Title: Multiple Myeloma Profile in Brazil: A Retrospective Observational Analysis

NCT Number: NCT03506386

Protocol Approve Date: 12 Feb 2018

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

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

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

**Observational/Non-Interventional Study Protocol**

**Short title:** MMyBRave Study

**Title:** Multiple Myeloma Profile in Brazil: A Retrospective Observational Analysis.

**Study ID:** NDMM-5004

**Sponsor:** Takeda Pharma Ltda.
Rua do Estilo Barroco, 721
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Phone: +55 11 5188 4400

**Study phase:** Medical Affairs, Non-registration Company Sponsored (Observational).

**Date of version of protocol:** 12 Feb 2018

# Chapter 1 Administrative information

## 1.1 Contacts

A separate contact information list will be provided to each site.

| Issue | Brazil Contact |
|---|---|
| Pharmacovigilance reporting | PPD |
| Responsible Medical Officer (carries overall responsibility for the conduct of the study) | |

## 1.2 Approval

**REPRESENTATIVES OF TAKEDA**

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

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

**SIGNATURES**

PPD

## Summary

### Observational/Non-Interventional Study

**Short Title of Study**

MMyBRave Study

**Study sites**

Approximately 25 to 30 experienced hematology/oncology centers from Brazil are expected to participate.

**Objectives**

Relatively little is known about the incidence and clinical features of multiple myeloma (MM) in Brazil. There is a need to clarify demographic and clinical characteristics for this population of patients. The aim of this study is to investigate the demographic and clinical characteristics, as well as the patterns of care and treatment results, for patients with MM treated at selected hematology/oncology centers in Brazil. The primary objective is to present a descriptive analysis of demographic and clinical characteristics, as well as of the treatment patterns for MM in Brazil. The secondary objectives are to describe the treatment duration and the overall survival of patients with MM in Brazil.

**Methodology**

This is an observational, non-interventional study, with retrospective evaluation of data and no control group. Participation in the study will not influence the usual local standards for patient assessment and care.

**Number of subjects**

Between 1000 and 1500 patients are expected to participate.

**Diagnosis/Disease/Condition and main criteria for inclusion**

Eligible patients will have been diagnosed with active MM between January 1, 2008, and December 31, 2016, at any one of the participating centers, regardless of disease stage or treatment modality. Diagnosis of MM will have been made as per investigator's discretion.

**Duration of data collection per patient**

For each patient, data collection will comprise the longest possible period of time since the diagnosis of MM (within the eligibility window of time, between January 1, 2008, and December 31, 2016) and the cut-off date for data collection (December 31, 2016), unless a patient has died or been lost to follow-up before that. The study is planned to last for approximately 24 months since its initiation (initiation defined as the initiation visit for the first site).

**Criteria for evaluation**

Population descriptors

Data collected for the study will include identification data, demographic data, baseline data on MM, additional baseline laboratory data, initial treatment for MM, subsequent treatment for MM, and outcome data. Each variable will be represented and defined in the electronic Case Report Form to be used in the study.

Main outcome variables

The primary outcome variables are related to the primary objective of the study of describing the demographic and clinical characteristics, as well as of the treatment patterns. The secondary outcome variables, which are related to the secondary objectives, will be the treatment duration and the overall survival. Duration of treatment will be defined with respect to selected lines or regimens of interest, considering the time elapsed from each treatment initiation to discontinuation, and censoring patients who are lost to follow-up before discontinuation (patients who died before discontinuation will be considered as events for these analyses). Overall survival will be defined as the time elapsed between the date of diagnosis until death, with censoring of patients who are alive when last seen or who are lost to follow up. For patients enrolled within the last 1-year period of retrospective data collection, data will only be analyzed for demographic, clinical characteristics, patterns and duration of treatment.

Health economics

No data for health-economic analyses will be collected.

**Statistical methods**

Descriptive analyses will include measures of central tendency and dispersion that are appropriate to the distribution of each quantitative variable. Normally distributed quantitative variables will be described by their range, mean and standard deviation, whereas

quantitative variables with non-normal distribution will be summarized by range, median and interquartile range. Qualitative variables will be described by frequencies and their 95% confidence interval, when appropriate. Quantitative variables will be compared between unpaired groups by t tests or Mann-Whitney tests, according to the underlying distributions of the variables. The chi-square test or Fisher's exact tests will be used to compare groups of patients with respect to qualitative variables. Correlations between quantitative variables will be explored by correlation coefficients, when appropriate. Linear and logistic regression models will be used to explore the association between baseline variables and outcomes when adjusting for confounders, if appropriate. The analysis of treatment duration and overall survival will be performed with the method of Kaplan and Meier, with multivariate analysis by the Cox model to adjust for confounders, when appropriate. Differences between groups will be compared using the log rank test.

