Title: CLINICAL AND SOCIODEMOGRAPHIC CHARACTERIZATION OF MULTIPLE MYELOMA PATIENTS WITH SYMPTOMATIC RELAPSE AND/OR REFRACTORY DISEASE IN SPAIN

NCT Number: NCT03188536

Protocol Approve Date: 31/03/2017

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 Study Protocol

Short title: CharisMMa Study

Title: "CLINICAL AND SOCIODEMOGRAPHIC CHARACTERIZATION OF MULTIPLE MYELOMA PATIENTS WITH SYMPTOMATIC RELAPSE AND/OR REFRACTORY DISEASE IN SPAIN"

Study code: TAK-MMR-2017-01

Sponsor: Takeda Farmacéutica España S.A.
C/ Alsasua, 20. 28023 – Madrid
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Type of study: Observational Cross-Sectional Epidemiological Study

Protocol version: Final V 1.0

Date of protocol version: 31/03/2017

1 Administrative details

1.1 Contacts

A list of contacts at each participating site will be provided separately.

Task	Contact
Serious adverse event (SAE) and pregnancy reporting	PPD
Responsible Medical Officer /Takeda (medical advice on the protocol and medical management of patients)	
Medical Monitor / Bioclever (carries overall responsibility for the conduct of the study)	

Study Lead Physician (overall responsibility for study conduct)	PPD

1.2 Approval

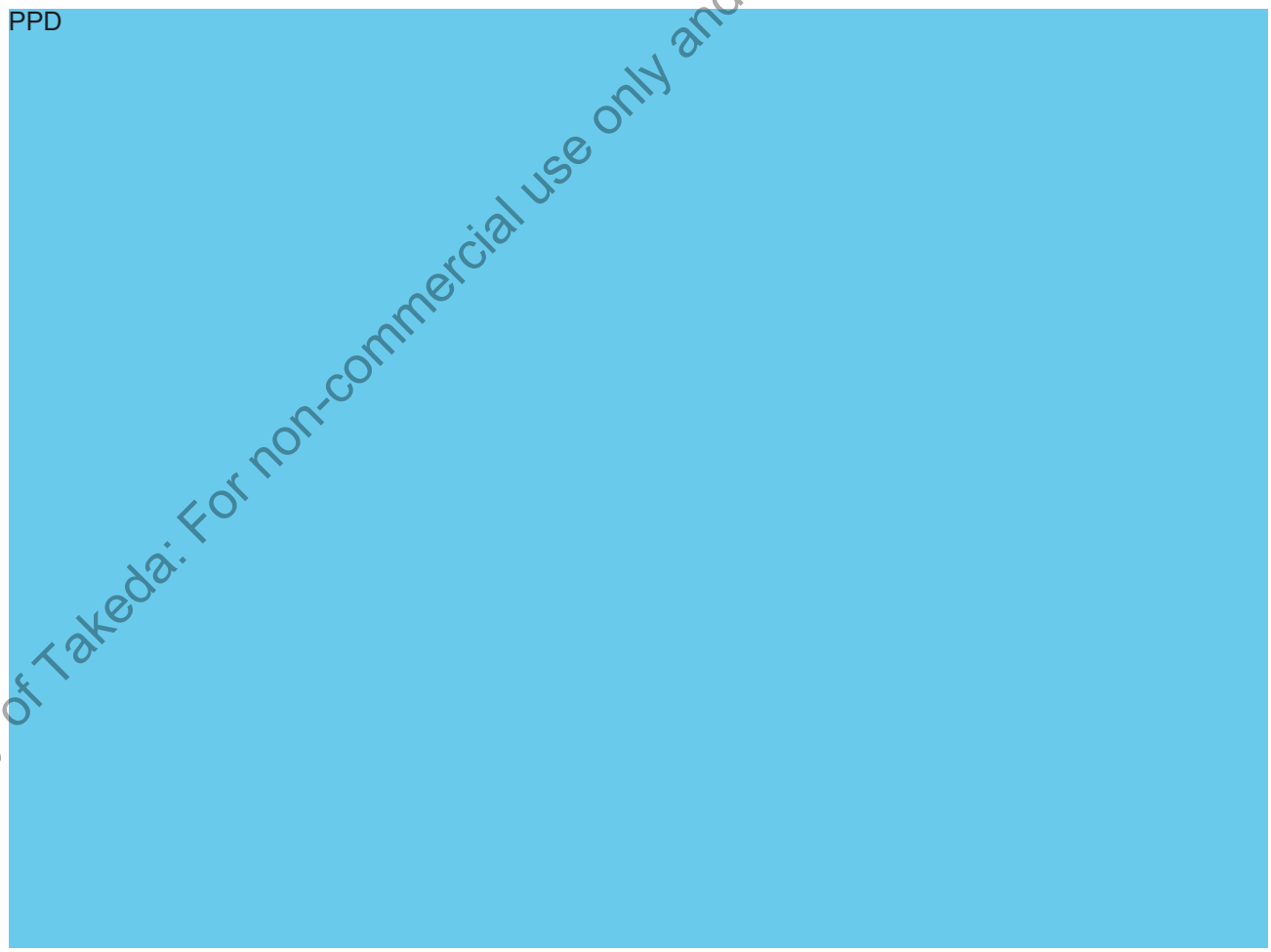
ON BEHALF OF TAKEDA

This study will be conducted with the utmost respect for the participants, in accordance with this protocol and the following national and international principles:

- The ethical principles stated in the latest applicable version of the Declaration of Helsinki (Fortaleza, 2013).[1]
- Good Clinical Practice (GCP) guidelines of the International Conference on Harmonization (ICH E6).[2]
- Good Pharmacoepidemiological Practice (GPP) guidelines.[3]
- All legislation applicable to clinical research matters, including that relative to confidentiality and data protection.

SIGNATURES

PPD



SUMMARY

Short title

CharisMMa Study

Identification of the Sponsor and address

Takeda Farmacéutica España S.A.

C/ Alsasua, 20. 28023 – Madrid (Spain)

Telephone: + 34 91 714 99 00

Fax: + 34 91 657 49 07

Study Title

"CLINICAL AND SOCIODEMOGRAPHIC CHARACTERIZATION OF MULTIPLE MYELOMA PATIENTS WITH SYMPTOMATIC RELAPSE AND/OR REFRACTORY DISEASE IN SPAIN"

Study code (According to official coding standards)

TAK-MMR-2017-01

Coordinators Investigators and address

PPD

Type of centers where the study is planned

The study will be performed in a total of 30 public sites in Spain

Primary Objective

To characterize the multiple myeloma (MM) patient with symptomatic relapse and/or refractory disease in Spain.

Study Design

Observational cross-sectional multicenter study. This study will not interfere in any way with the clinical and therapeutic management of the patient that will be conducted solely according to the criteria of the physician in line with standard clinical practice.

Disease or disorder under study

Multiple Myeloma

Data about study drug

There is no specific drug to be studied

Population in study and total number of subjects

This observational cross-sectional (single-visit) study will include approximately 350 adult patients with a diagnosis of MM who, after being treated already, have experienced a relapse of their disease (either after having been in remission for some time or because they are resistant to the treatment administered). There will be a test-retest analysis in 40 patients to validate the questionnaire.

Calendar

First patient first visit:	June 2017
Last patient last visit:	May 2018
Date of database close-out:	June 2018
Planned date for final study report:	September 2018

Funding source

Takeda Farmacéutica España S.A.

Participating sites

The study will be performed in a total of 30 sites in Spain.

Objectives

Primary objective:

- To characterize the multiple myeloma (MM) patient with symptomatic relapse and/or refractory disease in Spain.

Secondary objectives:

- To evaluate how the clinical and sociodemographic findings of the MM patient with symptomatic relapse and/or refractory disease can affect the selection of treatment after the latest symptomatic relapse and/or refractory episode.
- To identify any new relevant variables that are not currently collected in clinical records and that could influence in the disease management at relapse
- To evaluate the quality of life of the MM patient with symptomatic relapse and/or refractory disease using the EORTC QLQ-C30 and EORTC QLQ-MY20 questionnaires.
- To validate the psychometric properties of the Spanish translation of the EORTC QLQ-MY20 in MM patients with symptomatic relapse and/or refractory disease.
- To identify and quantify the use of healthcare resources since the latest symptomatic relapse and/or refractory episode.

