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

Protocol Approve Date: 12 February 2016

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

- Named persons or organizations associated with the study.
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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 1.0
Date of Protocol:	12 February 2016

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

Protocol Approvers

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For signatures, see Appendix 12.1.

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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 as a result of this study. However, patients will be asked to complete surveys (patient self-reported outcomes [PROs]) at home or at routine 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 and patient presentation, treatment patterns, and clinical outcomes associated with MM and the impact of treatment on safety, effectiveness, and quality of life, 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 disease and patient presentation, therapies, and clinical outcomes in both patients with newly diagnosed and not yet relapsed [ND] MM and relapsed/refractory [R/R] MM, by (a) geographic region, (b) ND MM and R/R MM, (c) patient attributes (demographics and clinical characteristics),

(d) disease characteristics (stage, risk category),(e) treatment choices, and (f) clinical outcomes.

Secondary objectives:

- Describe patterns of treatment combinations, sequencing, and repeated therapies; and the clinical outcomes for different strategies.
- Describe treatment duration and assess clinical outcomes of different types of treatment strategies (e.g., continuous treatment compared to intermittent treatment).
- Describe factors associated with treatment initiation or treatment change at relapse including biochemical progression and symptomatic progression.
- Describe factors associated with treatment modification.
- Describe health related quality of life (HRQoL) and healthcare resource utilization (HRU) among MM patients.
- Explore associations between disease and patient presentation, choice of therapy, 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 particular 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 as a result of this study. However, patients will be asked to complete surveys (PROs) at home or at routine visits. Epidemiological methods shall be used for the analysis of collected data.

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. Patient self-reported outcomes

	will be collected using a secure electronic data collection system (technical devices and/or paper survey forms will be provided for patients who cannot access the internet). Patients will complete HRQoL self-reported outcomes at inclusion and at predefined intervals following initiation of therapy. Patients will not be asked to travel to the site only for the purpose of this study.
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 5 years of follow-up, are lost to follow-up, or have died.
Assessments:	Demographic and biometric data; general medical history; and MM history, baseline data at inclusion, and disease characteristics, 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: European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC QLQ-C30), EORTC Quality of Life Questionnaire - 20-item Multiple Myeloma Module (EORTC QLQ-MY-20), Worker Productivity and Activity Impairment Questionnaire for General Health (WPAI-GH), 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9), and EuroQol patient-reported, 5-dimension, 5-response outcome instrument (EQ-5D-5L). 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. 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 surveys. Patients can also be enrolled in an observational or interventional study while participating in this study.
Sample Size:	The study will attempt to enroll a minimum of 5000 patients globally. The planned sample size is intended to provide a sufficient number of 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%.
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 treatment patterns, safety assessments, clinical outcomes, economic outcomes, and HRQoL outcomes observed during the study period. Disease and patient presentation, therapies, and clinical outcomes will be summarized descriptively by geography regions, patient characteristics, disease characteristics, and predictors of treatment choice. Also, treatment patterns will be summarized according to subgroups based on clinically relevant factors. Multivariable analysis of economic and PROs will be conducted

	using appropriate regression models. HRQoL outcomes will be summarized using descriptive statistics and longitudinal analysis. All 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:	12 February 2016

List of Abbreviations

Abbreviation	Definition
ADL	Activities of daily living
AE	Adverse event
CFR	Code of Federal Regulations
CI	Confidence interval
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	EuroQol patient-reported, 5-dimension, 5-response outcome instrument
QLQ-C30	Quality of Life Questionnaire – 30 item Cancer
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
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
IRB	Independent review board
ISS	International Staging System
MM	Multiple myeloma
MRD	Minimal residual disease
NCCN	National Comprehensive Cancer Network
ND	Newly diagnosed and not yet relapsed
OS	Overall survival
PFS	Progression-free survival
PRO	Patient self-reported outcomes
QALY	Quality adjusted life year
QLQ-MY-20	Quality of Life Questionnaire - 20-item Multiple Myeloma Module
R/R	Relapsed/refractory

Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Steering Committee
TSQM	Treatment Satisfaction Questionnaire for Medication
TSQM-9	9-item Treatment Satisfaction Questionnaire for Medication
US	United States
WPAI	Worker Productivity and Activity Impairment Questionnaire
WPAI-GH	Worker Productivity and Activity Impairment Questionnaire-General Health

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). The introduction of novel classes of agents with increased efficacy, including proteasome inhibitors (ixazomib, bortezomib, and carfilzomib) 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

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 and patient presentation, treatment patterns, and clinical outcomes associated with MM and the impact of treatment on safety, effectiveness, and quality of life, 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 disease and patient presentation, therapies, and clinical outcomes in both patients with newly diagnosed and not yet relapsed [ND] MM, and patients with relapsed/refractory [R/R] MM, by:

- Geographic region
- ND MM and R/R MM
- Patient attributes (demographics and clinical characteristics)
- Disease characteristics (stage, risk category)
- Treatment choices and,
- Clinical outcomes.

2.2 Secondary Objectives

The secondary objectives of this study are to

- Describe patterns of treatment combinations, sequencing, and repeated therapies; and the clinical outcomes for different strategies.
- Describe treatment duration and assess clinical outcomes of different types of treatment strategies (e.g., continuous treatment compared to intermittent treatment).
- Describe factors associated with treatment initiation or treatment change at relapse including biochemical progression and symptomatic progression.
- Describe factors associated with treatment modification.
- Describe health related quality of life (HRQoL) and healthcare resource utilization (HRU) among MM patients.

- Explore associations between disease and patient presentation, choice of therapy, 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 as a result of this study. However, patients will be asked to complete surveys (patient self-reported outcomes [PROs]) at home or at routine 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. Patient self-reported outcomes will be collected using a secure electronic data collection system (technical devices and/or paper survey forms will be provided for patients who cannot access the internet). Patients will complete HRQoL self-reported outcomes at inclusion and at predefined intervals following initiation of therapy.

This study will attempt to enroll a minimum of 5000 patients globally. 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 5 years of follow-up, are lost to follow-up, or have died. Patients will not be asked to travel to the site only for the purpose of 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 6-1.

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 surveys (PROs) at home or at routine visits.

The need for HRQoL endpoints in MM studies in order 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. Indeed, EORTC QLQ-C30 is the most commonly used HRQoL measure in cancer clinical trials, and more specifically in MM studies (Gulbrandsen et al. 2004; Dubois et al. 2006; Lawton and Brody 1969; Lee et al 2008; Kvam et al. 2010; Alegre et al. 2012; Delforge et al. 2012). Besides the original psychometric validation (Aaronson et al. 1993), the measurement properties of the EORTC QLQ-C30, including the clinically meaningful difference in scores of the global quality of life health status scale, have also been determined in MM populations (Wisløff et al. 1996; Kvam et al. 2011). In addition to EORTC QLQ-C30, HRQoL outcomes will also be assessed by the EORTC Quality of Life Questionnaire - 20-item Multiple Myeloma Module (QLQ-MY-20) (Stead et al. 1999), which has demonstrated excellent measurement properties (validity, reliability, responsiveness). Additional information on these questionnaires is provided in Section 6.3.5.1.

The impact of treatment administration burden on patients (many of whom are elderly and infirm, or who may live a long distance from treatment centers) will be captured by measuring work productivity and leisure time loss using the Worker Productivity and Activity Impairment Questionnaire (WPAI) (Reilly et al. 1993). The frailty index is based on the Charlson Comorbidity Index, the Katz Index of Independence in Activities of Daily Living (ADL) (Katz 1983), and the Lawton Instrumental Activities of Daily Living (IADL) (Lawton and Brody 1969) scales, all of which will be completed by the treating healthcare provider. A

number of health-technology assessments, such as those in Scandinavian countries, consider these indirect costs in their coverage deliberations.

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 6.3.5.3.

