Title: An International, Multi-Centre, Retrospective Study to Describe Treatment Pathways, Outcomes, And Resource Use in Patients with Multiple Myeloma
(INTEGRATE)

Protocol Approve Date: 15 October 2017

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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.

Non-interventional study protocol

Title:	An international, multi-centre, retrospective study to describe treatment pathways, outcomes and resource use in patients with Multiple Myeloma (INTEGRATE)
Sponsor:	Takeda Pharmaceuticals International AG Thurgauerstrasse 130 8152 Glattpark-Opfikon (Zurich) Switzerland
Protocol ID:	NDMM-5002
Study phase:	Medical Affairs, Non-registration Company Sponsored (Observational)
Version No.:	1.0
Date Issued:	15 October 2017
Date Amended:	

1 Administrative information

1.1 Study contacts

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

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

[redacted]

2 Synopsis

2.1 Study title

An international, multi-centre, retrospective study to describe treatment pathways, outcomes and resource use in patients with Multiple Myeloma (INTEGRATE).

2.2 Background

Multiple myeloma is a hematological malignancy. There were approximately 114,000 new cases of MM globally in 2012 and the incidence is estimated to increase to approximately 141,500 cases by 2020. Estimates of the burden of MM, particularly in the Emerging Markets region, are affected by inconsistent and poor quality data. As such, there are limited real-world data from Emerging Market (EM) countries on treatment pathways, clinical outcomes and healthcare resource use among patients with MM, particularly those patients who relapse or are refractory to frontline therapy. Real world evidence (RWE) on the patient care pathway and resource use is required from a representative global population to support local clinical practice and payer decisions on treatment funding.

2.3 Study aim and objectives

This study will, in patients receiving frontline treatment for newly diagnosed Multiple Myeloma (NDMM), Cohort 1, and in patients with relapsed or refractory MM (RRMM), Cohort 2:

Primary objective

Describe time to next treatment (TTNT)* at each line of therapy[#]

Secondary objectives

1. Describe patient demographic and clinical characteristics.
2. Describe treatment patterns for MM.
3. Describe clinical outcomes:
    a. Relapse rate at 6, 12, 18, 24, 36 and 60 months.
    b. Overall survival (OS) rate at 6, 12, 18, 24, 36 and 60 months.
    c. Number of relapses per patient.
4. Describe for each line of therapy[#]:

a. Best response after start of treatment, as defined by the International Working Group Uniform Response Criteria for Multiple Myeloma or as determined by treating physician.
b. Time to first response.
c. Time to best response.
d. Duration of best response.
e. Adverse events experienced.
f. The MM-related healthcare resource use associated with each line of therapy.
g. The MM-related healthcare costs associated with each line of therapy[†].

*Limited retrospective availability of clinical data to measure progression-free survival.

[#]Line of therapy as determined by progression status, i.e. treatments received prior to first progression = 1st line, treatments received between 1st and 2nd progression = 2nd line, etc.

[†]Allocation of costs (for secondary objective 4g) is optional. Sections of the protocol that relate specifically to secondary objective 4g are shown in italics and may be deleted if the country is not participating in this part of the study.

2.4 Methods

This is an international, multi-centre, retrospective, observational research study to be conducted across 13 countries in the EM region. It will be a retrospective review of medical records of adult patients newly diagnosed with MM (NDMM) who have received frontline treatment with chemotherapy (Cohort 1) and patients with a diagnosis of RRMM (Cohort 2).

Pseudonymised (anonymised-coded) data will be collected according to the agreed minimum dataset using a standardised study case report form (CRF). Web-based data collection will be employed. Pseudonymised data from all participating centres and countries will be provided to the appointed CRO for pooled analysis and reporting.

Study sample

Approximately 2600 patients will be recruited in total across the 13 participating countries within the EM region. The number of sites in each country which are needed to achieve the required sample size will be determined based on local feasibility within each country. The overall study sample, and patients per country, will consist of approximately 50% patients in the NDMM group (Cohort 1) and 50% in the RRMM group (Cohort 2). To account for different population sizes, between 100-400 patients will be consecutively enrolled from each country to yield approximately 2600 patients in total (see section 7.3 for further information). Patients will be screened for eligibility by a member of the direct care team at each site.

Inclusion criteria

- Patients who have newly diagnosed symptomatic MM (Cohort 1) or presented with RRMM (Cohort 2) between 01st January 2010 and 31st December 2011 (inclusive).
- Patients who have completed at least one full line of treatment.
- Age ≥ 18 years at first diagnosis of MM (Cohort 1) or at diagnosis of RRMM (Cohort 2).
- Alive or deceased.
- Patient provides written informed consent for study data collection (as required by local regulations).

Exclusion criteria

- Patients for whom the minimum study dataset (Table 3) is unavailable from their hospital medical records.
- Patients with smouldering myeloma.
- Patients with monoclonal gammopathy of unknown significance (MGUS).
- Patients enrolled in a clinical trial of an investigational medicinal product during the observation period.

Duration of data collection

Data (paper and/or electronic, as applicable locally) will be collected from the date of NDMM or RRMM diagnosis until the death of the patient or the date of data collection (whichever occurs first).

Criteria for evaluation

Population descriptors

Data will be collected in relation to geographical location, subject gender, age, ethnicity, diagnosis and staging/sub-type of disease, relevant clinical laboratory results/procedures and comorbidities, where available.

Main outcome variables

Key variables will include those related to treatments, clinical outcomes, treatment-related adverse events and healthcare resource use (HRU).

Health economics

Data will be collected in relation to MM related resource use and the details and source of costs will be agreed at country-level and will be detailed in the statistical analysis plan (SAP), where data are available and study sites and countries agree to collect these data.

Data analysis

Descriptive analyses will be conducted to describe patient demographics and clinical characteristics, treatment patterns, clinical outcomes, HRU and costs.

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List of abbreviations and definition of terms

ADR	Adverse Drug Reaction
AE	Adverse Event
allo / auto	Allogeneic / Autologous
allo-SCT	Allogeneic Stem Cell Transplantation
ASCT	Autologous Stem Cell Transplantation
ASR	Age Standardised Rate
CA	Competent Authority
CR	Complete Response
CRAB criteria	Calcium (elevated), Renal failure, Anemia, Bone lesions (criteria)
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Computerised Tomography
DMP	Data Management Plan
DS	Durie-Salmon staging
ECOG	Eastern Cooperative Oncology Group
EM	Emerging Markets
FISH	Fluorescence In Situ Hybridization
FLC	Free Light Chain
G-CSF	Granulocyte-Colony Stimulating Factor
GPP	Good Pharmacoepidemiology Practices
HCP	Health Care Professional
HIV	Human Immunodeficiency Virus
HRU	Healthcare Resource Use
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IDS	International Drug Safety
IEC	Independent Ethics Committee
IgH	Immunoglobulin heavy chain (translocations)
IMWG	International Myeloma Working Group
IQR	Interquartile Range
IRB	Institutional Review Board
ISPE GPP	International Society for Pharmacoepidemiology