Methodology

Observational, cross-sectional, multicenter study of 350 patients with test-retest analysis in 40 patients. This study will not interfere in any way with the clinical and therapeutic management of the patient that will be conducted solely according to the criteria of the physician in line with standard clinical practice.

A total of 30 investigators from the Hematology Departments of 30 public hospitals throughout Spain will consecutively include a total of 350 patients attending a routine visit at their office and who meet the inclusion criteria, during a recruitment period of 12 months.

The study will be performed in the context of a single visit, in which the patient will be invited to participate in the study, the protocol will be explained, and if the patient wishes to participate, he/she will be asked to sign an informed consent form.

Study data will be collected in a single visit. Questionnaires will be completed by the patient and entered into the electronic case report form (eCRF) by the principal investigator (PI).Other data will be collected from the clinical records, examinations and tests performed according to the criteria of the physician and in line with standard clinical practice. For the test-retest analysis to validate the EORTC QLQ-MY20 questionnaire, a second questionnaire (EORTC QLQ-C30 and EORTC QLQ-MY20) will be provided to 40 patients to complete at home, 7 days after the visit, which should be returned to the site by post, in a pre-paid envelope. These 40 patients will be the first 2 patients enrolled in each site, until a total of 40 patients have been reached.

Sociodemographic and clinical data corresponding to the time of the visit will be collected, along with health resource use since the latest symptomatic relapse and/or refractory episode. Clinical data from before the study visit will also be collected from the patients' clinical records: diagnosis, prior relapses, and data on the latest symptomatic relapse and/or refractory episode.

Number of patients

A sample size of 350 patients has been calculated on the basis of an estimation of a proportion in case of maximum indetermination (proportion of 50%) with a 95% confidence interval and a precision of 5%, in the MM population with symptomatic relapse and/or refractory disease, approximately 3,480[7] patients in Spain in 2016. This represents the inclusion of at least 10% of the population with relapsing or refractory MM (RRMM).

According to previous publications on questionnaire validation in other languages[22], 20 patients are sufficient for a test-retest analysis. Taking into account the possibility of questionnaires with invalid data and those that might not be returned after 7 days, we decided to ask 40 patients to complete the second questionnaire.

Study disease and main inclusion criteria

Multiple myeloma.

Adult patients with a diagnosis of MM who have received at least one previous treatment line and have experienced symptomatic relapse and/or refractory disease in the previous 6 months, who are still in follow-up at the time of the study visit.

Data collection

All study data will be collected in a specifically designed electronic CRF.

Only 40 of the study patients will be needed to send a second questionnaire (EORTC QLQ-C30 and QLQ-MY20) by post, in a pre-paid envelope.

Study variables

Sociodemographic variables in the study visit

- Age (years)
- Sex
- BMI (kg/m^2)
- Area of residence
- Educational level
- Cohabitation
- Degree of dependence
- Working situation
- Need for financial assistance
- Healthy habits:
  - Physical activity
  - Smoking habit (yes/no)
  - Alcohol use (yes/no)

Clinical variables on diagnosis and during previous relapses

- Age at diagnosis
- Type of MM: heavy chain, light chain, Bence-Jones protein
- ISS disease stage at time of diagnosis
- CRAB signs at time of diagnosis
- Cytogenetic abnormalities at time of diagnosis
- Risk according to cytogenetic profile at diagnosis

- Previous relapses (before the latest): Number of previous treatment lines; Number of previous relapses; Treatments used (therapeutic group); Refractory to treatment prescribed? (yes/no); Response time
- Transplant ECOG on diagnosis

Clinical variables at latest symptomatic relapse and/or refractory episode

- Date of latest symptomatic relapse and/or refractory episode.
- ISS disease stage at latest symptomatic relapse and/or refractory episode.
- CRAB signs at latest symptomatic relapse and/or refractory episode.
- Other clinical variables in latest symptomatic relapse and/or refractory episode (number and site of plasmacytoma, diffuse osteopenia, fractures, neurological symptoms, infections, paraprotein levels, free light chain levels in serum/urine, and LDH).
- Cytogenetic abnormalities at latest symptomatic relapse and/or refractory episode
- Risk according to cytogenetic profile at relapse
- Treatment started after latest symptomatic relapse and/or refractory episode (line number, treatment [therapeutic group])
- Concomitant diseases at time of latest symptomatic relapse and/or refractory episode.

Variables in the study visit

- Current treatment (therapeutic group)
- Oral vs IV
- Distance between home and hospital (km)
- Type of transport used
- Hospital visits required for latest treatment (number of visits/month)
- Cost of transport to the hospital to receive treatment (Euros/month)
- Use of healthcare resources since the latest symptomatic relapse and/or refractory episode
- Evaluation of quality of life
  - EORTC QLQ-C30 questionnaire
  - EORTC QLQ-MY20 questionnaire

Statistical methods

A descriptive analysis of all variables will be used to characterize the profile of MM patients with symptomatic relapse and/or refractory episode:

- For qualitative variables, the number and percentage of patients in each category will be used.
- For quantitative variables, central tendency and dispersion measurements will be presented.

To evaluate which clinical and sociodemographic findings are related with the selection of treatment after symptomatic relapse, the relationship between the sociodemographic variables collected during the study visit and the clinical variables collected at the time of the latest symptomatic relapse and/or refractory episode will be evaluated.

- For qualitative variables, numbers and percentages of the variable categories for each treatment will be presented. To evaluate the relationship with treatment, Chi-squared or Fisher's exact tests will be performed and the resulting p-value will be presented. When the relationship with treatment has statistical significance a post-hoc analysis will be performed.
- For quantitative variables, central tendency and dispersion descriptions will be presented for each treatment. To evaluate the relationship with treatment, ANOVA or non-parametric Kruskal-Wallis tests will be performed and the resulting p-value will be presented. When the relationship with treatment has statistical significance a post-hoc analysis will be performed.

To evaluate psychometric properties of the Spanish version of the EORTC QLQ-MY20 questionnaire, a feasibility, reliability and validity analysis will be performed.

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Abbreviations

AE:	Adverse event
AR:	Adverse reaction
BMI:	Body mass index
CRAB:	Calcium, Renal insufficiency, Anemia or Bone lesions
CREC:	Clinical research ethics committee
CRF:	Case report form
CRO:	Contract research organization
ECOG:	Eastern Cooperative Oncology Group
EORTC:	European Organization for Research and Treatment of Cancer
FISH:	Fluorescent in situ hybridization
GCP:	Good clinical practice
GPP:	Good pharmacoepidemiological practice
IC:	Informed consent
ICH:	International Conference on Harmonization
ISS	International Staging System
LDH:	Lactate dehydrogenase
LOC:	Local Operating Company
MedDRA:	Medical Dictionary for Regulatory Activities
MM:	Multiple myeloma
PI:	Principal investigator
PIS:	Patient information sheet
QoL:	Quality of life
RRMM:	Relapsing/refractory multiple myeloma
SAE:	Serious adverse event
SAR:	Serious adverse reaction

2 Introduction

Multiple myeloma (MM) is a proliferative clonal disorder of cytogenetically heterogeneous plasma cells.[4] It is the second most common blood cancer[5] and accounts for more than 10% of all blood cancers, and 1% of all cancers.[6] Incidence in Europe is estimated at 4.5-6.0/100,000 cases/year.[6] An estimated 6,080 patients with a diagnosis of MM were being treated in Spain in 2016, including patients receiving first-line treatment who are transplant candidates, non-candidates, and patients on second, third and fourth-line treatment.[7]

MM is biologically complex disease, and, as a consequence, the clinical profile is variable.[9] Symptomatic MM is characterized by signs of systemic damage, summarized under the acronym CRAB (Calcium, Renal insufficiency, Anemia or Bone lesions).[8] Another characteristic of the disease is immune system damage that can lead to severe infections.[9]

