## Summary Table of Study Protocol

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|---|---|
| **Title** | Real-world Evidence of the Use of Carfilzomib Among Multiple Myeloma **Patients** in Europe **Who Have Received at Least One Prior Therapy.** |
| **Protocol version identifier** | **Amendment 3** |
| **Date of last version of the protocol** | **24 May 2017** |
| **EU Post Authorisation Study (PAS) Register No** | Not applicable (NA) |
| **Active Substance** | Carfilzomib in combination with lenalidomide and dexamethasone, or in combination with dexamethasone alone |
| **Medicinal Product** | Carfilzomib |
| **Product Reference** | NA |
| **Procedure Number** | NA |
| **NCT Number** | **NCT03091127** |
| **Marketing Authorisation Holder(s)** | Amgen Ltd |
| **Joint PASS** | No |
| **Research Question and Objectives** | Research question: How is carfilzomib used in routine practice in Europe?<br>Primary objective: To describe carfilzomib utilisation in routine clinical practice, including dosage, administration schedule, regimen, duration of treatment, and reason for discontinuation |
| **Countries/Regions of Study** | Austria, Belgium, Central and Eastern Europe (CEE) region, France, Greece, Israel, Italy, the Netherlands, the Nordics & Baltics region, Portugal, and **the United Kingdom** (provided that reimbursement granted at local level) |
| **Author** | PPD |

## Marketing Authorisation Holder

| | |
|---|---|
| **Marketing authorisation holder(s)** | Amgen Ltd |
| **MAH Contact** | PPD<br>1 Uxbridge Business Park<br>Sanderson Road<br>Uxbridge, UB8 1DH<br>United Kingdom<br>PPD |

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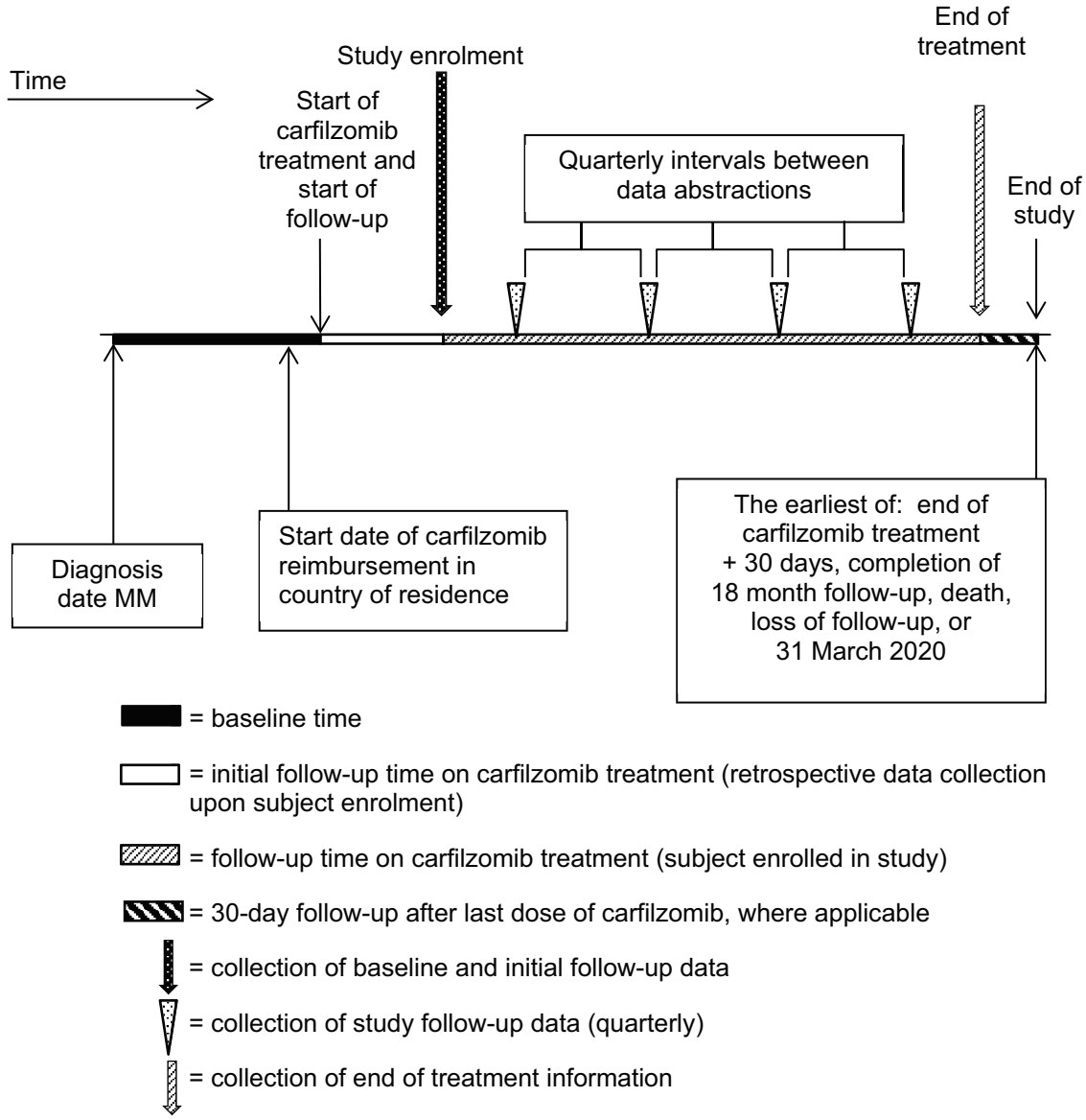
**Investigator's Agreement**