ISS	International Staging System
LCL	Lower confidence limit
LCO	Local Operating Country
MGUS	Non-IgM monoclonal gammopathy of undetermined significance
MM	Multiple Myeloma
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
ND	No Data Available
NDMM	Newly Diagnosed Multiple Myeloma
OS	Overall Survival
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PR	Partial Response
PSUR	Periodic Safety Update Report
QA	Quality Assurance
RRMM	Relapsed Or Refractory MM
RWE	Real World Evidence
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sCR	Stringent Complete Response
SD	Stable Disease
SPC	Summary of Product Characteristics
SPEP/UPEP	Serum Protein Electrophoresis/Urine Protein Electrophoresis
StDev	Standard Deviation
TLFs	Tables, Listings and Figures
TTNT	Time To Next Treatment
UCL	Upper Confidence Limit
VGPR	Very Good Partial Response

3 Introduction

Multiple myeloma (MM) is a progressive haematological malignancy characterized by multiple bone marrow tumour foci and secretion of the M-protein. MM occurs more commonly in older people, with a median age of 70 years at diagnosis. Typical presentations at diagnosis include bone destruction, hypercalcaemia, anaemia and renal impairment. Most patients with MM have cytogenetic abnormalities. For example, patients with certain gene signatures, such as IgH translocations of chromosomes 4 and 16 or deletion of the p arm of chromosome 17, have worse prognosis [1].

There were 114,000 new cases of MM globally in 2012 but the reported incidence varied from 0.4 to 5 per 100,000 population, with a higher incidence in more developed regions [2]. As such, the majority of 80,000 known deaths due to MM in 2012 occurred in developed countries. Inconsistent and poor quality of data available in some countries may partly explain the marked apparent variation in global incidence and mortality rates [3,4]. Even with potential under-estimation of cases, the incidence of MM in Africa and South East Asia is predicted to increase from 17,077 in 2015 to 26,544 in 2030 [3]. Globally, the incidence of MM will increase with ageing populations and improvements in diagnosis.

MM is a heterogeneous disease and survival ranges from weeks to years after diagnosis [1]. There is currently no curative treatment for MM and treatment options are dependent on patient's age and comorbidities. Patients who respond to initial treatment might maintain progression free survival for several years. However, inevitably, relapse will occur and patients will become progressively less responsive to treatment (refractory MM). Standard care in developed countries consists of a triple drug regimen. Commonly used regimens include bortezomib, dexamethasone and a third agent (thalidomide, doxorubicin, cyclophosphamide or lenalidomide) [5,6]. A combination of melphalan and prednisolone, in addition to bortezomib or thalidomide may also be used [7]. Although MM is more common in older patients, those who are younger (typically aged under 65 years) and without serious comorbidities will usually also receive autologous stem cell transplantation (ASCT).

Emerging Market (EM) countries are those where there is rapid growth in economy, such as Argentina, Saudi Arabia and Turkey. There are limited real-world data from Emerging Market (EM) countries on treatment pathways, clinical outcomes and healthcare resource use among patients with MM, particularly those patients who relapse or are refractory to frontline therapy. Yet the GLOBOCAN series from the International Agency for Research on Cancer indicate that cases of MM in these countries will rise considerably in the future and thus place an increasing demand on limited healthcare resources. Real world evidence (RWE) on the burden of MM is therefore needed in these countries to help inform clinical decision making. Payers will also require local information on resource use for different treatment options to make informed decisions for their own country. A large, international observational study of MM treatments and outcomes is underway in 15 countries (INSIGHT-MM), but initial results are not due until 2018 and the study is not expected to be completed until 2024 [8]. Therefore, more timely, high quality RWE on the patient care pathway and resource use is required from a representative global population to support clinical practice and payer decisions on treatment funding. Table 1 shows the incidence and prevalence of MM, and deaths associated with MM, in 13 EM countries that will participate in this study.

Table 1: Epidemiological data on multiple myeloma for 13 Emerging Market countries

GLOBOCAN series of the International Agency for Research on Cancer, 2012					
Emerging Market countries	**Incidence per 100,000 Age standardised rate (ASR)**	**Deaths per 100, 000 (ASR)**	**Prevalence ASR per 100,000**	**Male (ASR)**	**Female (ASR)**
Argentina	1.7	1.2	1.7	1.8	1.7
Australia	3.7	1.9	6.4	7.5	5.4
China	0.6	0.5	0.4	0.5	0.3
Colombia	1.4	1.1	1.0	1.0	1.1
Hong Kong	ND*	ND	ND	ND	ND
Mexico	1.3	0.9	1.0	1.1	0.9
Republic of Korea	1.8	1.1	2.2	2.1	2.2
Russian Federation	1.2	0.9	1.6	1.6	1.7
Saudi Arabia	1.0	0.8	0.4	0.5	0.4
Singapore	1.3	0.6	1.5	1.6	1.3
South Africa	2.0	1.7	1.1	1.1	1.2
Taiwan	ND*	ND	ND	ND	ND
Turkey	2.9	2.3	2.0	2.1	1.8
World	1.5	1.0	1.5	1.6	1.3

*ND – No data available

Sources: Bray et al, 2013 [2]; Ferlay et al, 2013 [3].

4 Study objective(s)

4.1 Primary objective

To describe time to next treatment (TTNT)* at each line of therapy# in patients receiving frontline treatment for newly diagnosed Multiple Myeloma (NDMM), Cohort 1, and in patients with relapsed or refractory MM (RRMM), Cohort 2.

*Limited retrospective availability of clinical data to measure progression free survival (PFS)

[#]Line of therapy as determined by progression status, i.e. treatments received prior to first progression = 1st line, treatments received between 1st and 2nd progression = 2nd line, etc

4.2 Secondary objectives

To describe the following, in patients receiving frontline treatment for NDMM (Cohort 1) and in patients with RRMM (Cohort 2):

1. Patient demographic and clinical characteristics.
2. Treatment patterns for MM.
3. Clinical outcomes:
   a. Relapse rate at 6, 12, 18, 24, 36 and 60 months.
   b. Overall survival (OS) rate at 6, 12, 18, 24, 36 and 60 months.
   c. Number of relapses per patient.
4. For each line of therapy[#]:
   a. Best response after start of treatment, as defined by the International Working Group Uniform Response Criteria for Multiple Myeloma (see appendix 1) or as determined by treating physician..
   b. Time to first response.
   c. Time to best response.
   d. Duration of best response.
   e. Adverse events experienced.
   f. The MM-related healthcare resource use associated with each line of therapy.
   g. The MM-related healthcare costs, associated with each line of therapy†.

[#]Line of therapy as determined by progression status, i.e. treatments received prior to first progression = 1st line, treatments received between 1st and 2nd progression = 2nd line, etc.

†Allocation of costs (for secondary objective 4g) is optional. Sections of the protocol that relate specifically to secondary objective 4g are shown in italics and may be deleted if the country is not participating in this part of the study.

All objectives will be described for the study sample overall and by each participating country.

5 Study administrative structure

Takeda Pharmaceuticals International AG is the sponsor of this non-interventional study, and will engage the services of a Contract Research Organisation (CRO) to operationalise the study globally. Takeda Pharmaceuticals International will retain overall responsibility for the study, but will delegate tasks as necessary to the CRO. A core protocol will be provided to the CRO, and they will be expected to identify/recruit study sites and manage subject recruitment. The data collection will be carried out by hospital staff. The appointed CRO will train the data collectors and provide support with data query management. Pseudonymised data from all participating centres and countries will be provided to the CRO for pooled analysis and reporting.