MM is a recurrent, progressive disease that is still incurable today. Almost all MM patients, including those who maintain prolonged response to first-line treatment, end up relapsing, and some of them also develop resistance to the drugs administered.[10] Moreover, the disease becomes more and more aggressive with each relapse, and remissions achieved with successive lines of treatment tend to become shorter.[11] The recurrent or refractory patient, then, is still a clinical and therapeutic challenge.[10, 12]

In recent years there has been a significant improvement, thanks to the development of new drugs with different mechanisms of action[13] leading to a considerable change in the MM treatment paradigm, particularly for relapsing or refractory patients who until now had few therapeutic options.[12, 14]

Nevertheless, the therapeutic management of these patients does not depend uniquely on the availability of new drugs: the characteristics of the patient, the clinical aspects of the disease[14-16], and other considerations, such as comorbidities and sociodemographic conditions also play a part.[14, 17-19] Various patient risk factors, such as age, general status, and the individual's history of toxicity to previous treatments will also influence the treatment strategy.[20] Various studies have demonstrated the significant impact of comorbidities on mortality[18] and disease progress in each patient.[9,19]

Since this disease is long term in many cases, it is equally important to evaluate the patient's opinion of the impact on their quality of life of not only the disease, but also the side effects of the treatments. This information may help the physician select the most appropriate treatment in order to achieve better therapeutic adherence and satisfaction. The EORTC QLQ-C30 questionnaire[20] and the QLQ-MY20 module[21] are self-administered tools

commonly used in the evaluation of quality of life in MM patients. The Spanish version of this tool has been validated, with the exception of its psychometric properties.[21, 22]

An accurate epidemiological characterization of this population may be useful for the appropriate assignation of resources, as shown in a recent study performed on a French national register of hematological diseases.[23] No registries or published data are available on the therapeutic management of the MM patient according to their characteristics, and data on results obtained in standard clinical practice are scarce. No epidemiological studies have been performed in MM patients that might contribute to defining if treatments administered are adjusted to the patient's characteristics and how these affect their quality of life (QoL). Taking into account that relapsed or refractory MM patients in particular may be exposed to long cycles of treatment with drugs with a not inconsiderable risk of adverse events, the outcome of which may depend on previously administered treatments, the hematologist's choice of therapeutic strategy is crucial, and must be made in consideration of the patient as a whole, and not only in terms of their disease.

Accordingly, then, the aim of this study is to characterize the profile of the relapsed and/or refractory MM patient in Spain. The secondary objective, among others, is to evaluate the feasibility, reliability and validity of the Spanish version of the EORTC QLQ-MY20 for this type of patient.

The study findings will foreseeably generate new useful hypotheses for expanding the knowledge base of MM and the course and impact of the disease according to patient profile.

3 Study objectives

3.1 Primary objective

- To characterize the multiple myeloma (MM) patient with symptomatic relapse and/or refractory disease in Spain.

3.2 Secondary objectives

- To evaluate how the clinical and sociodemographic findings of the MM patient with symptomatic relapse and/or refractory disease can affect the selection of treatment after the latest symptomatic relapse and/or refractory episode.
- To identify any new relevant variables that are not currently collected in clinical records and that could influence in the disease management at relapse To evaluate the quality of life of the MM patient with symptomatic relapse and/or refractory disease using the EORTC QLQ-C30 and EORTC QLQ-MY20 questionnaires.

- To validate the psychometric properties of the Spanish translation of the EORTC QLQ-MY20 in MM patients with symptomatic relapse and/or refractory disease.
- To identify and quantify the use of healthcare resources since the latest symptomatic relapse and/or refractory episode.

4 Administrative study structure

4.1 Coordinators Investigators study

PPD

4.2 Participating sites

The study will be conducted in the Hematology Departments of 30 hospitals in Spain.

Takeda Farmacéutica España S.A. will maintain a file of the responsible study investigators in each site.

4.3 Sponsor personnel:

Takeda Farmacéutica España S.A will maintain a registry of relevant study personnel.

4.3.1 Physician responsible for the study

PPD

4.3.2 Individual responsible for study pharmacovigilance

PPD

4.4 Contract research organization (CRO)

The CRO will keep a list of all personnel involved in the study.

The CRO will conduct the following tasks:

- Administrative procedures and study initiation.
- Study communications.
- Remote study monitoring.
- Data management.
- Statistical analysis.
- Final study report.

4.5 Essential documents

The following essential documents must be sent to Takeda Farmacéutica España S.A. before the study is initiated in each site:

- Written agreement between Takeda and the participating site.
- Signed and dated commitment of the investigator to the protocol and any eventual amendments, with original signature.
- Patient information sheet (PIS) and informed consent (IC) in the local language, approved by the corresponding Clinical Research Ethics Committee (CREC).
- CREC approval.
- Approval from the local authorities, if applicable.

5 Ethics

5.1 Risk-benefit evaluation

Participation in the study will not involve any additional risk to the patients. Patients will not obtain any direct benefit from participation.

The procedures required for study conduct involve only the collection of certain sociodemographic data or data from the clinical records, and completion of the EORTC QLQ-C30 and EORTC QLQ-MY20 quality of life questionnaires during a routine clinical visit.
The information obtained from this study will be clinical and epidemiological in nature, and is expected to add to the knowledge of characteristics of the relapsed or refractory MM patient in Spain, and may contribute in the future to the improvement in the knowledge of the disease management.

5.2 Ethical aspects of the study

The study will be performed in accordance with the provisions of the protocol, the Declaration of Helsinki (Fortaleza, 2013), Good Pharmacoepidemiological Practice (GPP) guidelines, and locally applicable regulations, primarily Order SAS 3470/2009.
If, during this study, new information emerges that would affect its conduct, the Sponsor will prepare the necessary amendments to the protocol, the PIS, or both, and these will be sent to the corresponding CREC for their evaluation and opinion according to applicable regulations.
Takeda Farmacéutica España S.A., as the sponsor, is responsible for complying with ICH requirements for annual update reports to the CREC.

5.3 Confidentiality and data protection

Data collected for the study will be handled in concordance with the provisions of the European Directive 95/46/EC and its transposition to the Personal Data Protection Act 15/1999, 13 December 1999 (and subsequent regulations) and Act 41/2002, 14 November 2002, regulating patient autonomy and rights and obligations in the area of clinical information and documentation.
Each patient included in the study will be assigned a participation code, so that no identifying personal data (name, surnames, clinical record number, date of birth, etc.) will appear in the electronic CRF of the study.
The principal investigator (PI) is responsible for maintaining an updated record (code list) of all subjects, linking their personal data with the code assigned for this study, for the follow-up of subjects and study coordination. This record will be kept in the strictest confidence in the study site, and only the investigator and other members of the study team will have full knowledge of the subject's identity.
The patient will be informed, as stated in the PIS, that the Sponsor personnel or representative, the study monitor, and/or the responsible authorities may require direct access to the patients' clinical records and data for auditing purposes.

5.4 Clinical Research Ethics Committee and Health Authorities

Clinical Research Ethics Committee

The Sponsor, by way of the study CRO,

- will submit the required documents to the corresponding CREC for their evaluation and approval.

They are also responsible for sending additional documents such as:

- Periodical updates on study progress.
- Notification of study completion.
- Summary of study results.

Takeda Farmacéutica España S.A., by way of the CRO, will maintain an updated list of all submissions and approval dates of the documents presented to the CREC and will provide a copy of these documents to the individual responsible for the study in the site.

Health Authorities

The Sponsor, by way of the study CRO, will submit the documents required for processing the study to the responsible health authorities. Takeda Farmacéutica España S.A. by way of the CRO, will maintain an updated list of submissions and approval dates and a copy of all documents submitted.

5.5 Patient information and informed consent

The investigator must provide all necessary oral and written information on the study to each patient, so that the patient can understand the scope of the study and give, if they wish, their written consent to participate. Before making the decision, the patient must be given sufficient time to discuss any question they may have and for those questions to be resolved.

Given the observational nature of the study, consent refers to access to significant clinical records data and completion of the QoL questionnaires, and not to any clinical, diagnostic or therapeutic procedure.

All participating patients have the right to withdraw their previously given consent any time they want, with no need to provide explanations and without affecting their medical care in any way.