Given the nature of the study, there is potential for several types of biases related to the profile of Study Sites, to patient selection, and to the availability of follow-up information. In order to minimize such potential biases, every effort will be made to select Study Sites with broad geographic and socioeconomic representation within Brazil. Moreover, investigators will be encouraged to enroll all eligible patients, in order to minimize selection bias that may result from excluding patients who have been lost to follow-up or who may have had irregular follow-up at the Study Site. Importantly, investigators will also provide data on patients who have been diagnosed within the eligibility period but are already deceased, with the aim of minimizing the risk of overestimating the overall survival of patients from Brazil with MM, something that could happen if only surviving patients were analyzed. Finally, investigators will be encouraged to provide information on the maximum possible period of follow-up for each patient still alive, preferably until the closest possible date to the cut-off date of 31 December 2016.

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**List of Abbreviations and Definition of Terms**

| | |
|---|---|
| ADR: | Adverse Drug Reaction |
| AE: | Adverse Event |
| CRAB: | HyperCalcemia, Renal failure, Anemia, and Bone lesions |
| eCRF: | Electronic Case Report Form |
| FLC: | Free light chain |
| FISH: | Fluorescent *in situ* hybridization |
| GPP: | Good Pharmacoepidemiology Practices |
| ICD-10: | International Classification of Diseases, 10th revision |
| IMWG: | International Myeloma Working Group |
| ERB: | Ethics Review Board |
| MedDRA: | Medical Dictionary for Regulatory Activities |
| MM: | Multiple myeloma |
| MRI: | Magnetic resonance imaging |
| OS: | Overall survival |
| SADR: | Serious Adverse Drug Reaction |
| SAE: | Serious Adverse Events |
| SDV: | Source Data Verification |
| SSR: | Special Situation Report |
| WHO-Drug: | World Health Organization Drug Dictionary |

## Chapter 2 Introduction

Multiple myeloma (MM), a multifocal plasma-cell neoplasm characterized by the production of monoclonal protein and skeletal destruction [1], is one of the most frequent hematological malignancies, accounting for nearly 1% of all cancers and 15% of hematologic neoplasms [2, 3]. Until 2014, MM was defined by the presence of at least 10% plasma cells in the bone marrow (or a tissue biopsy), serum or urine monoclonal protein, and end-organ damage denoted by the CRAB acronym: hypercalcemia, renal failure, anemia, and bone lesions [1]. More recently, the International Myeloma Working Group (IMWG) updated the diagnostic criteria for MM, adding three biomarkers that can be used to diagnose the disease in patients without CRAB features: clonal bone marrow plasma cells ≥60%, serum free light chain (FLC) ratio ≥100 (as long as the involved FLC level is ≥100 mg/L), or more than one focal lesion on magnetic resonance imaging (MRI) [4]. These changes were implemented in order to enable earlier diagnosis and the initiation of effective therapy to prevent end-organ damage, and most patients diagnosed through the three biomarkers have what was previously termed “smoldering myeloma”. Of note, the spectrum of plasma-cell neoplasms also includes several premalignant states (collectively referred to as monoclonal gammopathies of undetermined significance) and other malignant disorders, such as primary amyloidosis and plasma-cell leukemia.

Treatment for MM has evolved significantly along the past two decades, with the most important therapeutic advances being the introduction of high-dose chemotherapy [5], bisphosphonates [6], and novel classes of systemic anticancer agents, such as immune modulators [7-9], proteasome inhibitors [10-12], and monoclonal antibodies [13, 14]. As a result of these improvements, the expected median overall survival (OS) in newly-diagnosed MM has increased over the past two decades from around 2 years to approximately 5 years among transplantation-ineligible patients treated with current regimens [15-18], and typically longer in the transplantation setting [19, 20]. Unfortunately, many of these treatments are not available in Brazil or other countries with limited resources, where treatment patterns may vary widely and often differ from published guidelines [21]. The extent to which such shortcomings in treatment availability affect patient outcomes is currently unknown.

The epidemiological features of MM have been more extensively investigated in some countries and ethnic groups. It is well known, for example, that the incidence of MM is higher in blacks than in whites [22], and lower in Asia than in the US and Western Europe, despite a progressive increase in this incidence in some Asian countries [23]. Since the clinical features of MM may also differ across world regions, it is important to characterize the profile of this disease in different geographic locations [24]. In addition to the contribution of environmental factors, such as obesity and diet [25, 26], the incidence of MM is likely to be influenced by genetic constitution [27]. Relatively little is known about the incidence and clinical features of MM in Brazil, a country where relatively free miscegenation of populations of Native American, Mediterranean and African ancestry has occurred for several centuries. In Brazil, for example, the nationwide incidence of MM is largely unknown, because the disease does not appear in the annual estimates provided by the National Cancer Institute [28].