5.1 Study sites

The study is planned to be conducted in approximately 130 sites in across 13 countries within the Emerging Markets region (Argentina, Australia, China, Colombia, Hong Kong, Mexico, Republic of Korea, Russian Federation, Saudi Arabia, Singapore, South Africa, Taiwan and Turkey).

In each participating country, a geographically dispersed sample of up to 10 centres covering the range and distribution of care settings typical for that country (e.g. hospitals, cancer institutes, and academic medical centres) will be selected. Sites will be sourced from national databases (where available), Steering Committee advice, CRO experience and other local insights, and pre-screened using a feasibility questionnaire.

Sites will be selected on the basis that:

- They have specialist MM treatment centres.
- They manage patients throughout the whole treatment journey (from diagnosis to relapse and beyond) or can access data relating to the whole treatment journey.
- There are appropriate and sufficient personnel available for abstracting medical records and data collection internally (if hospital staff are required to collect the data after appropriate training).
- The have adequate means to identify eligible patients robustly and systematically for the study (e.g. database, department records or equivalent).

- Adequate numbers of eligible patients are available for inclusion in the study (minimum 5 - 10 patients in the RRMM group).

Takeda Global Research will keep a record of the individuals responsible for each participating Study Site, the Site Responsibles.

5.2 Sponsor personnel

Takeda Local Operating Country (LOC) will keep a record of all relevant sponsor personnel.

5.3 Contract Research Organisation (CRO)

The CRO will keep a record of all involved CRO personnel involved in any aspect of the study, e.g. site selection, study start up, data collection, query management, safety reporting, analysis and study reporting.

5.4 Essential documents

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

- Written agreement between Takeda and/or the CRO and the Study Site 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 (notified to / approved by Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) as locally required)
- Written IEC / IRB approval / vote according to local regulations
- Authority approval according to local regulations
- Local insurance certificate as applicable

6 Ethics

This study is an observational study where the existence of the study has no impact on the subject except for collection of informed consent (where required as per country regulations) to use of the subject’s data.

6.1 Ethical conduct of the study

This study will be conducted in accordance with the protocol, the current version of the Declaration of Helsinki [9], International Society for Pharmacoepidemiology (ISPE) Good Pharmacoepidemiology Practices (GPP) [10] and any applicable local regulations. Special attention will be paid to data protection. The CRO will ensure adherence to any country-specific requirements for data protection.

Takeda/the appointed CRO will ensure that the protocol, any amendments, and the Subject Information Sheet/Informed Consent Form are submitted to the relevant IECs/ IRBs according to local requirements. As the sponsor, Takeda is responsible for meeting the International Conference on Harmonisation (ICH) requirement for yearly updates to the IECs/IRBs, if applicable.

6.2 Independent Ethics Committee / Institutional Review Board and Authorities

IEC/IRB

According to applicable regulations, the appointed CRO or the Site Study Responsible will:

- notify or obtain approval from the relevant IEC/IRB of the protocol, any amendments and the Subject Information Sheet and Informed Consent Form, where relevant.

The appointed CRO or the Site Study Responsible will submit required documents to the IEC/IRB, such as:

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

Takeda Global Research will keep an updated list of all submission and approval dates of all documents submitted to the IEC/IRB and will provide the Site Responsible with a copy of this list. Copies of the documents will be distributed upon request.

6.3 Subject information and written informed consent

Eligible patients will be approached to provide written informed consent for their medical records to be reviewed for study data collection (if this is required by local laws and regulations). A waiver will be sought from ethics committees wherever possible to seek consent to access the medical records of deceased patients for the purpose of this study.

The Site Study Responsible must give the subject oral and written information about the study in a form that the subject can understand, and obtain the subject's written consent before collection of identifiable subject information (hereinafter referred to as personal data). Before consenting, the subject 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 subject must agree that sponsor personnel, their representatives or IEC/IRB or CA personnel (national or other) may require direct access to the subject's data / personal records which were collected, processed and stored in an anonymous form.

The subject 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 subject or legal guardian, if applicable, has the right to withdraw his/her 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.

7 Study design and plan

This study is a 'non-interventional study' as defined in: G-STND-PV-006, Directive 2001/20/EC [11] and will follow the guidelines for GPP [10].

This means that:

- The assignment of a subject 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 subjects
- Epidemiological methods shall be used for the analysis of collected data.

This is a two cohort, international, multi-centre, retrospective observational research study involving retrospective review of medical records (paper and/or electronic, as applicable locally) of patients who have newly diagnosed symptomatic MM (Cohort 1) or patients presenting with RRMM (Cohort 2) between 01st January 2010 and 31st December 2011 (inclusive).

Pseudonymised data will be collected according to the agreed minimum dataset (see section 10) using a standardised study case report form (CRF). Key variables will include those related to patient characteristics, diagnosis, treatment information, resource use, clinical outcomes, and adverse events.

Web-based data collection will be employed. Data collected on the CRF will include, in summary, the following:

1. Inclusion and exclusion criteria
2. Baseline status of patient including medical history and stage of disease
3. Name, date and dosage of MM treatment regimen
4. MM treatment-related adverse events
5. Parameters for response evaluation
6. Any other parameters necessary to evaluate the study endpoints
7. Survival status of patient
8. HRU data
9. Reason for end of observation period

For each patient included with NDMM (Cohort 1), data will be collected from the date of diagnosis until the death of the patient, or the date of data collection (whichever occurs first). For patients with RRMM (Cohort 2), a summary of treatments received prior to diagnosis of RRMM will be collected; detailed data will be collected from the date of RRMM diagnosis until the death of the patient or the date of data collection (whichever occurs first). It is possible that patients are counted in both Cohorts 1 and 2 if they present with NDMM and RRMM within the eligibility period.

Resource use data will be collected for periods when the patient is receiving active treatment for MM or RRMM, to enable the healthcare resource use [*and costs*] associated with each line of treatment to be quantified.

The collection of data will be carried out by hospital staff. QuintilesIMS will train the data collectors and provide support with data query management. Pseudonymised (anonymised-coded) data from all participating centres will be provided to QuintilesIMS for pooled analysis and reporting.

It is expected that data collection for the study will last approximately 12 months.

7.1 Study schedule

The appointed CRO will ensure that End-of-Study notification is submitted to the concerned authorities and IEC/IRB for each site, for each country and for the complete study, as locally required.

Global Research will ensure that results are posted on "clinicaltrials.gov" and as required by local authorities.

Based on upcoming knowledge, Takeda might choose to terminate the study prematurely. In such case the Committee(s), study sites, IECs/IRBs and authorities will be informed promptly by the appointed CRO.

7.2 Discussion of study design

A retrospective chart review is an appropriate and scientifically robust method of collecting data that currently exists in patients' medical records. By including both living and deceased patients (where possible), bias of excluding patients with more severe disease is avoided. A prospective study design would not be practical with this patient population and the length of follow up that would be required to determine study endpoints. The observation period chosen (from 2010 and 2011 to 2016 and 2017, respectively) provides a relatively recent review of clinical practice while providing sufficient follow up for study endpoints.