If new information should emerge during the course of the study that might require a change in the PIS, this will be provided as soon as possible to the patients so that they can give their consent again, if they agree.

The rights, safety and wellbeing of the study patients are the most important aspects to be taken into account and must prevail over the interests of science and society.

The study personnel involved in the conduct of this observational study will be qualified in terms of education, training and experience for performing their corresponding tasks.

5.6 Protocol amendments

The study will be conducted as described in the approved protocol.

If a substantial amendment is made that requires a significant modification of any aspect of the protocol and/or PIS:

- The PIS and IC must be revised and sent to the CREC for review and approval.
- The revised form must be used to obtain consent from patients who are already included in the study if they are affected by the amendment, and
- The new form must be used to obtain consent from new patients before inclusion.

Any significant deviation must be documented in the CRD and reported to the CREC.

6 Study design

Observational cross-sectional multicenter study. This study will not interfere in any way with the clinical and therapeutic management of the patient that will be conducted solely according to the criteria of the physician in line with standard clinical practice.

A total of 30 investigators from the Hematology Departments of 30 public hospitals throughout Spain will consecutively include a total of 350 patients attending a routine visit at their office and who meet the inclusion criteria, during a recruitment period of approximately 12 months.

In the study visit, the patient will be invited to participate in the study, the protocol will be explained, and if they wish to participate, they will be asked to sign an informed consent form.

During the study visit, sociodemographic and clinical data and the QoL questionnaires[20,21] corresponding to the time of the visit and clinical data from before the study visit (diagnosis, previous relapses before the latest, and data on the latest symptomatic relapse and/or refractory episode) will be collected from the patients' clinical records, examinations and tests performed according to the criteria of the physician and in line with standard clinical practice.

Data will also be collected for the evaluation of the use of healthcare resources after the latest relapse and/or refractory episode (number of hospital admissions, number of days admitted, visits to the emergency room, visits to specialists, etc.).

For the test-retest analysis to validate the EORTC QLQ-MY20 questionnaire, a second questionnaire (EORTC QLQ-C30 and EORTC QLQ-MY20) will be provided to 40 patients to

complete at home, 7 days after the visit, which should be returned to the site by post, in a pre-paid envelope. These 40 patients will be the first 2 patients enrolled in each site, until a total of 40 patients have been reached.

Data will be recorded in an electronic CRF.

6.1 Study timing

First patient first visit: Jun 2017

Last patient last visit: May 2018

Date of database close-out: June 2018

Planned date for final study report: September 2018

	2017												2018											
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
CREC		X																						
Study start			X	X	X																			
Recruitment						X	X	X	X	X	X	X	X	X	X	X	X							
Single visit						X	X	X	X	X	X	X	X	X	X	X	X							
End of study																	X							
Database closure																		X						
Analysis										X									X					
Final report																					X			
Publication																						X	X	X

Takeda Farmacéutica España S.A., by way of the CRO, will duly notify the corresponding CREC of study completion, in accordance with the local regulations applicable to the study.

Takeda Farmacéutica España S.A. guarantees that the results will be published on the "clinicaltrials.gov" website and any other website required by applicable local regulations.

Takeda may, in the light of future findings, decide to suspend the study prematurely. In this case, the corresponding CREC and health authorities will be duly notified.

6.2 Rationale for study design

The cross-sectional design is appropriate for describing the characteristics of a population with respect to a series of variables at a certain point in time.

The aim of this study is to evaluate the characteristics of symptomatic relapsed or refractory MM patients, so the cross-sectional design of this study is considered appropriate. The selected design is considered appropriate for validating the questionnaire which will be performed as a complementary activity.

Cross-sectional studies are optimal for estimating prevalence, for simultaneously studying multiple resulting variables and for identifying potential associations between certain factors and the outcome of interest. Thus, these studies are useful for generating hypotheses that can be subsequently evaluated in other studies with more appropriate designs, since transversal studies are limited by being unable to establish a cause-effect relationship or sequentiality. However, they have the advantage of avoiding the patient attrition associated with follow-up studies.[24, 25]

Information provided by cross-sectional studies is generally used for developing and planning population health strategies.[24]

The evaluation of the psychometric properties of the EORTC QLQ-MY20 is designed according to the method used for original evaluation of the instrument and in subsequent evaluations of translated versions.[21, 22, 26]

6.3 Selection of the study population

Inclusion Criteria

- Adults (≥ 18 years) of both sexes.
- Patients with a diagnosis of MM who have received at least one previous treatment line.
- Patients who have experienced symptomatic relapse and/or refractory disease in the 6 months before the study.
- Patients who continue in follow-up at the time of the study visit.
- Patients currently treated in the site who have clinical records available.
- Patients capable of understanding and completing the questions in the EORTC QLQ-C30, and EORTC QLQ-MY20 questionnaires.

Exclusion criteria

- Patients who do not agree to participate in the study or who do not give written informed consent.

6.4 Treatments

Not applicable. This is an observational study and no medications will be administered.

7 Study procedures

7.1 Study variables

7.1.1 Sociodemographic variables

- Current age (years)
- Sex:
  - Female
  - Male
- BMI (kg/m^2)
- Area of residence
  - Rural
  - Urban
- Educational level:
  - Illiterate
  - No studies (can only read/write)
  - Primary studies
  - Secondary studies
  - University studies
- Cohabitation:
  - Lives alone
  - Lives with the family
  - Lives alone with help from a caregiver
    - Daily
    - 2-3 times/week
    - Permanent
    - Night-time
- Degree of dependence:

- Independent
- Dependent Grade I: individual requires help to perform Activities of Daily Living (ADL) at least once a day or needs intermittent support for personal autonomy.
- Dependent Grade II: individual needs help to perform ADLs 2 or 3 times a day or needs extensive support for personal autonomy, but does not need the permanent support of a caregiver.
- Dependent Grade III: individual needs help to perform ADLs several times a day, and due to total loss of physical, mental, intellectual or sensory autonomy, needs the indispensable and continuous support of another person, or needs generalized support for personal autonomy.

- Working situation:
  - Unemployed
  - In active employment
    - Full time
    - Part time
  - Temporarily/permanently disabled
  - Retired
  - Student
  - Other
- Need for financial assistance
  - Yes
  - No
- Healthy habits
  - Physical activity
    - High [jogging, walking or climbing briskly up a hill; fast cycling; aerobics; fast swimming; competitive sports and games (e.g., traditional games, football, volleyball, hockey, basketball); strenuous work with a spade or ditch-digging; lifting heavy weights (> 20 kg)]
    - Moderate/low [fast walking; dancing; gardening; domestic tasks; hunting and traditional foraging; active participation in games and sports with children and walking pets; general construction work (e.g., roofing, painting, etc.); lifting moderate weights (< 20 kg)]
    - Inactive
  - Current smoking habit (Yes/No)

- Alcohol use (yes/no)

7.1.2 Clinical variables on diagnosis and during previous relapses

- Age at diagnosis
- MM type: heavy chain, light chain, Bence-Jones protein
- ISS disease stage at time of diagnosis:
  - Stage I. Low risk. β2-Microglobulin < 3.5 mg/L and albumin ≥ 3.5 g/dL
  - Stage II. Not ISS stage I or III
  - Stage III. High risk. β2-Microglobulin ≥ 5.5 mg/L
- CRAB signs at time of diagnosis:
  - Increased blood calcium (serum Ca >0.25 mmol/L (>1 mg/dL) upper limit of normal or >2.75 mmol/L (>11 mg/dL).
  - Renal failure: creatinine clearance < 40 mL/min or serum creatinine > 117 µmol/L (>2 mg/dL).
  - Anemia: reduction of Hb > 2 g/dL below lower limit of normal or Hb < 10 g/dL.
  - Bone lesions: one or more osteolytic lesion on standard radiograph, CT or PET-CT.
- Cytogenetic abnormalities at time of diagnosis:
  - t (4;14)
  - t (11;14)
  - t (14;16)
  - t (14;20)
  - t (6;14)
  - Trisomies
  - d (17p)
  - g (1q)
  - Others (specify)
- Risk according to cytogenetic profile at diagnosis[15, 27]
  - Standard risk: Trisomies, t (11;14); t (6;14)
  - Intermediate risk: t (4;14), g (1q)
  - High risk: d (17p), t (14;16), t (14;20)
- Previous relapses (before the latest):
  - Number of treatment lines
  - Number of previous relapses
  - For each line of treatment:

  - Treatment(s) used (therapeutic group)
  - Oral or IV
  - Refractory to prescribed treatment? (Yes/No)
  - Response time
- Received a stem cell transplant? (Yes/No) (Auto/Alo)
- ECOG on diagnosis (ECOG 0 – ECOG 5)

7.1.3 Clinical variables at latest symptomatic relapse and/or refractory episode

- Date of latest symptomatic relapse and/or refractory episode.
- ISS disease stage at latest symptomatic relapse and/or refractory episode:
  - Stage I. Low risk. β2-Microglobulin < 3.5 mg/L and albumin ≥ 3.5 g/dL
  - Stage II. Not ISS stage I or III
  - Stage III. High risk. β2-Microglobulin ≥ 5.5 mg/L
- CRAB signs at latest symptomatic relapse and/or refractory episode:
  - Increased blood calcium: serum Ca >0.25 mmol/L (>1 mg/dL) upper limit of normal or >2.75 mmol/L (>11 mg/dL).
  - Renal failure: creatinine clearance < 40 mL/min or serum creatinine > 117 µmol/L (>2 mg/dL).
  - Anemia: reduction of Hb > 2 g/dL below lower limit of normal or Hb <10 g/dL.
  - Bone lesions: one or more osteolytic lesion on standard radiograph, CT or PET-CT.
- Other clinical variables at latest symptomatic relapse and/or refractory episode:
  - Plasmacytomas
    - Medullary (Yes/No, Number)
    - Extramedullary (Yes/No, Number)
  - Diffuse osteopenia
    - Yes (Grade)
    - No
  - Fractures
    - Yes (Number, Site [Specify])
    - No
  - Neurological symptoms
    - Yes

        - MM related?
            - Yes
            - No
        - No
    - Infections
        - Yes
        - No
    - LDH (IU/L)
    - Paraprotein levels (g/L) (serum and urine)
    - Free light chain levels (g/L) (serum and urine)
- Concomitant diseases at time of latest symptomatic relapse and/or refractory episode:
    - Diabetes
    - Neuropathy
    - Nephropathy
    - Chronic obstructive pulmonary disease
    - Cardiovascular disease
        - Yes (Type [Specify])
        - No
    - Liver failure
    - Psychiatric and/or neurological disorders:
        - Depression/depressive symptoms
        - Anxiety
        - Others (specify)
    - Other secondary disorders (specify)
- Cytogenetic abnormalities at latest relapse and/or refractory episode:
    - t (4;14)
    - t (11;14)
    - t (14;16)
    - t (14;20)
    - t (6;14)
    - Trisomies
    - d (17p)
    - g (1q)
    - Others (specify)

- Risk according to cytogenetic profile at latest symptomatic relapse and/or refractory episode[15, 27]
    - Standard risk: Trisomies, t (11;14); t (6;14)
    - Intermediate risk: t (4;14), g (1q)
    - High risk: d (17p), t (14;16), t (14;20)
- Treatment started after latest symptomatic relapse and/or refractory episode:
    - Treatment line (number)
    - Treatment(s) (therapeutic group)

7.1.4 Variables in the study visit

Current treatment

- Currently receiving treatment (Yes/No)

Costs related with healthcare resources

- Distance between home and hospital (km)
- Type of transport used:
    - Own vehicle
    - Public transport
    - Ambulance
- Hospital visits required for latest treatment (no. visits/month)
- Cost of transport to the hospital to receive treatment (Euros/month)
- Use of healthcare resources since the latest symptomatic relapse and/or refractory episode
    - Where was the patient admitted?
        - UCI → Number of UCI admissions
        - Hospital → Number of hospital admissions
        - Emergency room → Number of visits to the emergency room
        - Others
    - Number of days admitted
    - Number of visits to specialists
        - Which specialist?
            - Oncologist →Number of visits
            - Hematologist →Number of visits
            - GP→Number of visits
            - Phychologist→Number of visits

- Other. Specify, and number of visits

- Need of some test?
  - Yes
    - TAC → Number of tests
    - RM → Number of tests
    - XRay→ Number of tests
    - Others. Specify, and number of tests
  - No

- For each number of visit: the patient comes to the hospital:
  - Alone
  - Accompanied (Is the accompanying person in active employment? [Yes/No])

Evaluation of quality of life

- EORTC QLQ-C30 questionnaire[20]
- EORTC QLQ-MY20 questionnaire[21].

7.2 Data source

All study information will be collected during the single study visit, including sociodemographic and clinical data corresponding to the time of the visit and clinical data from before the study visit (diagnosis, relapses/refractory episodes) taken from the clinical records, examinations and tests performed according to the criteria of the physician and in line with standard clinical practice.

This information will be recorded in an electronic CRF created for the purpose.

7.3 QoL questionnaires

- EORTC QLQ-C30 questionnaire[20]. Self-administered QoL questionnaire designed for use in cancer patients. The time frame is the previous week. This questionnaire consists of 30 items grouped in 5 functional scales (physical, role, emotional, cognitive, and social). The score for each item ranges from 1 to 4 (1: not at all, 2: a little, 3: quite a bit, 4: very much), except for items 29 and 30 that are scored from 1 to 7 (1: worst possible, 7: excellent). The scores obtained are standardized to 0-100. A higher score in the function scale indicates a better functional status. A higher score in the global health scale indicates a better global health status. A higher score in the symptom score indicates a higher level of problems due to symptoms.

- EORTC QLQ-MY20 questionnaire.[21,22] Self-administered questionnaire specifically for MM patients. It should be completed alongside the EORTC QLQ-C30 questionnaire.[20] It consists of 20 questions grouped in 3 scales. For each item, the lowest possible response is “not at all” and the greatest possible response is “very much”, with a score ranging from 1 to 4, respectively. Linear transformation will be used to convert the final score to a scale of 0-100.

8 Pharmacovigilance

8.1 Definitions

Adverse event (AE)

An AE is defined as *any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with that treatment.*

An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to that medicinal product.

Adverse reaction (AR)

Any response to a medication that is harmful and unintended, occurring at doses that are normally applied in humans for the prophylaxis, diagnosis or treatment of diseases, or the restoration, correction or modification of physiological functions. Unlike an AE, in the case of an AR, there is a suspected causal relationship between the study medication and that AR.

This term also includes all the harmful clinical consequences derived from dependence, abuse and inappropriate use of medications, including those caused by use not included in the approved conditions and those caused by medication errors.

Special Situation Report (SSR)

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

Product Complaint

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, labeling, or design of the product.

8.2 Classification

Seriousness

A **serious adverse event (SAE)** or a **serious adverse reaction (SAR)** is any AE or AR that at any dose:

- results in death.
- is life-threatening, understood as any reaction or event in which the patient was at risk of death at the time of the event; it does not refer to an event which might have caused death if it had been more severe.
- requires hospitalization of the patient or prolongs existing hospitalization.
- results in persistent or significant disability/incapacity, or
- causes a congenital abnormality or defect.

For reporting purposes, any suspected AEs or ARs that are considered significant from a medical point of view will also be handled as serious, even if they do not meet the above-mentioned criteria, including significant medical events that require intervention to prevent one of the above-mentioned outcomes (e.g., intensive treatment for bronchospasm, blood dyscrasias, or convulsions, even if they do not result in hospitalization, or development of dependence or abuse). Additionally, all suspected transmission of an infectious agent via a medication will also be reported as serious.

Severity

- *Mild*: Transient symptoms that do not interfere with the patient's activities of daily living.
- *Moderate*: More pronounced symptoms that interfere moderately with the patient's activities of daily living.
- *Severe*: Symptoms that interfere considerably with the patient's activities of daily living.

Causality

- *Related*: There is a reasonable temporal relationship between the administration of the medication and the appearance of the event, and no obvious alternative explanation is available.

- *Unrelated*: There is at least one alternative explanations for the event that occurred; for example, the event may be explained by any of the following: a) the patient's clinical condition (according to clinical history, disease progression, indication), b) concomitant medication for which this event is listed in the product information, or c) the event occurred before administration of the medication.