Finally, the EuroQol patient-reported, 5-dimension, 5-response outcome instrument (EQ-5D-5L) (Herdman et al. 2011) is a self-reported preference based measure of health status suitable for calculating quality adjusted life year (QALY) to inform economic evaluations, and it is widely accepted by heath-technology assessment agencies worldwide; it has been commonly used in clinical-trial based economic evaluations (including in MM). Additional information on the EQ-5D-5L is provided in Section 6.3.5.4.

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 a minimum of 5000 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, or the end of the study, whichever comes first. This target is considered to be sufficient to achieve a satisfactory degree of precision and to provide valuable data on the study objectives (see Section 7.2).

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 in the course of their care. No additional treatments or procedures will be utilized for this study, although patients will be asked to complete surveys. 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 population 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:

- Is 18 years of age or older.
- Is experiencing one of the following:
    - Newly diagnosed and not yet relapsed MM with documented month and year of diagnosis, criteria met for diagnosis, stage, and MM-directed treatment history, including duration.
    - Relapsed/refractory MM with documented data in the medical record regarding diagnosis (month and year), prior exposure to classes of medications (e.g., proteosome inhibitors, immunomodulatory drugs), and number of previous lines of therapies.
- Is willing and able to sign informed consent to participate.
- Is willing and able to complete patient assessment questionnaires.

4.1.2 Exclusion Criteria

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

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

- Unable or unwilling to complete HRQoL and PROs.

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, South America, Australia, and Africa. In addition, this study has the potential to partner with MM registries or other observational MM studies, with the ultimate 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 healthcare provider for patients who may be included at their respective hospital or clinic, 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).

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 in the course of 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 an observational or interventional study that requires withdrawal from this study, the patient may be re-included into this study when the study is finalized.

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.

4.3.2 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 loss to follow-up if necessary. Every attempt will be made by the site to document the reason of study withdrawal.

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 in the course of 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 surveys.

6 Study Assessments and Collection of Data

Before collecting any data, all potential patients or legal guardians will sign an ICF. Patients and legal guardians 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.

6.1 Schedule of Assessments

The Data Collection Schedule is provided in Table 6-1. 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 6-1 Data Collection Schedule

Frequency	Inclusion	Quarterly from Inclusion	Every 6 months from Inclusion	Annually from Inclusion
Visit Window		**±1 month**	**±2 weeks**	**±1 month**
Site Assessments				
Local capabilities and routine practices in the management of patients with MM, size and type of site; age and training of investigator including time from specialization	X			X
Drugs and regimens currently used with respect to first-line and subsequent lines of therapy, usual dosage, duration, and endpoints of therapy.	X			X
Patient Assessments				
Obtaining informed consent	X			
Inclusion/Exclusion criteria	X			
Demographic information[1] and medical history[2]	X			
Date of initial diagnosis (month and year) and criteria used	X			
Diagnostic and presenting symptoms[3]	X			
Disease characteristics[4]	X			
Imaging results, ECOG performance status, and frailty status[4]	X	X		
Data from stem cell transplants	X	X		
Selected laboratory test results[5]	X	X		
MRD, GEP, FISH, and cytogenetic results (if available in clinical records)	X	X		
MM-directed treatment history (drug, route, regimen and duration) and best response to therapy[6]	X			
Number of previous lines of therapies used and prior exposure to classes of medications (e.g., proteosome inhibitors,	X			

Frequency	Inclusion	Quarterly from Inclusion	Every 6 months from Inclusion	Annually from Inclusion
Visit Window		**±1 month**	**±2 weeks**	**±1 month**
immunomodulatory drugs)[7]				
Documentation of each relapse		X		
Current treatments, treatment regimens (drug, route, regimen, and duration)	X			
Reason for clinic visit		X		
Treatment from previous visit[8]		X		
Effectiveness[9]		X		
Patient self-reported outcomes[10]	X		X	
Healthcare resource utilization[11]		X		
Safety assessments[12]	X	X		

Abbreviations: ADL, activities of daily living; AE, adverse event; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; GEP, gene expression profiling; IADL, instrumental activities of daily living scale; ISS, International Staging System; MM, multiple myeloma; MRD, minimum residual disease; ND, newly diagnosed and not yet relapsed; R-ISS, revised ISS; R/R, relapsed refractory.