Despite this relative paucity of information, previous observational studies have shown the feasibility of collecting demographic and clinical data that may help in understanding the local characteristics of MM in Brazil, as well as in assessing outcomes and planning treatment policies [29-31]. In the latest observational study in Brazil, patients who had the diagnosis of MM were accrued as late as December 2007 [31]. Given recent advances in diagnosis and therapy for MM, the current observational study will allow for further and more contemporary insight about this disease in Brazil, especially with regard to patient demographic and clinical features, patterns of care, and treatment results. This will allow for continued monitoring of improved outcomes from the use of the more novel interventions, as well as to assess existing gaps and unmet needs in comparison with other countries and health-care settings.

## Chapter 3 Study Objectives

The aim of this study is to investigate the demographic and clinical characteristics, as well as the patterns of care and treatment results, for patients with MM treated at selected experienced hematology/oncology centers in Brazil and who had their disease diagnosed between January 1, 2008, and December 31, 2016.

### 3.1 Primary Objectives

The primary objective is to present a descriptive analysis of demographic and clinical characteristics of these patients, as well as of the treatment patterns for MM in Brazil.

### 3.2 Secondary Objectives

The secondary objectives are to describe the treatment duration and OS for these patients, and to investigate factors potentially associated with OS, such as disease stage and other baseline prognostic features.

## Chapter 4 Study Administrative Structure

### 4.1 Study Sites

The study is planned to be conducted in 25 to 30 Study Sites that represent the five geographic regions of Brazil. These Study Sites will be experienced hematology/oncology centers selected due to their large experience in treating patients with MM and willingness to participate in the study.

### 4.2 Sponsor Personnel

Takeda Brazil Research Team will keep a record of all relevant sponsor personnel, and other medical and drug safety staff responsible for the study.

### 4.3 Essential Documents

The following essential documents must be received by Sponsor before the study is initiated at a site:

- Written agreement between Takeda Pharma Ltda. (Takeda Brazil), Principal Investigator, Study Site Responsible/Clinic/Hospital and Administrative Intervenient as locally applicable.
- Signed and dated protocol agreement and amendment agreements, if any, with the original signature of the Site Responsible.
- Subject Information Sheet and Informed Consent Form in local language (approved by Ethics Review Boards [ERBs]).
- Written ERB approval according to local regulations.

- Authority approval according to local regulations.

## Chapter 5 Ethics

Given the observational nature of this study, no impact on the patients is expected, except for collection of informed consent to use of their data. Thus, patient care and outcomes are not expected to be influenced by study participation. Two different situations are expected with regard to patient participation in the study, always considering patients who have been diagnosed with MM within the eligibility window for participation: (1) patients who are already deceased or have been lost to follow-up; and (2) and patients who are alive and not lost to follow-up.

### 5.1 Ethical conduct of the Study

This study will be conducted in accordance with the protocol, the current version of the Declaration of Helsinki [32], Good Pharmacoepidemiology Practices (GPP) [33], and local regulations, with special attention to data protection. Sponsor will ensure that the protocol, any amendments and the Subject Information Sheet/Informed Consent Form are submitted to the relevant ERBs, according to local requirements. For patients who are already deceased or have been lost to follow-up, Study Sites will request from the relevant ERB a waiver to obtain informed consent, according to the local regulations. Takeda as the sponsor is responsible for meeting the International Conference of Harmonization requirement for yearly updates to the ERBs, if applicable.

### 5.2 Ethics Review Board and Authorities

**ERB**

According to applicable regulations, the Site Study Responsible will notify or obtain approval from the relevant ERB for the protocol, any amendments and the Subject Information Sheet/Informed Consent Formsubmit required documents to the ERB, such as:

- periodic updates on the progress of the study;
- notification of the end-of-study;
- a summary of the study results.

Sponsor will keep an updated list of all submission and approval dates of all documents submitted to the ERB. Copies of the documents will be distributed upon request.

**Authorities**

Takeda Brazil Research Team will send required documents to the competent authority and/or other national or regional authorities. Takeda Brazil Research Team will keep an updated list of submission and approval dates and a copy of all documents submitted.