Outcome

- *Fatal*: The patient dies as a result of the event. If the patient dies from causes other than the event, the outcome should be classified as “not recovered” or “recovering”.
- *Recovered/Resolved*: The patient has recovered completely from the event or his/her condition has returned to the same situation as before the event.
- *Recovering/resolving*: The event is improving but the patient has still not fully recovered.
- *Not recovered/Not resolved*: The event persists at the time of the communication and the patient has not yet recovered.
- *Recovered with sequelae/Resolved with sequelae*: As a result of the event, the patient has persistent and significant disability or incapacity (e.g., blindness, deafness or paralysis).
- *Unknown*: The outcome is unknown.

8.3 Notification of adverse events and adverse reactions

In this study, standard clinical practice will not be modified and no investigational drugs will be used. Investigators will be responsible for complying with Order SAS/3470/2009, 16 December 2009, which publishes the regulations on post-approval observational studies in medications for human use, in which it is stated that suspected serious adverse reactions that are detected must be reported to the point of contact designated by the responsible authorities in the matter of pharmacovigilance of the autonomous community in which the healthcare professional who reports the case is practicing, within a maximum period of 15 calendar days after becoming aware of the suspected adverse reaction, including a reference to the study code.

Investigators in the participating sites must send to Takeda adverse reaction reports or any other relevant safety information/special situation associated with any product marketed by Takeda, whether initial or follow-up, severe or mild, using the Takeda adverse reaction notification form (see ANNEX 8) within 24 hours of becoming aware of the event, using the

electronic mail address farmacovigilancia@takeda.com. Product complaint information should also be reported to the same mailbox.

If the sponsor requires additional information for the evaluation of an adverse reaction, and sends queries to the investigator of the corresponding site, the information provided by that investigator will be considered as follow-up information on the adverse reaction and thus must be reported to the point of contact designated by the responsible authorities in the matter of pharmacovigilance in the autonomous community in which the healthcare professional who reports the case is practicing, at the same time as to the sponsor who requested the information, including a reference to the initially reported adverse reaction. This notification to the responsible authorities and to the sponsor will be made as described in this section.

If the CRO becomes aware of any adverse reaction or any other relevant safety information associated with any product marketed by Takeda, the CRO will be obliged to report it to the pharmacovigilance department of Takeda within 24 hours of receipt, using the Takeda adverse reaction notification form and the electronic mail address farmacovigilancia@takeda.

Every three months, Takeda Pharmacovigilance will send the CRO a list of adverse events received for reconciliation purposes. The CRO will then send any discrepancies to Takeda Pharmacovigilance for resolution.

Only one AE/AR should be reported in each form. A diagnosis should be established, if possible. If this is impossible, the investigator should record each sign or symptom in separate forms. The seriousness, intensity, and causality of the AE/AR should be evaluated.
Notifications regarding Takeda medications will be followed up until outcome by the Pharmacovigilance Unit, in accordance with the established protocols and the applicable regulations, for which the collaboration of the investigator will be required.
All safety data collected or reported to Takeda during the conduct of the study according to the standard procedure for marketed drugs must be included in the final study report.

9 Data quality control and assurance

9.1 Quality control

All data will be verified, and electronic database entries will be reviewed against the source documents and a quality control check will be performed to ensure that the investigator complies with the protocol and applicable regulations, in accordance with the specific study data management plan. Regulations applicable to observational studies do not specify monitoring requirements for this type of study.

An electronic database will be created in which all data from each clinical record will be recorded. Access to the database will be restricted, for security reasons, to the investigator, the data manager and personnel responsible for data review. The database will contain internal consistency rules and filters to minimize possible errors in data entry.

Logic controls will be run to check for inconsistent study data and laboratory values outside normal limits. During the data entry period, consistency of the inclusion/exclusion criteria values and clinical evaluations will be checked.

9.2 Quality Assurance Unit Audits

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

9.3 CREC and health authority inspections

Representatives of the CREC or the health authorities may request an on-site data inspection. If the responsible investigator in the site receives notification of an inspection, he/she must immediately contact Takeda Farmacéutica España S.A. and must provide access to the requested files.

9.4 Data management

The Data Management Plan must be approved by the sponsor before the database design and study CRFs are complete. The Data Manager will be the CRO. If the IC of a patient is missing, the data from that patient will not be entered in the database, and only the inclusion/exclusion criteria and the visit date will be recorded. If it is subsequently found that no IC is available for a patient, the data entered in the system will be maintained as recorded, but these data will not be used for the statistical analysis and the patient will be considered a screening failure. If a patient is mistakenly included more than once in the study, the information for the initial inclusion will be retained. The statisticians will be

informed of the duplicate inclusion of a patient, so that those data are not taken into account in the analysis.

The method of coding clinical data will be documented in the Data Management Plan, indicating the dictionaries used and variables to be coded.

In the database, patients will be coded according to the site code and patient number; no identifying or identifiable personal data will appear.

9.4.1 Tools for data collection and flow

The participating site will receive tools for data collection (electronic CRF) from the Sponsor or the CRO. All attempts should be made in every case to enter the complete data set.

The responsible investigator in the site must sign the data set for each patient, thus confirming the information collected just before the database closure. AE/ARs will be collected as specified in Section 7 of this protocol, and SARs will also be reported as described in Section 8 of this protocol.

10 Statistical methods and calculation of the sample size

This section describes the statistical analysis foreseen at the time of planning the study. Possible modifications and reasons for any changes, as well as any additional analysis and the final statistical analysis will be described in detail in the revised Statistical Analysis Plan before database closure. All modifications or subsequent deviations will be explained in the study clinical report.

10.1 Statistical analysis plan

The principal objective of this study is to characterize the profile of the relapsing/refractory MM patient in Spain. To this end, sociodemographic data, current clinical and therapeutic data, clinical data relative to the latest relapse and clinical data at diagnosis and previous relapses will be collected.

A descriptive analysis of all variables will be used to characterize the profile of MM patients with symptomatic relapse and/or refractory episode:

- For qualitative variables, the number and percentage of patients in each category will be used.
- For quantitative variables, central tendency and dispersion measurements will be presented.

To evaluate which clinical and sociodemographic findings are related with the selection of treatment after relapse, the relationship between the clinical and sociodemographic variables collected before starting treatment with the prescribed treatment will be evaluated.

- For qualitative variables, numbers and percentages of the variable categories for each treatment will be presented. To evaluate the relationship with treatment, Chi-squared or Fisher exact tests will be performed and the resulting p-value will be presented.
- For quantitative variables, central tendency and dispersion descriptions will be presented for each treatment. To evaluate the relationship with treatment, ANOVA or non-parametric Kruskal-Wallis tests will be performed and the resulting p-value will be presented.

No type of data imputation will be performed. Only patients observed will be analyzed, and the number of missing data will be described in each analysis.

Validation of the EORTC QLQ-MY20 questionnaire.

To validate the psychometric properties of the EORTC QLQ-MY20 questionnaire, feasibility, reliability and validity will be evaluated using the following constructs:

- Questionnaire *feasibility*:
    - Percentage of non-responses in the questionnaire.
    - Floor and ceiling effects for each questionnaire item.
- *Internal consistency* will be evaluated using Cronbach's α. A result of 0.7 or higher is considered acceptable for psychometric scales.[21]
- *Temporal stability* will be evaluated in a test-retest analysis, and the intraclass correlation coefficient will be presented.
- *Construct validity* will be evaluated using a factor analysis.[21]
- *Clinical validity* will be evaluated by the comparison of results in pre-defined groups (ISS stage, presence/absence of fractures, and β2-microglobulin levels) that will indicate the capacity of discrimination between patients in different clinical situations.[21] The groups will be defined as follows:
    - ISS Stage I-II vs III
    - Fractures: fractures currently present vs. absent
    - β2-microglobulin: <4 mg/L vs. $\geq$4 mg/L.

- *Convergent validity* will be evaluated by calculating the correlation between the EORTC QLQ-MY20 questionnaire scores with the global health scores from the EORTC QLQ-C30 questionnaire.