1. Including age, sex, race, ethnicity (optional based on country requirements), height, weight, and geographic region.
2. General medical history, including medications, co-morbidities, and hospitalizations.
3. For ND MM: Diagnostic and presenting symptoms, including CRAB symptoms at diagnosis (calcium, renal, anemia [including hemoglobin levels], bone involvement, and bone marrow [percent of plasma cells]) and results at the time of diagnosis for M protein, serum protein electrophoresis, urine protein electrophoresis, and serum free light chain level or ratio, if available in clinical records.
   For ND and R/R: Diagnostic and presenting symptoms at most recent assessment (bone involvement and bone marrow [percent of plasma cells]) and results at the most recent assessment for M protein, serum protein electrophoresis, urine protein electrophoresis, and serum free light chain level or ratio, if available in clinical records.
4. Including but not limited to type of MM, risk category, sites of the disease, stage of the disease using the ISS and R-ISS, imaging results, Eastern Cooperative Oncology Group performance status, and frailty status. The frailty index will be based on the Charlson Comorbidity Index, the Katz Index of Independence in ADL, and the Lawton IADL scales, all of which will be completed by the treating healthcare provider.
5. Selected laboratory test results of known prognostic, predictive markers (e.g., LDH, beta-2 microglobulin, albumin, creatinine clearance), if available in clinical records.
6. For patients with ND MM only.

7. For patients with R/R MM only.
8. Including changes to treatment from previous visit including drug and duration, dose modifications, and reason(s) for medication changes (e.g., AE, patient request, treatment fatigue, financial toxicity, other).
9. Including response to each regimen; progression status on each regimen; time to next therapy; and vital status, date of death, and cause of death.
10. Including, European Organization for Research and Treatment of Cancer(EORTC) Quality of Life Questionnaire - C30 (EORTC QLQ-C30), EORTC Quality of Life Questionnaire - 20-item Multiple Myeloma Module (EORTC QLQ-MY-20), Worker Productivity and Activity Impairment-General Heath (WPAI-GH), 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9), and EuroQol patient-reported, 5-dimension, 5-response outcome instrument (EuroQol EQ-5D-5L).
11. Including but not limited to inpatient and intensive care unit admissions, reasons for admission, length of stay, outpatient clinic visits, and emergency room visits.
12. Serious AEs and non-serious AEs leading to treatment discontinuation (temporary and permanent) or drug modification, and second primary malignancies.

6.2 Site Assessments

6.2.1 Annual Multiple Myeloma Survey

The treating healthcare provider will complete the e-Practice Survey in the eCRF annually to:

- Characterize changes in local capabilities and routine practices in the management of patients with MM.
- Describe drugs and regimens currently used with respect to first-line and subsequent lines of therapy, usual dosage, and duration, and endpoints of therapy.

6.2.2 Site and Treating Healthcare Provider Demographics Survey

- Size and type of site.
- Age and training of the treating healthcare provider, including time from specialization.

6.3 Patient Assessments

The Steering Committee (SC) members may identify additional measurements that address important information gaps in MM care and outcomes during the study. Additional measurements identified after this protocol has been approved and will be included and submitted as a protocol amendment (see Section 10.2.1).

6.3.1 Demographic Information and Medical History

Demographic and biometric information will include age, sex, race, ethnicity (optional, based on country requirements), height, weight, and geographic region.

Medical history will include relevant medical history (including medications, co-morbidities, and hospitalizations).