For patients who are alive and not lost to follow-up, the Site Study Responsible must give the patient (and if applicable, legal guardian) oral and written information about the study in a form that the patient (and if applicable, legal guardian) can understand, and obtain the patient's (and if applicable, the legal guardian's) written consent before collection of identifiable patient information (hereinafter referred to as personal data). Before consenting, the patient (and if applicable, legal guardian) must be left with ample time to consider and to pose questions. Since the study is observational, the consent only concerns the data collection per se and is not consent to any interventional procedure or treatment. The patient must agree that sponsor personnel, their representatives or ERB or competent authority personnel (national or other) may require direct access to the patient's data/personal records which were collected, processed and stored in an anonymous form. The patient must agree that his/her data will be processed and stored in an anonymous form for evaluation of this study and any later overviews. Data may also be transferred in anonymous form to third parties, e.g., other companies or authorities, that may be located in other countries with potentially different regulations for data. The patients and, if applicable, legal guardian, have the right to withdraw their consent at any time without prejudice. In the Informed Consent Form it is stated that if consent is withdrawn, any data collected before withdrawal of consent will be kept. The original, signed Informed Consent Forms must be kept on the Site. For details, see the Subject Information Sheet and Informed Consent Form.

For patients who are already deceased or have been lost to follow-up, a waiver regarding Subject Consent will be obtained from the relevant ERB before study initiation. Informed Consent will therefore not be obtained for these patients. On the other hand, data may also be transferred in anonymous form to third parties, e.g., other companies or authorities, that may be located in other countries with potentially different regulations for data.



## Chapter 6 Study Design and Plan

This study is a 'non-interventional study' as defined in G-STND-PV-006, G-SOP-MA-005,

and the Directive 2001/20/EC [34]; moreover, the study will follow the guidelines for GPP [33]. This means that:

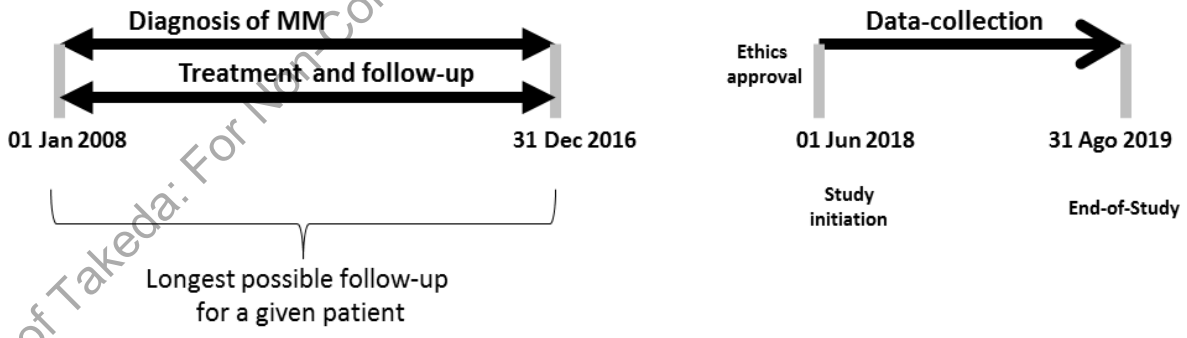
- The assignment of a patient to a particular therapeutic strategy is not decided in advance by the study protocol but falls within current practice;
- No additional diagnostic or monitoring procedures shall be applied to the patients;
- Epidemiological methods shall be used for the analysis of collected data.

## 6.1 Study Schedule

| | |
|---|---|
| Planned start of study: | May 2018 |
| Planned collection of first data point: | June 2018 |
| Planned last patient in: | May 2019 |
| Planned collection of the last data point: | August 2019 |
| Planned completion of the Study Report: | July 2020 |

The Start of Study is defined as the date of first Site Initiation Visit. The End of study is defined as the last data point collected.
The study report should be signed within 12 months after the collection of the last data point.

The study timeline is represented schematically below:




Takeda Brazil Research Team will ensure that End-of-Study notification is submitted to the concerned authorities and ERB for each site, as locally required.

Takeda Brazil Research Team and Global Research will ensure that the study plan and results are posted on “Clinicaltrials.gov” and, if required by local authorities, on other study registries.

Based on upcoming knowledge, Takeda might choose to terminate the study prematurely. In such case the study sites, ERBs and authorities will be informed promptly.