Including 13 countries in the study with multiple sites in each country ensures a geographically dispersed sample of sites from different settings (hospitals, cancer institutes, and academic medical centres) is included which ensures the data is representative of the EM region.

7.2.1 Study limitations

Patients may have received some of their treatment in outlying hospitals separate from the participating centres, and the available summary of treatment received there may not be as detailed as that from the participating hospital itself. This may limit the completeness of treatment information reported in the study.

Retrospective studies rely on the quality of the data routinely recorded in patients' medical records. In studies where data are derived medical records, it is unlikely that all cases will be captured for each of the clinical outcomes of interest, such as relapse rate and death (for overall survival rate). Furthermore, there is likely to be some delay between relapse occurrence and patients presenting to their physician with suspected relapse.

Additionally, the data collected will represent the practices of individual physicians / centres and may vary from non-participating physicians (e.g. those who refused study participation, failed to complete the study requirements on time and were excluded from the study, or were unresponsive to the screening invitation). Patients of non-participating physicians may have profiles, treatments, and outcomes that differ from those of study patients; thus, the generalisability of study results may be limited.

Adverse events may be under-reported or under-documented in a routine clinical setting compared to what would be expected from a controlled trial or prospective study. Assessment of treatment response may be different in a routine clinical setting as compared to the monitoring that would be expected in a controlled trial setting or prospective study.

Within each country's sample of between 100 and 400 patients (minimum of 50 NDMM and 50 RRMM), the number of patients who relapse after ASCT, and who receive each treatment option after ASCT relapse, may be prohibitively small for analysis. For therapies at second line and beyond, the number of patients and duration of follow-up may be too small to measure PFS. Follow-up periods may be short in some of the RRMM patients (who were also in the NDMM group). All patients included in the study will have an observation period of 5-6 years after diagnosis of MM or presentation with RRMM, which may not be sufficient to describe median OS and PFS for all lines of therapy.

7.3 Selection of study population

It is intended that 50% of patients will be those with MM newly diagnosed during the study eligibility period and 50% with RRMM. To account for different population sizes, between 100-400 patients will be consecutively enrolled from each country to yield approximately 2600 patients in total. The sample will be stratified equally with approximately 50% patients per country in the MM group (Cohort 1) and 50% in the RRMM group (Cohort 2).

The maximum number of patients to be recruited in any one country will be determined by the CRO, in consultation with Takeda, who will monitor recruitment on an ongoing basis and notify sites when patient recruitment should cease. The number of patients to be recruited at each site (including site-specific recruitment targets and maximum number of patients per site) will also be decided by the CRO, in consultation with Takeda depending on the size of the local patient population and expected number of eligible patients.

Inclusion criteria

1. Patients who have newly diagnosed symptomatic MM (cohort 1) or presented with RRMM (cohort 2) between 01st January 2010 and 31st December 2011 (inclusive).
2. Patients who have completed at least one full line of treatment.
3. Age ≥18 years at first diagnosis of MM (Cohort 1) or at diagnosis of RRMM (Cohort 2).
4. Alive or deceased.
5. Patient provides written informed consent for study data collection (as required by local regulations).

Exclusion criteria

1. Patients for whom the minimum study dataset (Table 3) is unavailable from their hospital medical records.
2. Patients with smouldering myeloma (as defined in appendix 2).
3. Patients with monoclonal gammopathy of unknown significance (MGUS) (as defined in appendix 2).
4. Patients enrolled in a clinical trial of an investigational medicinal product during the observation period.

Patients will be identified at each site using hospital central management information systems, local department databases, pharmacy databases, or multidisciplinary team records (as applicable locally), and screened for eligibility by a member of the direct care team at each site. Physicians will be asked to select consecutive patients for inclusion in the study, according to study-specific inclusion/exclusion criteria (see above) and date of MM or RRMM diagnosis, until the target sample size has been met.

Written informed consent will be obtained from each patient prior to participation (where required by local regulations). Patients newly diagnosed with MM between 2010 and 2011 and who are subsequently diagnosed with RRMM may be included in both groups, provided that RRMM was also diagnosed between 2010 and 2011. Examples of study eligibility are shown in Table 2.

Table 2: Patient eligibility for study Cohort 1 (NDMM) and Cohort 2 (RRMM) – examples

Example	Date of new MM diagnosis	Date of RRMM diagnosis	Study eligibility
1	01 March 2011	-	Include in NDMM group (Cohort 1) only
2	01 May 2008	01 May 2010	Include in RRMM group (Cohort 2) only
3	01 February 2010	01 December 2011	Include in both NDMM and RRMM groups
4	01 November 2009	01 November 2014	Exclude – patient not eligible

7.4 Treatments

Non-interventional/observational – no treatments/pharmacotherapy are required as part of this study.

8 Conduct

Written informed consent will be obtained prior to any patient specific data collection, where this is required according to country regulations. The patient level data to be collected from the medical records is shown in Tables 3 and 4 below.

Table 3: Minimum dataset

Variable
Patient characteristics
• Centre location (centre, country)
• Gender
• Date of birth
• Date of MM diagnosis and each subsequent relapse
• Date of start of frontline treatment
• Prior therapies for MM (Cohort 2 only)
Treatment pathways
For each line of treatment:
• Name of therapy regimen
• Total doses administered
• Total cycles administered
• Start and end dates
• Reason for treatment change
For transplant:
• Transplant eligible (Yes / No)
• Date of transplant
• If transplant not undertaken, reason for this
Clinical Outcomes
• All date(s) of documented relapse or disease progression during the study observation period (from start of frontline treatment)
• Date of death, if patient died
• Cause of death, if patient died (MM related / adverse event / treatment related / other)
• Date of assessment
• Response (CR, VGPR, PR, SD, PD, sCR) or as determined by treating physician
Treatment-related adverse events following each therapy:
• Date detected

• Type (Serious / non-serious)

Resource Use
From start of frontline treatment until the date of the patient's death or the date of data collection (whichever occurs first). Only for periods when the patient is receiving active treatment for MM. For each type of resource, indicate (Yes / No) whether visit was for adverse event management.
• Hospital admission dates
• Hospital discharge dates
The details and source of costs will be agreed at country-level and will be detailed in the SAP