6.3.2 Multiple Myeloma History and Baseline Data at Inclusion

Multiple myeloma baseline data at inclusion will include, but not be limited to the following:

- Date of initial diagnosis (including month and year) and criteria used.
- For ND MM: Diagnostic and presenting symptoms, including CRAB symptoms at diagnosis (calcium, renal, anemia [including hemoglobin levels], bone involvement, and bone marrow [percent of plasma cells]); and results at the time of diagnosis for M-protein, serum protein electrophoresis, urine protein electrophoresis, and serum free light chain level or ratio, if available in clinical records.
- For ND and R/R MM: Diagnostic and presenting symptoms at most recent assessment (bone involvement and bone marrow [percent of plasma cells]) and results at the most recent assessment for M protein, serum protein electrophoresis, urine protein electrophoresis, and serum free light chain level or ratio, if available in clinical records.
- Disease characteristics, including but not limited to type of MM, risk category, sites of the disease, stage of the disease using the International Staging System (ISS), revised ISS (R-ISS), imaging results, Eastern Cooperative Oncology Group (ECOG) performance status, and frailty status. The frailty index is based on the Charlson Comorbidity Index, the Katz Index of Independence in ADL (Katz 1983), and the Lawton IADL (Lawton and Brody 1969) scales, all of which will be completed by the treating healthcare provider.
- Dates and sites of stem cell transplants.
- Selected laboratory test results of known prognostic, predictive markers (e.g., LDH, beta-2 microglobulin, albumin, creatinine clearance), if available in clinical records.
- Minimal residual disease (MRD) results, gene expression profiling (GEP), FISH and cytogenetic results, if available in clinical records.

Imaging results, ECOG performance status, and frailty status, as well as the data from stem cell transplants, selected laboratory test results, MRD, GEP, FISH, and cytogenetic results, will be also recorded (if available) quarterly from inclusion.

For patients with ND MM, baseline data at inclusion will also include the following:

- MM-directed treatment history (drug, route, regimen and duration), best response to therapy.

For R/R patients, baseline data at inclusion will also include the following:

- Number of previous lines of therapies received.
- Prior exposure to classes of medications (e.g., proteosome inhibitors, immunomodulatory drugs).

For all patients, documentation of each relapse will be collected quarterly from inclusion to differentiate symptomatic relapse from biochemical-only relapse.

6.3.3 Multiple Myeloma Management

The following information will be collected to assess MM management:

- Current treatments, treatment regimens (drug, route, regimen, and duration) at inclusion.
- Changes to treatment from previous visit including drug and duration, dose modifications, and reason(s) for medication changes (e.g., AE, patient request, treatment fatigue, financial toxicity, other) at inclusion and quarterly during the study.

6.3.4 Effectiveness

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

- Response to each regimen.
- Progression status on each regimen.
- Time to next therapy.
- Vital status, date of death, and cause of death.

6.3.5 Patient Self-Reported Outcomes

Patient self-reported outcomes; including EORTC QLQ-C30, EORTC QLQ-MY-20, WPAI-GH, TSQM-9, and EuroQol EQ-5D-5L; will be assessed at inclusion, every 6 months, and at the time of MM-directed therapy change. Patient self-reported outcomes will be collected using a secure electronic data collection system (technical devices and/or paper survey forms will be provided for patients who cannot access the internet).

6.3.5.1 Health-Related Quality of Life

Health-Related quality of life will be assessed using the cancer specific EORTC QLQ-C30 and the QLQ-MY-20 at inclusion, every 6 months, and at the time of MM-directed therapy change. Assessments will be collected using a secure electronic data collection system.

6.3.5.1.1 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire

The EORTC QLQ-C30 (Aaronson et al. 1993) was designated to assess Health-Related Quality of Life (HRQoL) in a wide range of cancer patient populations and contains 30 items which include 5 functional scales (physical, role, cognitive, emotional, and social), 9 symptom scales (fatigue, nausea and vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial difficulties), and a global quality of life/health status scale. Most of the 30 items have 4 response levels (not at all, a little, quite a bit, and very much), with 2 questions relying on a 7-point numeric rating scale (very poor to excellent). Raw scores are converted into scale scores ranging from 0 to 100. For the functional scales and the global quality of life/health status scale, higher scores represent better HRQoL; whereas for the symptom scales lower scores represent better HRQoL.

6.3.5.1.2 Quality of Life Questionnaire - 20-item Multiple Myeloma Module

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. The QLQ-MY-20 has 4 independent subscales assessed on a 4-point Likert scale ranging from “Not at all” to “Very much”: 2 functional subscales (body image and future perspective), and 2 symptom subscales (disease symptoms and side-effects of treatment).