## 6.2 Discussion of Study Design

This is a multicenter, observational study of patients with MM in Brazil. As an observational study, it will retrospectively collect demographic and clinical data for various analyses. Treatment and patient evaluation will be left to the discretion of the Study Sites and local standards of care, which will not be influenced by the study. Participating investigators from each Study Site will collect patient data from institutional charts using a structured electronic Case Report Form (eCRF), entering them in a central database for analysis. Despite the explicit objective of characterizing patients from Brazil with MM, there is potential for several types of biases, including those related to the profile of Study Sites, to patient selection, and to the availability of follow-up information. In order to minimize such potential biases, every effort will be made to select Study Sites with broad geographic and socioeconomic representation. Moreover, investigators will be encouraged to enroll all eligible patients, in order to minimize selection bias that may result from excluding patients who have been lost to follow-up or who may have had irregular follow-up at the Study Site. Importantly, investigators will also provide data on patients who have been diagnosed within the eligibility period but are already deceased, with the aim of minimizing the risk of overestimating the OS of patients from Brazil with MM, something that could happen if only surviving patients were analyzed. This is particularly important, given that data collection will occur potentially several years after the actual patient treatment. Finally, investigators will be encouraged to provide information on the maximum possible period of follow-up for each patient still alive, preferably until the closest possible date to the cut-off date (31 December 2016), with the aim of obtaining more precision in long-term OS estimates. To the extent possible, statistical analyses will be conducted to adjust for known confounders when comparisons are made between groups of patients formed according to selected demographic or clinical characteristics.

## 6.3 Selection of Study Population

Study Sites will be selected based on their clinical expertise, expected commitment to patient accrual for the study, and geographic location, in order to ensure broad representation within the country. A total of 25 to 30 tertiary-care, experienced hematology/oncology centers are estimated to participate in the study, and the total number of patients expected is 1000 to 1500. The institutional charts from Study Sites, along with reports of results from laboratory and imaging studies, will constitute the source documents, and data from such charts will be collected using a study-specific eCRF by the Site Responsible or their designees. Each patient should be included in the study only once. For Study Sites with a system that allows identification of patients with MM electronically, *e.g.*, using International Classification of Diseases, 10th revision (ICD-10), this will be the preferred method of patient screening for eligibility. For Study Sites without such capabilities, patient screening will rely on manual selection of institutional charts or other means. In these cases, every effort should be made to identify every possible eligible patient.

In order to be eligible for the study, patients should meet all of the following criteria:

- Provision of written informed consent, for patients who are alive and not lost to follow-up (for patients already deceased or lost follow up, informed consent should have been waived by the corresponding ERB);
- Documented diagnosis of MM by the responsible physician between January 1, 2008, and December 31, 2016;
- Adults≥18 years of age;
- Absence of any plasma-cell disorder other than MM;
- Absence of any immunoglobulin-related disorder other than MM.

Data erroneously collected from patients who are alive and not lost to follow-up, and for who written informed consent is not available, will not be included in or will be deleted from the database.

## 6.4 Treatments

Treatment and evaluation for patients who are alive and not lost to follow up will be done according to local standards of care for each Study Site and will not be influenced by the study.

## Chapter 7 Conduct

Data will be collected for each patient from diagnosis of MM (within the period of interest, *i.e.*, between January 1, 2008, and December 31, 2016) until the cut-off date for data collection, December 31, 2016. Main data collected for the study will include:

| | |
|---|---|
| **Identification data** | • Study ID<br>• Site ID<br>• Patient number<br>• Informed consent obtained/waived and date |
| **Demographic data** | • Year of birth<br>• Gender<br>• Birthplace<br>• Race |
| **Baseline data on MM** | • Date of inclusion in the study<br>• Date of diagnosis of MM<br>• Criteria utilized for the diagnosis of MM<br>• MM features upon diagnosis<br>o At least 10% plasma cells in the bone marrow (or a tissue biopsy)<br>o Serum or urine monoclonal protein<br>o Evidence of end-organ damage (CRAB features)<br>o In the absence of CRAB features:<br>▪ Clonal bone marrow plasma cells ≥60%<br>▪ Serum FLC ratio ≥100 (as long as the involved FLC level is ≥100 mg/L)<br>▪ More than one focal lesion on magnetic resonance imaging (MRI)<br>• Monoclonal component<br>• Bone marrow involvement (% plasma cells)<br>• Date of bone marrow exam<br>• Bone lesions<br>• Extramedullary plasmocytoma(s) |