Table 4: Dataset of optional data items

Variable
Patient characteristics
• Ethnicity
• History of occupational toxicity or chemical exposure
• Height at diagnosis
• Weight at diagnosis
• Clinical stage at diagnosis
• Histological type and subtype of MM
• CRAB criteria
• Relevant co-morbid conditions
• Clonal bone marrow plasma cells
• FISH results with dates
• ISS & Durie-Salmon (DS) stage with dates
• ECOG
Treatment pathways
For each line of treatment:
• Clinical stage at initiation
• Dose / frequency and details (including reason) of any dose delays
• Reason for treatment discontinuation (if applicable)
• Frequency of tests received (including PET, CT, MRI, skeletal surveys,

serum/urine M-protein assays, light chain assays, bone marrow biopsy, SPEP/UPEP, FISH & cytogenic tests, immunofixation assay)
• Results and other details of tests received (including PET, CT, MRI, skeletal surveys, serum/urine M-protein assays, light chain assays, bone marrow biopsy, SPEP/UPEP, FISH & cytogenic tests, immunofixation assay)
• Other treatments (e.g. blood transfusions, antibiotic use)
For transplant:
• Type of transplant (allo / auto)
• Source of stem cells (bone marrow / peripheral)
• Type of allo-SCT (matched, related, unrelated)
• If transplant not undertaken, reasons (not eligible, e.g. advanced age, co-morbid conditions, chemo-resistant disease, cumulative toxicities, patient choice – reason; eligible - patient choice, insufficient finance, inability to mobilize stem cells, loss of response to chemotherapy, toxicity, other)
Clinical Outcomes
• Patient lost to follow up Y/N, if yes, last date seen
• Assessments of response to each line of therapy
Adverse events following each therapy:
• Description
Resource Use
From start of frontline treatment until the date of the patient's death or the date of data collection (whichever occurs first). Only for periods when the patient is receiving active treatment for MM. For each type of resource, indicate (Yes / No) whether visit was for adverse event management.
Admissions:
• Elective or emergency admission
• Reason for admission
• Length of stay (overall and by unit/ward - general, high dependency/intermediate, intensive care unit [ICU])
Emergency room visits:
• Emergency room visit dates
Outpatient visits:

• Outpatient visits dates
• New appointment or follow-up
• Health Care Professional seen
• Face to face or telephone
• Date of scan or procedure by scan / procedure type
• Home health care visit dates
• Assisted living facility, nursing home, hospice, rehabilitation facility – date of visits (or date of admission / discharge) by type of facility
• Radiotherapy episode dates
Treatment with G-CSF or other treatments:
• Start and stop dates
• Name of treatment
• Dose
• For G-CSF, specify whether pegylated (Yes/No)
The details and source of costs will be agreed at country-level and will be detailed in the SAP

9 Safety reporting

9.1 Definitions

Adverse event

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 unfavourable 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.

Adverse drug reaction

An adverse drug reaction (ADR) is any response to a medicinal product that is noxious and unintended and that occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of diseases or for the restoration, correction, or modification of physiological function. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse reaction also includes adverse clinical consequences associated with use of the product outside the terms of the Summary of Product Characteristics or other conditions laid down for the marketing and use of the product (including prescribed doses higher than those recommended, overdoses, or abuse).

As this study is a secondary analysis of medical records, an AE will only be considered as an ADR if there is an explicit statement in the medical record that the adverse event was caused by the medicinal product.

Special situation reports and product quality issues

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 authorisation, also known as “off-label”.
- Use of falsified medicinal product.

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

9.2 Classifications

Seriousness

A serious ADR or AE (SADR/SAE) is any ADR or AE which results in death, is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Life-threatening in this context refers to a reaction/event in which the subject was at risk of death at the time of the reaction/event. It does not refer to a reaction/event that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of dependency or abuse.

Any suspected transmission of an infectious agent via a medicinal product is considered a serious adverse reaction.

Causality

- Related: A reasonable temporal relationsship between the medicinal product administration and the event where there is no other obvious explanation for the occurrence of the event
- Not related: There is evidence for (an) alternative explanation(s) for the event (e.g. the event is explained by one or more of the following: a) the subject's medical condition (medical history, disease progress, indication), b) a concomitant medication for which the event is labelled, or c) AE occurrence prior to the introduction of the medicinal product.

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.

9.3 Collection and recording of adverse events, special situation reports and product quality issues

9.3.1 Spontaneously reported events

If, during the conduct of the study, a member of the research team is spontaneously informed of other AEs or SSRs that are not study endpoints, and the event pertains to a Takeda product (or unbranded generic), such information should be reported to the Sponsor or regulatory agency in the country in which the event occurred. As such reports are spontaneously notified, causality of any adverse events should be assumed unless there is evidence to the contrary. See appendix 3 for the drug safety officer email address for each country in the study for spontaneous reporting of events.

9.3.2 Events identified from chart review

AEs that are study endpoints (all AEs during treatment) and SSRs, as defined in appendix 4 - Table 3, should be systematically identified, abstracted, and summarized as part of any interim analysis and in the final study report.

9.3.3 Reporting of adverse drug reactions and special situation reports to regulatory agencies

The Sponsor shall notify regulatory agencies in accordance with local regulatory requirements or Sponsor's post-marketing commitments.

10 Data quality control and assurance

10.1 Quality control

All CRFs will be field-tested for reliability and validity with a minimum of 2-3 physicians, and their recruited MM patients.

As this study will involve recruitment and participation of multiple investigators (with their site staff) in multiple countries across the EM region, ensuring that understanding of questions, terms, and guidelines is uniform across physicians is essential to the quality of the data collected and the minimisation of biases in interpretation. A research brief and detailed data collection instructions including clear, concise definitions of questions, terms, and guidelines will be provided by the CRO.

Data cleaning and validation will be conducted prior to the conduct of statistical analyses. Database lock will occur at the end of the study, unless otherwise specified (refer to Section 10.4 on Data Management for more details). Data validation for key data points will be conducted on 10% of the completed CRFs via telephone or queries in eCRF (where used). Physicians will be asked to re-abstract or provide key data points based on the original source document, i.e., the medical record. Physicians should not share patient's confidential information when providing key data points.

In the case where certain data points are missing from patients' medical records, the method for the handling of this missing data (e.g. imputation of missing values or complete case analysis) will be detailed in the SAP.

10.1.1 Data-related quality controls

The data management processes employed will ensure strict oversight of data entry to ensure the appropriate quality control measures, e.g., CRF review for data logic, data inconsistency, data query and discrepancy resolution, and documentation are conducted.

All work will be subject to quality control and documentation procedures to ensure that the study reporting is accurate and thorough, and the analyses can be reproduced. If the data do not permit an analysis as planned (e.g., through insufficient sample size in a stratified analysis), or if clarifying analyses are required (e.g., an unexpected result that could be explained by a sub-group analysis), the CROs will inform the client and include the additional information and results in reporting.

10.2 Audit from Quality Assurance Unit

The Quality Assurance (QA) Unit may audit the study to ensure that study procedures comply with the protocol and standard operating procedures, and that collected data is correct and complete.

10.3 Inspection by Institutional Review Board/Independent Ethics Committee or competent authority

Representatives from IRB/IEC 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 Global Research and must make the records available as requested.

10.4 Data management

Data management will be the responsibility of the appointed CRO. Data Management will be carried out according to a Data Management Plan (DMP), which will identify the location of the CRO’s data management facility. The DMP must be written and approved before the design of the study database is finalised. 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 subject is known not to be available in spite of it being required, data for this subject is not entered into or is deleted from the database.

Data management processes: To include detailed processes for the following activities:

- Pilot study
- Study instruction handouts / materials
- Internal staff training
- Study monitoring and physician follow-up
- CRF editing and online review
- Data validations
- Documentation of missing and anomalous data and resolution directly with investigators

Data tabulations and statistical analyses will be conducted using SAS version 9.4 (this applies to tabulations i.e. data analysis, and statistical analyses, i.e. Tables, Listings, and Figures [TLFs]).