Three of the 4 QLQ-MY20 domains are multi-item scales: disease Symptoms (includes bone aches or pain, back pain, hip pain, arm or shoulder pain, chest pain, and pain increasing with activity); Side Effects of Treatment (includes drowsiness, thirst, feeling ill, dry mouth, hair loss, upset by hair loss, tingling hands or feet, restlessness/agitation, acid indigestion/heartburn, and burning or sore eyes); and Future Perspective (includes worry about death and health in the future, and thinking about illness). The Body Image scale is a single-item scale that addresses physical attractiveness. QLQ-MY20 domain scores are averaged and transformed linearly to a score ranging from 0 to 100. A high score for Disease Symptoms and Side Effects of Treatment represents a high level of symptoms or problems, whereas a high score for Future Perspective and Body Image represents better outcomes.

The EORTC QLQ-MY20 will be administered subsequent to the EORTC QLQ-C30.

6.3.5.2 Worker Productivity and Activity Impairment Questionnaire

The impact of treatment administration on the ability to work and perform regular activities in patients will be assessed by a specific version of the WPAI (Reilly et al. 1993); the WPAI-General Health (GH). The WPAI-GH version consists of 1 question assessing current employment status, 2 questions which assess the number of hours missed from work due to health problems and other reasons, 1 question which assesses the number of hours actually worked, 1 question assessing the impact of health affected productivity while working, and 1 question assessing the impact of health problems on non-work related daily activities. The WPAI-GH outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity and thus, worse outcomes.

6.3.5.3 Treatment Satisfaction Questionnaire for Medication

The TSQM-9 (Bharmal et al. 2009) will be administered 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 4 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.

6.3.5.4 EuroQol EQ-5D-5L

The EQ-5D-5L (Herdman et al. 2011) is a preference-based measure of health status suitable for calculating QALYs to inform economic evaluations. There are 2 versions of the EQ-5D available; the new EQ-5D-5L version has demonstrated improved measurement properties (e.g., improved sensitivity) compared to the EQ-5D-3L version. The new EQ-5D-5L version includes 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and 5 response levels for each domain (no problems, slight problems, moderate problems, severe problems, and extreme problems). The dimensions can be combined to describe the patient's health state. Patients are asked to indicate their health status by selecting the most appropriate level of severity on each of the 5 dimensions. Patient responses to the 5 dimensions of the EQ-5D-5L represent the patient's health state that is transformed to a utility score using preferably country-specific value sets for the calculation of QALYs that are used to inform economic evaluations.

6.3.6 Healthcare Resource Utilization

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

6.4 Safety Assessments

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

6.4.1 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 Reaction

For the purposes of this study, an adverse reaction is an AE that is considered related to drug 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.

6.4.2 Collecting and Recording of Adverse Events

All SAEs, regardless of causality, 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. All new second 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. All other non-serious AEs will not be collected.

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.

6.4.3 Reporting of Adverse Events

All SAEs, regardless of casualty, 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 base. Regardless of causality, SAEs, non-serious AEs leading to treatment discontinuation (temporary and permanent) or drug modification, and second primary malignancies will be reported by PPD via email alert to Takeda Department of Pharmacovigilance or designee within 24 hours after entry into the clinical database. 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.

The healthcare provider is required to report SAEs and AEs in accordance with the local regulatory requirements.

6.4.4 Assessment of Severity

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

- **Grade 1 Mild:** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2 Moderate:** minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
- **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

*Instrumental ADL 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.

6.4.5 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.

6.4.6 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential Takeda product complaint situation should immediately contact Takeda and report the event. Whenever possible, the associated Takeda product should be maintained in accordance with the label instructions pending further guidance from a Takeda Quality representative.

For Product Complaints

PPD

Product complaints in and of themselves are not AEs. If a product complaint results into a SAE, an SAE form should be completed and sent to Millennium Pharmacovigilance as indicated in Section 6.4.3.

