Evidence of damage to the body as a result of the plasma cell growth damage:
- Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
- Renal insufficiency: creatinine clearance <40 mL per min or serum creatinine >177 µmol/L (>2 mg/dL)
- Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
- Bone lesions: 1 or more osteolytic lesions on skeletal radiography, CT, or PET-CT

or

2. Detection of one of the following findings:
- ≥60 percent plasma cells in the bone marrow
- Free light chain (FLC) ratio of 100 or more (provided involved FLC level is at least 100 mg/L)
- MRI showing more than one lesion (involving bone or bone marrow)

Source: Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538-48.

Table 12-2 Katz Index of Independence in Activities of Daily Living

Activities Points (1 or 0)	**Independence** (1 Point) **NO** supervision, direction or personal assistance	**Dependence** (0 Points) **WITH** supervision, direction, personal assistance or total care.
BATHING **Points:**_____	**(**1 POINT) Bathes self completely or needs help in bathing only a single part of the body such as the back, genital area or disabled extremity.	**(0 POINTS)** Need help with bathing more than one part of the body, getting in or out of the tub or shower. Requires total bathing.
DRESSING **Points:**_____	**(1 POINT)** Get clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes.	**(0 POINTS)** Needs help with dressing self or needs to be completely dressed.
TOILETING **Points:**_____	**(1 POINT)** Goes to toilet, gets on and off, arranges clothes, cleans genital area without help.	**(0 POINTS)** Needs help transferring to the toilet, cleaning self or uses bedpan or commode.
TRANSFERRING **Points:**_____	**(1 POINT)** Moves in and out of bed or chair unassisted. Mechanical transfer aids are acceptable.	**(0 POINTS)** Needs help in moving from bed to chair or requires a complete transfer.
CONTINENCE **Points:**_____	**(1 POINT)** Exercises complete self-control over urination and defecation.	**(0 POINTS)** Is partially or totally incontinent of bowel or bladder.
FEEDING **Points:**_____	**(1 POINT)** Gets food from plate into mouth without help. Preparation of food may be done by another person.	**(0 POINTS)** Needs partial or total help with feeding or requires parenteral feeding.
TOTAL POINTS:_____ **SCORING:** 6 = High (*patient independent)* 0 = Low *(patient very dependent)*		

Table 12-3 Lawton – Brody Instrumental Activities of Daily Living Scale

Scoring: For each category, circle the item description that most closely resembles the client's highest functional level (either 0 or 1).			
A. Ability to Use Telephone		**E. Laundry**	
1. Operates telephone on own initiative-looks up and dials numbers, etc.	1	1. Does personal laundry completely	1
		2. Launders small items-rinses stockings, etc.	1
2. Dials a few well-known numbers	1	3. All laundry must be done by others	
3. Answers telephone but does not dial	1		0
4. Does not use telephone at all	0		
B. Shopping		**F. Mode of Transportation**	
1. Takes care of all shopping needs independently	1	1. Travels independently on public transportation or drives own car	1
2. Shops independently for small purchases	0	2. Arranges own travel via taxi, but does not otherwise use public transportation	1
3. Needs to be accompanied on any shopping trip	0	3. Travels on public transportation when accompanied by another	1
4. Completely unable to shop	0	4. Travel limited to taxi or automobile with assistance of another	0
		5. Does not travel at all	0
C. Food Preparation		**G. Responsibility for Own Medications**	
1. Plans, prepares and serves adequate meals independently	1	1. Is responsible for taking medication in correct dosages at correct time	1
2. Prepares adequate meals if supplied with ingredients	0	2. Takes responsibility if medication is prepared in advance in separate dosage	0
3. Heats, serves and prepares meals, or prepares meals, or prepares meals but does not maintain adequate diet	0	3. Is not capable of dispensing own medication	0
4. Needs to have meals prepared and served	0		
D. Housekeeping		**H. Ability to Handle Finances**	
1. Maintains house alone or with occasional assistance (e.g. "heavy work domestic help")	1	1. Manages financial matters independently (budgets, writes checks, pays rent, bills, goes to bank), collects and keeps track of income	1
2. Performs light daily tasks such as dish washing, bed making	1	2. Manages day-to-day purchases, but needs help with banking, major purchases, etc.	1
3. Performs light daily tasks but cannot maintain acceptable level of cleanliness	1	3. Incapable of handling money	0
4. Needs help with all home maintenance tasks	1		
5. Does not participate in any housekeeping tasks	0		
Score		**Score**	
		Total score_____	

A summary score ranges from 0 (low function, dependent) to 8 (high function, independent) for women and 0 through 5 for men to avoid potential gender bias.

Table 12-4 Charlson Comorbidity Index

Predicts 10-year survival in patients with multiple comorbidities (Charlson et al. 1987).

Age	<50 years 50-59 years 60-69 years 70-79 years ≥80 years	0 1 2 3 4
Diabetes mellitus	None Uncomplicated End-organ damage	0 1 2
Liver disease	None Mild Moderate to severe	0 1 3
Malignancy	None Any leukemia, lymphoma, or localized solid tumor Metastatic solid tumor	0 2 6
AIDS	No Yes	0 6
Moderate to severe CKD	No Yes	0 2
CHF	No Yes	0 1
Myocardial infarction	No Yes	0 1
COPD	No Yes	0 1
Peripheral vascular disease	No Yes	0 1
CVA or TIA	No Yes	0 1
Dementia	No Yes	0 1
Hemiplegia	No Yes	0 2
Connective tissue disorder	No Yes	0 1
Peptic ulcer disease	No Yes	0 1
Total score_____ Note: liver disease, diabetes, and cancer inputs are mutually exclusive (e.g. do not give points for both "mild liver disease" and "moderate or severe liver disease").		

10-year survival = $0.983^{(e^{CCI \times 0.9})}$, where CCI = Charlson Comorbidity Index.