| | |
|---|---|
| | • Cytogenetics<br>• Date of cytogenetics<br>• Type of cytogenetics (FISH or conventional kariotype)<br>• Cytogenetics abnormalities (del 17p, t(4; 14), others)<br>• Date of FISH<br>• Durie-Salmon stage upon diagnosis<br>• International Staging System stage upon diagnosis |
| **Additional baseline laboratory data** | • Hemoglobin level upon diagnosis<br>• Date of hemoglobin level<br>• Albumin level upon diagnosis<br>• Date of albumin level<br>• Creatinine level upon diagnosis<br>• Date of creatinine level<br>• Beta2-microglobulin level upon diagnosis<br>• Date of beta2-microglobulin level<br>• Total serum calcium level upon diagnosis<br>• Date of total serum calcium level<br>• Ionized serum calcium level upon diagnosis<br>• Date of ionized serum calcium level<br>• Lactic dehydrogenase level upon diagnosis<br>• Date of lactic dehydrogenase level |
| **Initial treatment for MM** | • Participation in clinical trial(s)<br>• Systemic treatment given<br>• Date of first cycle<br>• Date of discontinuation<br>• Transplantation planned<br>• Transplantation administered<br>• Transplantation type<br>• Number of transplantations performed<br>• Date of Day zero of each transplantation<br>• Bisphosphonate use with initial treatment<br>• Denosumab use with initial treatment |

| | |
|---|---|
| | • Radiotherapy use<br>• Other treatments used |
| **Subsequent treatment for MM** | • Participation in clinical trial(s)<br>• Second systemic treatment given<br>• Date of first cycle of second systemic treatment<br>• Date of discontinuation of second systemic treatment<br>• Third systemic treatment given<br>• Date of first cycle of third systemic treatment<br>• Date of discontinuation of third systemic treatment<br>• Fourth systemic treatment given<br>• Date of first cycle of fourth systemic treatment<br>• Date of discontinuation of fourth systemic treatment<br>• Transplantation planned at any time after initial treatment<br>• Transplantation administered at any time after initial treatment<br>• Transplantation type at any time after initial treatment<br>• Number of transplantations performed<br>• Date of Day zero of each transplantation<br>• Bisphosphonate use at any time after initial treatment<br>• Denosumab use at any time after initial treatment<br>• Radiotherapy use at any time after initial treatment<br>• Other treatments used at any time after initial treatment |
| **Outcome data** | • Vital status on last follow-up visit<br>• Date of last follow-up visit for living patients<br>• Date of death |
| **General information** | • Observations |

Additional details about variables and types of data fields will be provided in the eCRF.

## Chapter 8 Safety Reporting

### 8.1 Definitions

**Adverse Events**

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

A laboratory test result that meets the criteria for an SAE

A laboratory test result that requires the subject/patient to receive specific corrective therapy

A laboratory abnormality that leads to discontinuation of therapy

A laboratory abnormality that the health care provider considers to be clinically significant

**Serious Adverse Events**

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded.
- In the view of the Health care provider, places the subject/patient at immediate risk of death (a life threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- An SAE may also be any other medically important event that, in the opinion of the Health care provider, may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

**Adverse Drug Reactions**

An adverse drug reaction (ADR) is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

**Product Quality Issues**

A Product Quality Issue (PQI) refers to defects related to the safety, identity, strength, quality, or purity of the product or with the physical characteristics, packaging, labeling, or design of the product.

**Special Situation Reports**

A Special Situation Report (SSR) includes any of the following events:

- Pregnancy: Any case in which a pregnancy patient is exposed to a Takeda Product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Takeda Product. Exposure is considered either through maternal exposure or via semen following paternal exposure.
- Breastfeeding: Infant exposure from breast milk
- Overdose: All information of any accidental or intentional overdose
- Drug abuse, misuse or medication error: All information on medicinal product abuse, misuse or medication error (potential or actual)
- Suspected transmission of an infectious agent: All information on a suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.
- Lack of efficacy of Takeda Product
- Occupational exposure
- Use outside the terms of the marketing authorization, also known as “off-label”
- Use of falsified medicinal product
- A SSR should be reported even if there is no associated AE.

## 8.2 Classifications of severity and outcome

**Severity**

Severity is a clinical observation and describes the intensity of the event.

- Mild: Transient symptoms, no interference with the subject’s daily activities
- Moderate: Marked symptoms, moderate interference with the subject’s daily activities
- Severe: Considerable interference with the subject’s daily activities.

**Outcome**

- Fatal: The subject died due to the event. If the subject died due to other circumstances than the event the outcome should be stated as 'Not recovered' or 'Recovering'
- Recovered/Resolved: The subject has fully recovered from the event or the condition has returned to the level observed at baseline.
- Recovering/Resolving: The event is improving but the subject is still not fully recovered
- Not Recovered/Not Resolved: The event is ongoing at the time of reporting and the subject has still not recovered.
- Recovered with Sequelae/Resolved with Sequelae: As a result of the event, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf or paralysed).
- Unknown: If Outcome is not known or not reported.