A two-tailed level of significance of 0.05 will be used for all tests.
All statistical analyses will be carried out using the statistical package SAS© system, version 9.3 or higher.

10.2 Interim analyses

An interim analysis will be evaluated during the enrollment process. .

10.3 Sample size calculation

The aim of this study is to describe the epidemiological profile of the MM patient with symptomatic relapse and/or refractory disease in Spain, and to identify thereby potential differences that may be relevant for making clinical and therapeutic decisions. The sample was calculated on the basis of the estimation of a proportion in case of maximum indetermination (proportion of 50%).
To estimate a proportion of the MM population with symptomatic relapse and/or refractory disease, approximately 3,480[7] patients in Spain in 2016, with a 95% confidence interval and a precision of 5%, a total of 346 patients will have to be included. To facilitate the distribution of patients between the different participating sites, and taking into account the cross-sectional design of the study and the need to have all the information needed for the study as listed in the screening criteria available in the patient records, the risk of patient attrition is high, so the final sample size for the study was established at 350 patients. With this sample size, the psychometric properties of the EORTC QLQ-MY30 questionnaire can be validated.[21, 22, 26]
Moreover, for the test-retest analysis to validate the EORTC QLQ-MY20 questionnaire, a second questionnaire will be provided to 40 patients to complete 7 days after the visit, which should be returned to the site by post, in a pre-paid envelope. According to previous publications on questionnaire validation in other languages[22], 20 patients are sufficient for a test-retest analysis. Taking into account the possibility of questionnaires with invalid data or those that are not returned after 7 days, we decided to ask 40 patients to complete the second questionnaire.

11 Reports

A final clinical report will be prepared containing the study results and sent to Takeda Farmacéutica España S.A. for distribution. This form must be made available within one year following the date of the collection of the last study data point, and all participating sites and patients must be informed accordingly.

12 Publication of results

Takeda Farmacéutica S.A. agrees to disseminate the results obtained from this study. Takeda Farmacéutica S.A. reserves the right to use the data and results for regulatory purposes and to make internal presentations within the company or with commercial partners.

13 Study documentation archives

During the study conduct, the responsible investigator at the site must file at least the essential documents (section 3.5), the protocol, any amendment, the list of participants, the ICs, CRFs, and study progress reports in the site file. After database closure, the responsible investigator in the site must keep at least the list of participants and the IC documents in the site for at least 5 years. The responsible investigator in the site will in all cases comply with legal obligations with regard to archiving and retention of study documentation.

14 Funding

The study will be funded by the Sponsor (Takeda Farmacéutica España S.A.).

The study financial schedule is attached in Annex 7.

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ANNEX:

1. Sample patient information sheet

INFORMATION SHEET FOR ADULT PATIENTS

Study title: "CLINICAL AND SOCIODEMOGRAPHIC CHARACTERIZATION OF MYELOMA MULTIPLE PATIENTS WITH SYMPTOMATIC RELAPSE AND/OR REFRACTORY DISEASE IN SPAIN" CharisMMa Study
Sponsor: Takeda Farmacéutica España S.A.
Protocol Number:
PIS Version: v1
Principal investigator at the site: _____
Site: _____
Address: _____
Telephone: _____

We would like to inform you about a research study in which we are inviting you to participate. The study has been approved by the Clinical Research Ethics Committee of _____, in accordance with applicable legislation.

This information sheet contains the relevant information about the study, and you should read it and understand it before you decide if you want or do not want to participate in this study. Your doctor will also explain to you verbally about what is involved and you will be able to ask them about anything that occurs to you at any time.

INTRODUCTION

You have been invited to participate in a research study in multiple myeloma (MM) patients who have received at least one previous line of treatment and who have developed refractory disease and/or relapse. Our aim is to expand the existing knowledge base of this disease.

STUDY OBJECTIVE

The general objective of this study is to evaluate the clinical and epidemiological characteristics of MM patients who are experiencing symptomatic relapse and/or refractory disease after a previous treatment. Specifically, the aim is to describe the clinical profile of

these patients and to determine, on the basis of these characteristics, the optimal regimen for the patients.

A second objective of this study is to test the feasibility, reliability and validity of a questionnaire designed to evaluate quality of life (QoL) in MM patients.

An important issue in MM patients is how both the disease and the treatments administered can affect QoL. In medicine, QoL is evaluated by using scales and questionnaires. There is a specific questionnaire for evaluating QoL in MM called the EORTC QLQ-MY20. In this study, we want to test the feasibility, reliability and validity of this questionnaire.

STUDY INFORMATION

This observational cross-sectional (single-visit) study will include approximately 350 adult patients with a diagnosis of MM who, after being treated already, have experienced a relapse of their disease (either after having been in remission for some time or because they are resistant to the treatment administered).

As this is an observational cross-sectional study, participation in this study means that your doctor will only consult and record information from your clinical records and tests performed in this visit for the follow-up and/or treatment of your disease. Moreover, two QoL questionnaires will be completed.

Some of the patients (40 in all) will be asked to submit a second questionnaire after 7 days by post, in a pre-paid envelope. This is necessary to check the reliability of the EORTC QLQ-MY20 questionnaire, although you can decide if you want to participate in this specific part of the study or not.

In order for patients to keep themselves informed about the study progress and when study milestones are reached, Takeda has made available the following open access website, which will be updated as milestones are achieved during the course of the study. This site will contain public information only and in no case will any information on the patient or any confidential information be disclosed. www.charismmastudy.com

Risks derived from participation in the study

You will not be exposed to any additional risk derived from participation in this study.

Except for the completion of the QoL questionnaires, all examinations, tests and treatment will be exactly the same as if you did not participate in the study.

Benefits obtained from participation in the study

You will not obtain any additional medical benefit from participation in this study.

The information which is obtained may be scientifically important, and as such, may be useful in the future for other people who have the same disease as you.

ALTERNATIVES TO PARTICIPATION

If you decide not to participate, you will receive exactly the same treatment and care from your doctor.

Your medical care will not be affected in any way if you decide not to participate.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

You should know that your participation in this study is totally voluntary.

You have the right not to participate in this study and if you decide to participate, you have the right to change your mind and to withdraw your consent and to discontinue your participation at any time, without this affecting your medical care in any way.

CONFIDENTIALITY

The information collected in the study will be confidential and will comply with the provisions of the Personal Data Protection Act 15/1999, 13 December 1999, and the Royal Decree 1720/2007, 21 December 2007, approving the Regulations developing this law.

The documents and information that may be collected about you during the performance of this study will not contain either your name, nor your initials, nor any other identifying data; instead only a code will be shown, so that only your study doctor and co-workers can link those data with you and your clinical records.

The study results, after the information collected is analyzed, may be presented at medical meetings or published in scientific journals, but your name will never appear, nor will any personal information from which you could be identified.

Access to their personal information will be limited to the study doctor and co-workers, the health authorities, the Research Ethics Committee and representatives of the sponsor, who will be bound by professional secrecy, when they need to check the data and study procedures, but the confidentiality of your data will always be maintained according to current legislation.

In accordance with the current regulations regarding data protection, all the data in your clinical records, and the results from your participation in the study are included in a personal data file, under the responsibility of the hospital

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You may exercise your rights to access, rectify, cancel or oppose your data, by addressing the hospital in which the study is performed (see contact details in the header of this document).