At the conclusion of the study, final, locked datasets will be delivered in a format acceptable to the sponsor e.g., SAS. A detailed format and label program containing a description of each study variable and associated format will accompany their delivery.

Data handling

Data collection, processing, storage and usage will follow data protection / privacy regulations and guidelines in each country. All results will be reported in a de-identified, aggregate manner. Physicians will be identified only by assigned identifiers and patients will be distinguished by assigned identifiers. At the end of data collection, physicians will be instructed to maintain the master links between patient study identifier and the patient name and other direct identifiers on site for a period consistent with the study sponsor’s standard operating procedures. Before site closure, each site will be provided with an electronic copy of their own data.

If a subject is erroneously included in the study more than once only the data relating to the first inclusion will be kept in the database and be available for analysis. Data from later inclusions will be transferred to the first dataset when relevant, i.e. if collected within the time frame of the first follow-up period.

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

The subjects will be identified in the database only by Study ID, Site ID, subject number, gender, month and year of birth.

10.4.1 Data collection tools and flow

The Study Site will receive data collection tools (CRFs, access to electronic data capture etc) from Takeda. Whenever possible, complete data sets should be entered. Text field entries and any data collected on paper should be legible and follow the requested language standard.

The Study Site Responsible must sign off the complete data set for each subject, confirming the collected data. ADR data reported according to section 9 should be signed off separately by a physician who may or may not be involved in the study.

Web-based data collection will be employed. The data entry site will be password protected and physicians who have signified their preference for completing the study online will receive a password in order to access the study. Further details can be found in the DMP.

11 Statistical methods and determination of sample size

Satistical analyses will be performed by the appointed CRO. Descriptive analyses will be conducted to describe patient demographics and clinical characteristics, treatment patterns, clinical outcomes, healthcare resource use (HRU) [*and costs*].

11.1.1 Categorical and continuous endpoints

Key categorical endpoints will be summarised using both the number and percentage in each category. Only patients with data available for a particular variable will be included in the calculation of a percentage. The number with data for analysis will be shown for each analysis. Key continuous endpoints (e.g. duration of treatment, HRU) will be summarised using the summary statistics of mean and standard deviation (StDev), median and interquartile range (IQR).

11.1.2 Time to event endpoints

Key time to event endpoints (e.g. OS, PFS) will be summarised in terms of the total number of events observed and the proportion of patients who have died / progressed at a given milestone (Appendix 4 Table 3) after accounting for censoring using Kaplan-Meier curves.

In addition to the descriptive analyses, multivariate analyses will be conducted if possible to adjust for differences in patient demographic, clinical, and treatment characteristics, as well as risk factors that will be conducted for key time to event analyses, when treatment subgroups will be compared within the RRMM or NDMM cohorts wherever possible (Appendix 4).

11.1.3 Objectives-based analysis plan

The endpoints relating to each study objective are listed in appendix 4. Specific statistical analyses will be outlined in greater detail within the forthcoming SAP, which also include tables, listings and figures (TLFs) shells.

11.1.4 Interim and final analyses

An interim analysis is planned, based on all patients' data collected up to a pre-determined time point (approximately three to five months after first patient in). The interim analysis will include results for key variables, to be outlined in further detail in the SAP.

The final analysis will include the full study population and all analyses outlined above, to be delivered in the form of populated data tables and a final Clinical Study Report.

11.2 Statistical analysis plan

For details of the statistical analyses please refer to the SAP and the endpoints presented in appendix 4.

The SAP describes the statistical analyses as foreseen at the time of planning the study. Any known deviations from the planned analyses, the reason for such deviations and all alternative / additional statistical analyses that may be performed as well as the final statistical analysis must be described in a revised SAP before completion of data collection. All later deviations and / or alterations will be summarised in the Clinical Study Report.

This study is observational and epidemiological methods will be employed for data analyses.

Descriptive analysis will be performed of all collected data except data collected only for the purpose of data cleaning, i.e. all data listed in section 8.

The aim of this study is to describe the treatments and associated clinical outcomes for patients with NDMM and RRMM in different countries in EM regions. This will contribute to a greater understanding of current treatment patterns, which will help to inform future clinical decision making.

ADRs reported in the study as well as ADRs reported directly to authorities and to Takeda International Drug Safety (IDS) according to section 7.3 and not captured in the study database will be extracted from the overall safety database and the study database and listed or tabulated in the final report in the standard way of presenting such data in a Periodic Safety Update Report (PSUR).

11.3 Determination of sample size

The aim of this study is to describe the treatments and associated clinical outcomes for patients with MM and RRMM in different countries in Emerging Market regions. This will contribute to a greater understanding of current treatment patterns, which will help to inform future clinical decision making.

Approximately 2600 patients will be recruited in 13 participating countries within the EM region. The number of sites in each country which are needed to achieve the required sample size will be determined based on local feasibility within each country. The overall study sample, and patients per country, will consist of approximately 50% patients in the NDMM group (Cohort 1) and 50% in the RRMM group (Cohort 2). To account for different population sizes, between 100-400 patients will be consecutively enrolled from each country to yield approximately 2600 patients in total.

The reliability of different mean and median PFS (measured using TTNT as surrogate) estimates for various sample / sub-group sizes are shown in Table 5 and Table 6 respectively.

Table 5: Reliability of the mean PFS at various sample sizes

Observed mean PFS (months)	95% Confidence limits (CLs)							
	n = 25		n =50		n = 100		n = 200	
	LCL	UCL	LCL	UCL	LCL	UCL	LCL	UCL
12	10.4	13.6	10.9	13.1	11.2	12.8	11.4	12.6
15	13.0	17.0	13.6	16.4	14.0	16.0	14.3	15.7
18	15.6	20.4	16.3	19.7	16.8	19.2	17.2	18.8
21	18.2	23.8	19.0	23.0	19.6	22.4	20.0	22.0
24	20.8	27.2	21.7	26.3	22.4	25.6	22.9	25.1
27	23.4	30.6	24.5	29.5	25.2	28.8	25.7	28.3
30	26.0	34.0	27.2	32.8	28.0	32.0	28.6	31.4
33	28.6	37.4	29.9	36.1	30.8	35.2	31.4	34.6

LCL – Lower confidence limit

UCL – Upper confidence limit

Table 6: Reliability of the median PFS at various sample sizes

Observed median PFS (months)	95% Confidence limits (CLs)							
	n = 25		n = 50		n = 100		n = 200	
	LCL	UCL	LCL	UCL	LCL	UCL	LCL	UCL
10	7.9	12.1	8.3	11.7	8.5	11.5	8.7	11.3
12	9.5	14.5	10.0	14.0	10.3	13.7	10.4	13.6
14	11.1	16.9	11.7	16.3	12.0	16.0	12.2	15.8
16	12.7	19.3	13.3	18.7	13.7	18.3	13.9	18.1
18	14.3	21.7	15.0	21.0	15.4	20.6	15.7	20.3
20	15.9	24.1	16.6	23.4	17.1	22.9	17.4	22.6
24	19.1	28.9	20.0	28.0	20.5	27.5	20.9	27.1
27	21.5	32.5	22.5	31.5	23.1	30.9	23.5	30.5
30	23.8	36.2	25.0	35.0	25.6	34.4	26.1	33.9
33	26.2	39.8	27.5	38.5	28.2	37.8	28.7	37.3
36	28.6	43.4	30.0	42.0	30.8	41.2	31.3	40.7

LCL – Lower confidence limit

UCL – Upper confidence limit

For both the mean and median PFS time outcomes, samples of 50 or more give reliable outcomes as they generate reasonably reliable estimates of the standard deviation of the PFS distribution. Therefore, a sample of at least 50 (50-200) patients with NDMM and at least 50 (50-200) patients with RRMM per country will be used in this study. This will give reliable estimates of the mean and median PFS at a country level, both for the sample as a whole or for any subgroups of 50 or more (for countries with larger populations of eligible patients).