## 8.3 Collection of Adverse Events, Special Situation Reports and Product Quality Issues

Collection and notifying of Adverse Events, Special Situation Reports and Product Quality Issues to Takeda Pharmacovigilance

SAEs, AEs, ADRs, SSRs and PQIs in the medical record/source data that are part of the study objectives or endpoints

Events/issues which are part of the study objectives or endpoints will be systematically identified and collected from medical records or other applicable source records, and summarized as part of any interim analysis and in the final study report. Such events do not need to be notified as individual reports to Takeda Pharmacovigilance.

SAEs, AEs, SSRs and PQIs in the medical records/other applicable source data that are not part of the study objectives and endpoints

Events/issues which are not part of the study objectives and endpoints will not be abstracted or collected from medical records/ source records.

SAEs, AEs, ADRs, SSRs and PQIs spontaneously reported to the investigator(s) or research team

If during the conduct of the study the investigator(s) or a member of the research team is spontaneously informed by a healthcare professional or patient of an SAE, AE, ADR, SSR or PQI where the event/issue pertains to a Takeda product (or unbranded generic), such information should be forwarded to their local Takeda Pharmacovigilance department within

1 working day for all SAEs and , within 4 calendar days for for all other events. This included events spontaneously notified to the investigator(s) or research team which are study endpoints and also events spontaneously notified which are not study endpoints. As such reports are spontaneously notified, causality of any adverse events should be assumed unless there is evidence to the contrary.

**Pharmacovigilance contact details**

PPD

## Chapter 9 Data Quality Control and Assurance

### 9.1 Quality Control

Quality control during data collection and entry into the database will be the responsibility of the Site Responsible, who will supervise all activities regarding the study that take place in their Study Site.

The study will use electronic data collection, for which a set of automatic data checks with data queries will be programmed for data cleaning. Manual data monitoring will include on and off site visits and on site Source Data Verification (SDV) will include the check of the Signed Informed Consent for all subjects. Source documents (e.g., medical records, original laboratory records) and Signed Informed Consent should be available to study monitors whenever possible, and consent to such access will be explicitly included in the Informed Consent Form.

Additional details will be specified in the Monitoring Plan.

### 9.2 Audit from Quality Assurance Unit

Takeda Quality Assurance may audit the study to ensure that study procedures comply with the protocol and standard operating procedures, and that collected data are correct and complete.

## 9.3 Inspection by ERB or Competent Authority

Representatives from the ERB or Competent Authority may in rare cases wish to inspect the study on site. Upon receiving notification of such inspection, the Study Site Responsible must immediately contact Takeda Brazil Research Team and must make the records available as requested. The Inspector must be reminded up front that consent to access personal data has been waived from the patients in this study who were already deceased or lost to follow-up upon study initiation.

## 9.4 Data Management

Data Management will be carried out according to a Data Management Plan, which will be written and approved before the design of the study database is finalized. The data management provider should approve all data formats before the data collection tools are made available to the sites. If the written informed consent of a patient is known not to be available in spite of being required, data for this patient are not entered into or are deleted from the database. If a patient is erroneously included in the study more than once, only the data relating to the first inclusion will be kept in the database and made available for analysis. Data from later inclusions will be transferred to the first dataset when relevant, i.e., if collected within the data collection time frame.

The current Standard Coding Instructions for coding of medical history, concomitant illness (Medical Dictionary for Regulatory Activities, MedDRA), concomitant medication (World Health Organization Drug Dictionary, WHO-Drug) and adverse events/reactions (MedDRA) must be followed.

The subjects will be identified in the database only by Study ID, Site ID, patient number, year of birth, and gender. These identifiers will be captured and kept in the database for analysis.

### 9.4.1 Data Collection Tools and Flow

All data collected for the purpose of this study will be entered, stored and retrieved with the use of an electronic eCRF specifically designed for the study. The system will comprise a web-based interface for use by investigators, and a central database for storage and retrieval. The database will be physically stored at a data center designated by Takeda or the appointed vendor, with appropriate measures for back-up of data and stability of the system. The system will ensure patient confidentiality, as well as security and confidentiality

of the data for the duration of the study. Each Site Responsible or designee will receive from Takeda or the appointed vendor a login name and a password, and will hold the responsibility for data entry into the system. Investigators will be able to access the database for the whole duration of the study. The database will contain single-choice, multiple-choice and open-field options for the entry of patient demographic and clinical data. Moreover, the system will allow for automatic data checks and the negation of queries based on programming logic.