2. Informed consent form

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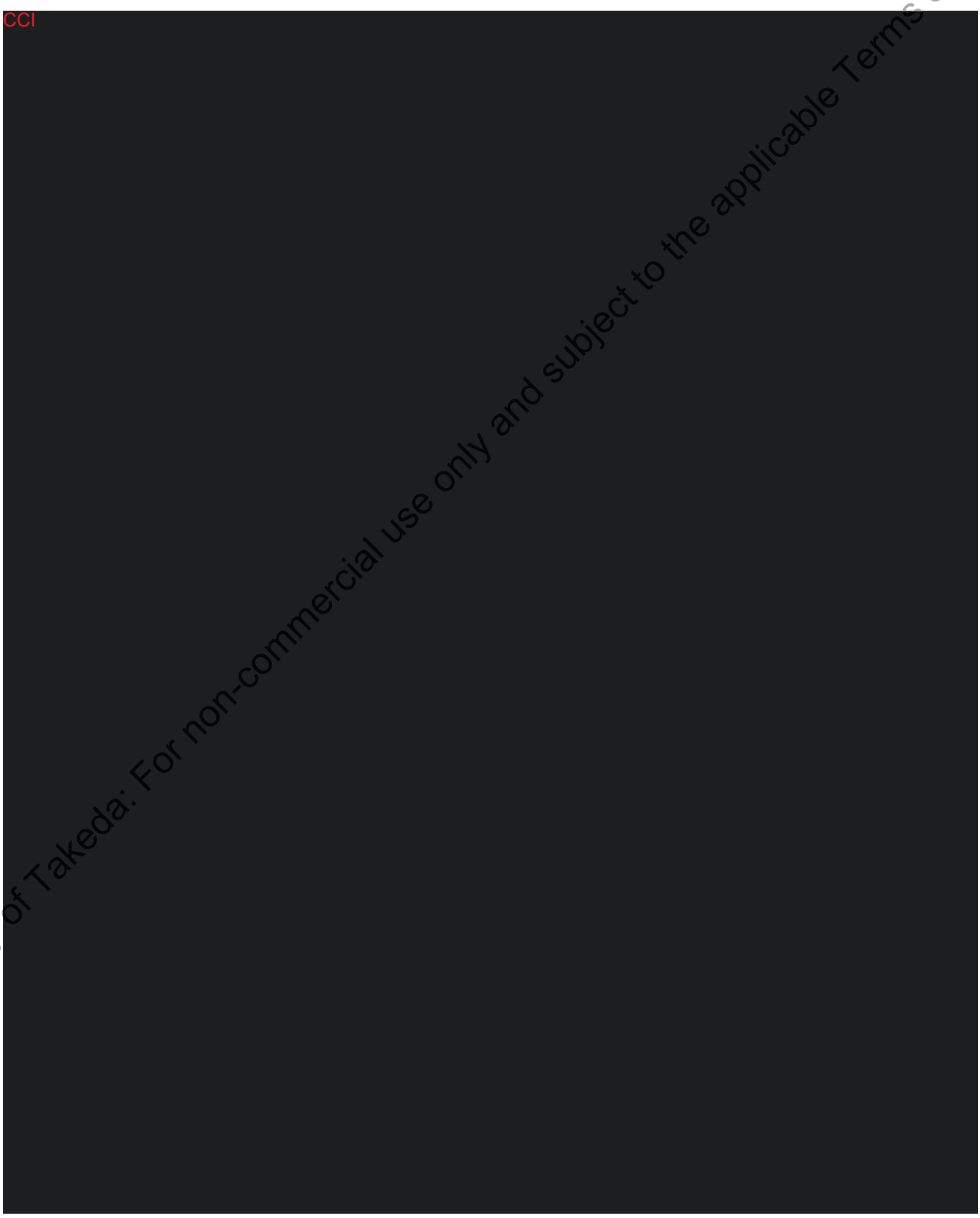

3. Case report form

Enclosed separately

4. Coordinating Investigator Commitment (sample)

Enclosed separately

5. Participating Investigator Commitment (sample)

Enclosed separately

6. Approval of Clinical research ethics committee

Enclosed separately

7. Financial agreement

Enclosed separately

8. Adverse reaction report form (sample)

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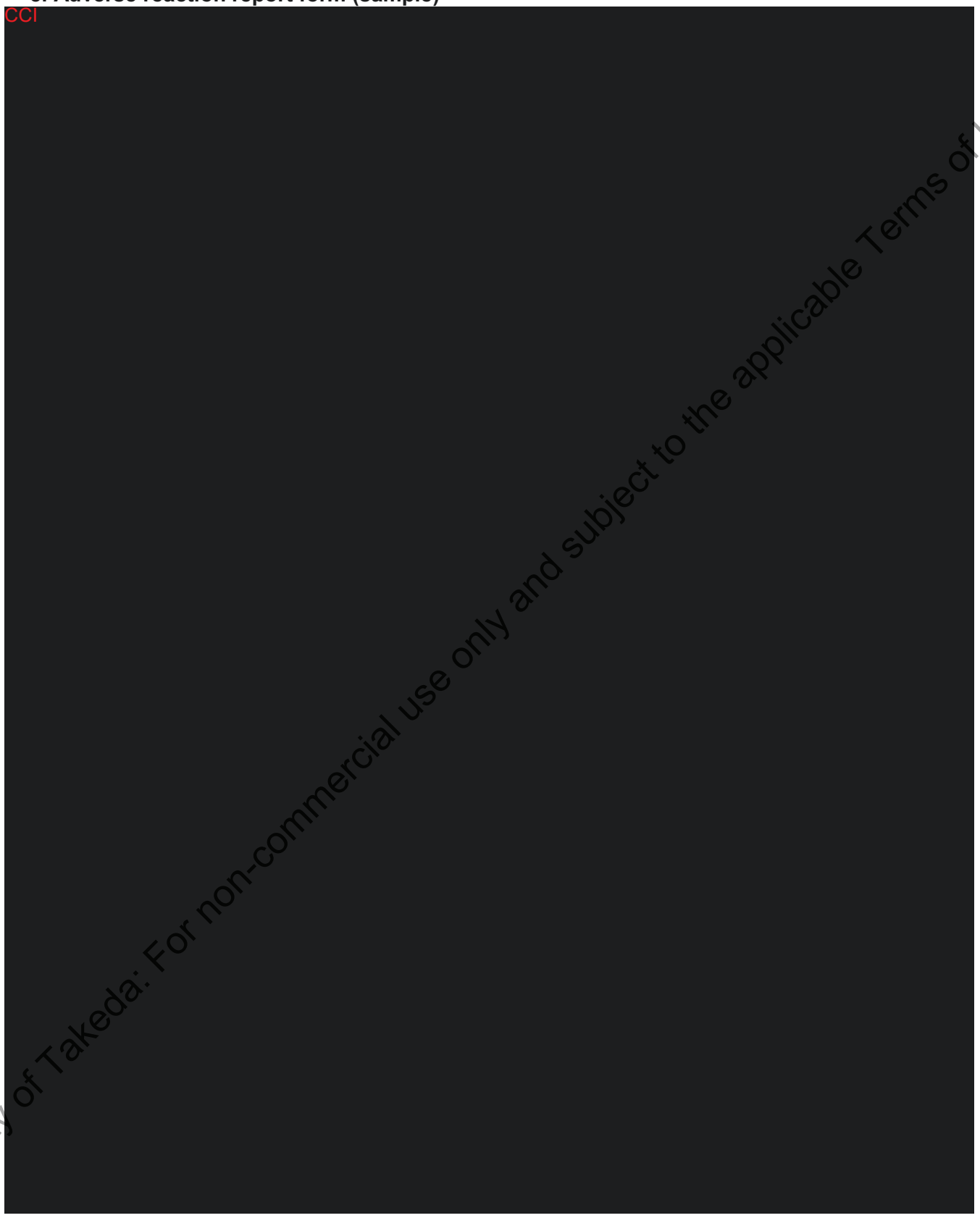

9. EORTC QLQ-MY20 questionnaire, MM module

Enclosed separately

10. EORTC QLQ-C30 questionnaire

Enclosed separately

11. ECOG scale

ECOG 0	The patient is completely asymptomatic and able to carry on all work and daily living activities.
ECOG 1	The patient has symptoms that prevent him/her performing strenuous tasks, but is able to carry out daily living activities and light work. The patient only stays in bed during night-time sleeping hours.
ECOG 2	The patient is unable to carry out any work activities, he/she has symptoms that mean he/she has to stay in bed several hours a day, in addition to night-time sleeping hours, but not than 50% of the day. The individual can perform most of their self-care alone.
ECOG 3	The patient is confined to bed more than 50% of the day due to symptoms. Requires help for most activities of daily living, for example, getting dressed.
ECOG 4	The patient confined to bed 100% of the day and needs help for all activities of daily living, such as personal hygiene, turning over in bed and even feeding.
ECOG 5	Dead

12. Principal investigators by site:

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