11.3.1 Primary endpoint

Endpoints will be presented for the overall sample and separately for each participating country.

TTNT will be used as a surrogate measure of PFS. TTNT is defined for Cohort 1 as the time from initiation of first treatment for MM and for Cohort 2 as the time from initiation of first treatment following presentation with RRMM, to date of next treatment or death, censored at date of data collection.

11.3.2 Secondary endpoints

Secondary study endpoints include patient characteristics (appendix 4 - Table 1), treatment pathways (appendix 4 - Table 2), clinical outcomes & adverse events (appendix 4 - Table 3), resource use [*and costs*] (appendix 4 – Table 4). Endpoints will be reported separately for NDMM (Cohort 1) and RRMM (Cohort 2) patients. Patients newly-diagnosed with MM between 2010-2011, who are subsequently diagnosed with RRMM (between 2010 and 2011), will be included in the analysis for both groups.

It is also intended that sub-group analyses will be performed in order to describe the outcomes associated with different treatment regimens, including ASCT and non-ASCT.

Secondary endpoints include descriptions of patient demographic and clinical characteristics, MM treatment pathways, adverse events and resource use for both the NDMM and RRMM groups. Outcomes that are simply counted (e.g. presence or absence of risk factors, use of specific treatments) will have less precision than the primary endpoint, while those that are measured (e.g. age and measurable risk factors) and healthcare resource use of hospital visits, inpatient admissions [*and their respective costs*] will be more precise, similar to the mean PFS. It is acknowledged that for some analyses (e.g. patients receiving each treatment after ASCT) the number of patients in each country with data available is likely to be small.

12 Reports

A Clinical 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 one year from collection of the last data point, and the participating sites should be informed about the results when the report is finalised.

13 Publications

It is planned that results of this study will be presented at an upcoming conference (venue to be determined based on timing of results availability) and/or submitted for publication in appropriate peer reviewed medical journal(s).

14 Archiving of study documentation

During the course of the study the Site Responsible must as a minimum file the essential documents (Section 5.4), the protocol, any amendments, the list of participating subjects, the written informed consents, the CRFs 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 5 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.

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Appendices

Appendix 1: International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma[12]

Response	IMWG Response Criteria
sCR	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow[1] by immunohistochemistry or immunofluorescence[2]
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or > 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h
PR	≥ 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h If the serum and urine M-protein are unmeasurable[3], a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

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[1] Confirmation with repeat bone marrow biopsy not needed.

[2] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.

[3] All relapse categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR patients must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression-free survival.

Appendix 2: International Myeloma Working Group (IMWG) Criteria for the Diagnosis of Multiple Myeloma[13,14]

Plasma Cell Disorder	**Diagnostic Criteria**
Symptomatic multiple myeloma	• M-protein in serum and/or urine • Bone marrow (clonal) plasma cells* or plasmacytoma • Related organ or tissue impairment (end organ damage, including bone lesions) * If flow cytometry is performed, most plasma cells (>90%) will show a 'neoplastic' phenotype. Some patients may have no symptoms but have related organ or tissue impairment.
Smouldering multiple myeloma	Both criteria must be met: • Serum monoclonal protein (IgG or IgA) ≥30g/L or urinary monoclonal protein ≥500mg per 24h and/or clonal bone marrow plasma cells 10-60% • Absence of myeloma-defining events or amyloidosis
Non-IgM monoclonal gammopathy of undetermined significance (MGUS)	• Serum monoclonal protein <30g/L • Clonal bone marrow plasma cells <10% • Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder

Appendix 3: Spontaneous reporting to Sponsor

Country	Drug safety email
Argentina	PPD
Australia	[redacted]
China	[redacted]
Colombia	[redacted]
Hong Kong	[redacted]
Mexico	[redacted]
Russia	[redacted]
Saudi Arabia	[redacted]
Singapore	[redacted]
South Africa	[redacted]
South Korea	[redacted]
Taiwan	[redacted]
Turkey	[redacted]

Appendix 4: Study endpoints

Table 1: Endpoints relating to patient characteristics

	Cohorts 1 and 2
	Patients diagnosed with MM or RRMM between 01 January 2010 and 31 December 2011, who received at least one active treatment during this period
Patient characteristics	• Gender distribution • Distribution, mean (StDev) and median (IQR) age at MM diagnosis • Distribution of ethnicity • Distribution of history of occupational toxicity or chemical exposure • Distribution of MM type and subtype • Distribution, mean (StDev) and median (IQR) height at MM diagnosis • Distribution, mean (StDev) and median (IQR) weight at MM diagnosis • Distribution, mean (StDev) and median (IQR) age at MM diagnosis and start of frontline treatment. • Distribution, mean (StDev) and median (IQR) age at MM diagnosis, at start of frontline treatment and at date of each subsequent relapse (Cohort 2 only) • Distribution of transplant eligible/transplant ineligible patients • Prior therapies for MM (including frontline, induction-related, consolidation, pre-ASCT, post ASCT maintenance therapy and post-relapse) (Cohort 2 only) At MM or RRMM diagnosis: • CRAB criteria (including values, where relevant): calcium, renal function, anemia, bone lesions) • Clonal bone marrow plasma cells (percentage) • FISH result (if available)

	• Number of previous treatment regimens. (Cohort 2 only) • Distribution of co-morbid conditions: • Cardiovascular disease • Dementia • Chronic pulmonary disease • Rheumatologic disease • Peptic ulcer disease • Hepatic disease • Diabetes • Hemiplegia • Renal disease • In-situ malignancies • Secondary malignancies • HIV / AIDS • Obesity • Other conditions At diagnosis, at start of frontline treatment and at start of other treatments (or each relapse for Cohort 2): • Clinical staging (where available). • International Staging System (ISS) stage or Durie-Salmon stage • ECOG