6.5 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

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.

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 the contemporary, real-world disease and patient presentation, therapies, and clinical outcomes in both patients with ND MM, and R/R MM by geographical region are:

- Demographics, co-morbidities; diagnostic and presenting symptoms (see Section 6.3.2); risk category; sites of disease; ECOG performance status; frailty status; MRD; GEP, FISH, and cytogenetic results; ISS/R-ISS stage; imaging results; and laboratory test results for presentation.
- Stem cell transplant, treatment, and duration for treatments.
- Overall survival, progression status and response to each regimen, and time to next therapy for clinical outcome measures.

7.1.2 Secondary Outcome Measures

The secondary outcome measures of this study are:

- Patterns of treatment combinations, sequencing, and treatment rechallenge and clinical outcomes for different strategies.
- Treatment duration and clinical outcomes between continuous treatment and intermittent treatment strategy.

- Triggers of treatment initiation or treatment change at relapse including biochemical progression or symptomatic progression.
- Reasons for treatment modifications.
- HRQoL and HRU among MM patients.
- Associations between presentation, disease characteristics, choice of therapy 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 a minimum of 5000 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.

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	5000	0.486	0.514
0.6	270	0.541	0.657		0.6	5000	0.586	0.613
0.7	270	0.643	0.752		0.7	5000	0.687	0.713
0.8	270	0.748	0.843		0.8	5000	0.789	0.811
0.9	270	0.858	0.930		0.9	5000	0.891	0.908

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%. 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.

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 for all patients included overall and by cohorts and geographic regions.

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
- Country
- Continuous treatment versus intermittent treatment
- 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 characteristics – stage, risk category
- Treatment choices

Others 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; 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 and patient presentation, therapies, and clinical outcomes will be summarized descriptively, and segmented by geographic regions and cohort. Within selected subgroups (section 7.4), comparisons based on clinically relevant factors will be made, such as the following:

- Number of drug combinations (e.g., doublet compared to triplet or more)
- Race (e.g., black compared to non-black), gender, age
- Monoclonal antibody therapy compared to non-monoclonal antibody therapy
- Treatment intent (e.g., maintenance therapy)
- Prognostic indicators.

7.5.2 Secondary Analyses

Healthcare resource utilization 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 quality of life 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 vs. intermittent) 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. overall survival, progression status and response to each regimen, and time to next therapy) and therapy regimens, disease and patient presentation. This will provide adjusted estimates for some of the clinically relevant comparisons in Section 7.5.1. Important model covariates to minimize bias include demographics, prognostic indicators, previous therapies, geographic regions, enrolment calendar year, 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 SC. Details of the interim data summaries will be provided in the SAP.

7.5.4 Final Analysis

The final analysis will be conducted within 1 year after the last patient in the study has completed at least 5 years of follow-up or until he/she dies. 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. An interim study report will be generated as directed by the SC. The final analysis report will be conducted as described in Section 7.5.4. One final follow-up study report is planned during the study based on instructions from the SC. 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 systems 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 subjects 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 and surveys, 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 guidances:

- 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
- GPP 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.

Before recruitment and inclusion in the study, each patient or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the healthcare provider is assured that the patient or legal guardian understands the implications of participating in the study, the patient or legal guardian 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 or legal guardian.

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 (or the patient's legal guardian), 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

The PPD will retain study data for a minimum of 3 years following the final publication of study findings or discontinuation of the survey, 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 survey, 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.

The 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 survey

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 5 years of follow-up, are lost to follow-up, or have died.

11 Reference List

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12 Appendices

12.1 Appendix: Signature Pages

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 12 February 2016

Protocol accepted and approved by:

Title

PPD

Title

PPD

Title

Title

Title

Title

Title

PPD

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 12 February 2016

I have read and understood all sections of the protocol entitled "A global, prospective, non-interventional, observational study of presentation, treatment patterns, and outcomes in multiple myeloma patients – the INSIGHT MM study". I will follow the protocol during the lifetime of the study until study end.

Protocol received, read and accepted by:

Title

Signature Date