Given that source documents (institutional charts and reports of results from laboratory and imaging studies) will not necessarily be available for auditing in the future, the Site Responsible will ensure that data collection for the study be done in a proper way and by individuals who are under their direct supervision. Moreover, the Site Responsible will ensure data are attributable, accurate, complete, contemporaneous, and consistent. The Site Responsible must sign off the complete data set for each subject, confirming the collected data. Serious and non-serious AE collected according section 8 should be signed off separately, in a specific form, by a study team member previously trained.

# 10 Statistical Methods and Determination of Sample Size

The statistical analyses will be performed by Takeda or an appointed vendor. This section describes the statistical analyses as foreseen at the time of planning the study, and further details are provided in the Statistical Analysis Plan. Any known deviations from the planned analyses, the reason for such deviations and all alternative or additional statistical analyses that may be performed as well as the final statistical analysis will be described in a revised Statistical Analysis Plan before completion of data collection. All later deviations or alterations will be summarised in the Final Study Report.

## 10.1 Statistical Analysis Plan

This study is observational, and epidemiological methods will be employed for data analysis. Before analysis, all data entered in the database will be assessed for completeness and coherence. Descriptive analyses will be performed of all collected data, except data collected only for the purpose of data cleaning, i.e., all data listed in section 7. Descriptive analyses will include measures of central tendency and dispersion that are appropriate to the distribution of each variable. As a general rule, normally distributed quantitative variables will

be described by their range, mean and standard deviation, whereas quantitative variables with non-normal distribution will be summarized by range, median and interquartile range. Qualitative variables will be described by frequencies and their 95% confidence interval. Quantitative variables will be compared between unpaired groups by t tests or Mann-Whitney tests, according to the underlying distributions of the variables. The chi-square test or Fisher's exact tests will be used to compare groups of patients with respect to qualitative variables. Correlations between quantitative variables will be explored by correlation coefficients, when appropriate. Linear and logistic regression models will be used to explore the association between baseline variables and outcomes when adjusting for confounders, if appropriate. The analysis of treatment duration and OS will be performed with the method of Kaplan and Meier, with multivariate analysis by the Cox model to adjust for confounders, when appropriate. Differences between groups will be compared using the log rank test. OS will be defined as the time elapsed between the date of diagnosis until death, with censoring of patients who are alive when last seen or who are lost to follow up. Duration of treatment will be defined with respect to selected lines or regimens of interest, considering the time elapsed from their initiation to their discontinuation, and censoring patients who are lost to follow-up before discontinuation (patients who die before discontinuation will be considered as events for these analyses). The role of transplantation will be investigated using landmark analysis, in order to control for guaranteed-survival bias. No subgroup analyses are planned regarding Study Site, but other subgroup analyses may be performed to assess outcomes in selected patients subsets defined by baseline characteristics.

Site Responsible and their designees should make every effort to ensure that data collection is as complete as possible. Techniques for imputation of missing data will not be employed. For further details of the statistical analyses, please refer to the Statistical Analysis Plan.

## 10.2 Interim Analyses

A partial analysis is planned for this study when around 50% of the forecasted number of patients is enrolled.

## 10.3 Handling of missing data

Given that all analyses are descriptive in nature, no imputation of missing data will be performed, except when detailed in the SAP.

### 10.4 Determination of Sample Size

Given the observational nature of this study, its main objective of describing demographic and clinical features of patients with MM, and the lack of specific hypothesis regarding treatment effects or other objective measures, the sample size for the study is not determined on the basis of statistical assumptions, but rather on the expected number of patients that will be feasibly accrued by the Study Sites. Considering the number and expected commitment of Study Sites, and a recruitment period of 24 months, between 1000 and 1500 patients are expected to be enrolled.

## Chapter 11 Reports

A Non-Interventional Study Report based on the results obtained will be prepared and submitted to Global Research for distribution. The Final Study Report should be available within 1 year from collection of the last data point, and the Study Sites will be informed about the results when the report is finalized.

## Chapter 12 Publications

Takeda aims to have the results of this study published. Takeda has the right to use the data and results for regulatory purposes and for internal presentation within the company and to partners.

## Chapter 13 Archiving of Study Documentation

During the course of the study the Site Responsible must as a minimum file the essential documents (Section 4.4), the protocol, any amendments, the list of participating subjects, the written informed consents, the eCRFs and the progress reports in the Study Site File. After final database lock, the Site Responsible must as a minimum store the list of participating subjects and the signed Informed Consent Forms on site for 25 years. The Site Responsible should store additional study documentation for a longer period of time as required by any local regulations and/or hospital requirement.

## Chapter 14 References

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