Table 2: Endpoints relating to treatment patterns

	Cohort 1 and 2

	Patients diagnosed with MM or RRMM between 01 January 2010 and 31 December 2011, who received at least one active treatment during this period
Treatment patterns	• Proportion of patients who receive / do not receive ASCT • Reason for why patient did not receive ASCT (advanced age, co-morbidities, chemo-resistant disease, cumulative toxicities, patient refusal, other) • Distribution of frontline treatment regimens • Median (IQR) number of treatment cycles associated with each regimen • Median (IQR) number of treatment months associated with each regimen • Non-ASCT patients (include transplantation in prior line but not eligible for second transplantation, identified as non-eligible treatment at front line and never received transplantation) • Distribution of treatment regimens received at each stage of treatment • Mean (StDev) and median (IQR) number of cycles received at each stage of treatment, for each treatment regimen • Median (IQR) number of treatment months associated with each stage of treatment, for each treatment regimen • Mean (StDev) and median (IQR) time from relapse (after frontline treatment) to first treatment post-relapse • Mean (StDev) and median (IQR) time to initiation of each subsequent treatment, both from relapse and from start of previous treatment. (Cohort 2 only) • Mean (StDev) and median (IQR) duration of each stage of treatment • Proportion of patients receiving positron emission tomography (PET) / computerised tomography (CT) assessment / Magnetic Resonance Imaging (MRI), skeletal surveys • Frequency of positron emission tomography (PET) / computerised tomography (CT) assessment / Magnetic Resonance Imaging (MRI), skeletal surveys • Distribution of results of positron emission tomography (PET) / computerised tomography (CT) assessment / Magnetic Resonance Imaging (MRI), skeletal surveys • Proportion of patients having serum /urine M-protein assays, light chain assays, bone marrow biopsy, SPEP/UPEP,

immunofixation assessments

- Frequency of serum /urine M-protein assays, light chain assays, bone marrow biopsy, SPEP/UPEP, immunofixation assessments
- Distribution of results of serum /urine M-protein assays, light chain assays, bone marrow biopsy, SPEP/UPEP, immunofixation assessments
- Proportion of patients receiving and frequency of cytogenetic tests and FISH
- Mean (StDev) and median (IQR) number of regimens lines of therapy per patient

Patients undergoing ASCT:

- Time from relapse after frontline treatment to ASCT (if applicable). (Cohort 2 only)
- Source of ASCT (bone marrow, peripheral)
- Distribution of ASCT induction regimens administered
- Length of induction therapy before ASCT
- Patterns of G-CSF prescribing (dose, date and numbers of courses)
- Length of consolidation/maintenance after transplantation

Patients who relapse after ASCT:

- Distribution of post-ASCT regimens received at each stage of treatment. (Cohort 2 only)
- Mean (StDev) and median (IQR) number of cycles received at each stage of treatment, for each treatment regimen. (Cohort 2 only)
- Mean (StDev) and median (IQR) number of treatment months associated with each stage of treatment, for each treatment regimen. (Cohort 2 only)
- Mean (StDev) and median (IQR) time from ASCT to first treatment after relapse. (Cohort 2 only)
- Mean (StDev) and median (IQR) time to initiation of each subsequent treatment from ASCT. (Cohort 2 only)

	• Mean (StDev) and median (IQR) time to initiation of each subsequent treatment from completion of previous treatment. (Cohort 2 only) • Mean (StDev) and median (IQR) duration of each stage of treatment. (Cohort 2 only) • Proportion of patients receiving PET/CT/MRI at each stage of the treatment pathway and frequency of assessment. (Cohort 2 only) • Proportion of patients undergoing subsequent ASCTs, median (IQR) number of ASCTs per patient and time from first to subsequent ASCTs. (Cohort 2 only) • Proportion of patients undergoing allogeneic stem cell transplantation. (Cohort 2 only) • Mean (StDev) and median (IQR) number of regimens lines of therapy per patient. (Cohort 2 only)

Table 3: Endpoints relating to clinical outcomes

	Cohorts 1 and 2
	Patients diagnosed with MM or RRMM between 01 January 2010 and 31 December 2011, who received at least one active treatment during this period
Clinical outcomes	Clinical outcomes to be presented for each treatment line received by non-ASCT patients, for ASCT therapy, and each post-ASCT treatment line in patients who relapse: • Best response to frontline treatment from start of therapy (CR, VGPR, PR, SD, PD, sCR) as defined by International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma, 2010 or as determined by treating physician • Proportion of patients with documented relapse or disease progression after start of frontline treatment • Median (IQR) duration of best response to frontline treatment from start of therapy, defined as the time from when the criteria for response are met to first documentation of relapse or disease progression • Median (IQR) time to first response, defined as the time from start of therapy to first documentation of relapse or disease progression • Median (IQR) time to best response, as defined by International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma, 2010 or as determined by treating physician • Proportion of patients alive at 6, 12, 18, 24, 36 and 60 months after start of frontline treatment • Relapse rate at 6, 12, 18, 24, 36 and 60 months after start of frontline treatment For patients who received ASCT: • Best response at end of induction, and 3, 6, 12 and 18 months after ASCT • Proportion of patients with documented relapse or disease progression after ASCT • Proportion of patients in response who are assessed as high risk of relapse

	• Relapse rate at 6, 12, 18, 24, 36 and 60 months • Median (IQR) number of relapses per patient during the observation period. (Cohort 2 only) For deceased patients: • Mean (StDev) and median (IQR) time to death (from diagnosis and from completion of frontline therapy) • Mean (StDev) and median (IQR) time to death (from diagnosis, from first relapse, from ASCT and from relapse after ASCT). (Cohort 2 only) • Distribution of cause of death (MM related / adverse event / other)
Treatment-related adverse events	• Distribution of treatment-related adverse events including infections, pneumonia, GI symptoms, liver/renal function impairment, hematologic toxicity, secondary primary malignancies (SPM), fatigue, rash and peripheral neuropathy (PN) associated with: o ASCT. o Each treatment regimen received by non-ASCT patients o Each post-ASCT treatment regimen • Distribution of adverse event seriousness (serious / non-serious)

Table 4: Endpoints relating to resource use [*and costs*]

	Cohorts 1 and 2
	Patients diagnosed with MM or RRMM between 01 January 2010 and 31 December 2011, who received at least one active treatment during this period
Resource use [*and costs*]	Resource use [*and costs*] will be reported for: • Frontline chemotherapy regimen (per patient) • ASCT (per patient per procedure) (Cohort 2 only) • Allogeneic stem cell transplantation (per patient per procedure) (Cohort 2 only) • Chemotherapy regimen (per patient) (Cohort 2 only) • Each post-ASCT chemotherapy regimen (per patient) (Cohort 2 only) Overall MM-related resource use [*and costs*] will be reported for each treatment line, as well as the resource use [*and costs*] associated with adverse event management. The following resource use parameters will be reported: • Mean (StDev) number of hospitalisations. • For hospitalisations; mean (StDev) length of stay, overall and by unit/ward (general, high dependency/intermediate, intensive care unit [ICU]). • Mean (StDev) number of emergency room visits • Mean (StDev) number of outpatient visits by healthcare professional seen • Mean (StDev) number of home health care visit days • Mean (StDev) number of assisted living facility, nursing home, hospice and rehabilitation facility visits and length of stay by type of facility • Mean (StDev) number of each type of scan / procedure including:

	• Cytogenetic tests • Skeletal surveys, serum/urine M-protein assays, light chain assays, FISH, gene expression profiling and other diagnostic tests • Mean (StDev) number of days of G-CSF treatment • Mean (StDev) number of days of treatment with medicines • Dose and duration of concomitant medications e.g. bisphosphonates, analgesics *[The costs associated with each frontline treatment will be calculated from the above resource use parameters using country-specific reference costs]*