I have read the attached protocol entitled Real-world Evidence of the Use of Carfilzomib Among Multiple Myeloma **Patients** in Europe **Who Have Received at Least One Prior Therapy**, dated **12 March 2018**, and agree to abide by all provisions set forth therein.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

| Signature | |
|---|---|
| Name of Investigator <<*Coordinating Investigator*>> | Date (DD Month YYYY) |

**Study Design Schema**




MM = multiple myeloma

## 1. Table of Contents

## List of Tables



## List of Appendices

## 2. List of Abbreviations/Definitions

| Abbreviation | Definition |
|---|---|
| Baseline period | The period from a subject's initial MM diagnosis date until day 0 of cycle 1 of carfilzomib treatment. |
| BSA | body surface area |
| CEE | Central and Eastern Europe |
| CI | confidence interval |
| CR | complete response |
| CRAB | HyperCalcaemia, Renal dysfunction, Anaemia and lytic Bone lesions |
| CRF | case report form |
| **CT** | **computed tomography** |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DOR | duration of response |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EDC | electronic data capture - the electronic database housing the eCRFs |
| EMA | European Medicines Agency |
| EOS | end of study; 30 days after the final dose of carfilzomib (unless preceded by 18 months of follow-up, subject death, loss to follow-up, withdrawal of consent, or 31 March 2020). |
| EOT | end of treatment; day on which final dose of carfilzomib is administered |
| FDA | Food and Drug Administration |
| Follow-up period | The period from day 1 of cycle 1 of carfilzomib **regimen until** 30 days after the final carfilzomib administration (EOS) or until 18 months after initiation of carfilzomib treatment, death, withdrawal of consent, 31 March 2020, or loss to follow-up (whichever occurs earliest). |
| HSCT | hematopoietic stem cell transplantation |
| ICMJE | International Committee of Medical Journal Editors |
| IEC | Independent Ethics Committee |
| IMiD | immunomodulatory drug |
| IMWG | International Myeloma Working Group |
| IRB | Institutional Review Board |
| ISS | International Staging System |
| LDH | lactate dehydrogenase |
| LSLV | last subject last visit |
| LVEF | left ventricular ejection fraction |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MM | multiple myeloma |

| Abbreviation | Definition |
|---|---|
| MR | minimal response |
| MRI | magnetic resonance imaging |
| PD | progressive disease |
| PET-CT | positron emission tomography–computed tomography |
| PI | proteasome inhibitor |
| PR | partial response |
| PSP | patient support programme |
| Q | quarter |
| QT interval | Measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle, representing electrical depolarization and repolarization of the ventricles |
| RCTM | Regional Clinical Trial Manager |
| sCR | stringent complete response |
| SD | stable disease (in the context of MM natural history) |
| SD | standard deviation (in the context of variability around estimates of numerical endpoints) |
| SmPC | summary of product characteristics |
| SOP | standard operating procedure |
| Treatment period | The period from day 1 of cycle 1 of carfilzomib treatment until the day of the final carfilzomib administration or until 18 months after initiation of carfilzomib treatment, death, withdrawal of consent, loss to follow-up or EOS (whichever occurs earliest). |
| US | United States |
| VGPR | very good partial response |

## 3. Responsible Parties

| | |
|---|---|
| **Sponsor** | **Amgen Limited**<br>**1 Uxbridge Business Park**<br>**Sanderson Rd**<br>**Uxbridge UB8 1DH** |

Details on principal investigator and coordinating investigator for each country in which the study is to be performed are available upon request.

## 4. Abstract

- Study Title

  Real-world Evidence of the Use of Carfilzomib Among Multiple Myeloma **Patients** in Europe **Who Have Received at Least One Prior Therapy**.

- Study Background and Rationale

  With the recent addition of carfilzomib as a treatment option for multiple myeloma (MM), no data is available yet on how the drug is being used outside of the clinical trial setting. This study will therefore provide essential data to demonstrate the real-world utilization of carfilzomib.

- Research Question and Objectives

  Primary Objective:

  - To describe carfilzomib utilisation in routine clinical practice, including dosage, administration schedule, regimen, duration of treatment, and reason for discontinuation.

  Secondary Objectives:

  - Describe the population treated with carfilzomib in terms of demographics, MM disease characteristics, treatment history, and comorbidities.
  - Describe the safety profile of carfilzomib in routine clinical practice.
  - Describe response to treatment as assessed by the physician and recorded in the medical file.
  - Describe healthcare resource utilisation of subjects treated with carfilzomib, in terms of unplanned hospitalisations.
  - Describe the reasons for choosing carfilzomib as the MM treatment of choice.
  - Describe specific concomitant therapy (bisphosphonates, thromboprophylaxis, antihypertensive treatment, anti-infective treatment) and whether these therapies were used as prophylaxis or as treatment.
  - Describe a cardiovascular assessment at carfilzomib **regimen** initiation **and at occurrence of cardiac adverse events,** where available per routine care (electrocardiogram [ECG], echocardiography, left ventricular ejection fraction [LVEF]).

Exploratory Objectives:

- Describe treatment response as assessed by physician and per International Myeloma Working Group (IMWG) criteria, where recorded per routine practice: duration of response (DOR), time to response, time to best response.
- Describe time to progression.
- Describe primary and relevant secondary outcomes by patient frailty level as recorded by the physician at end of treatment (EOT).
- Describe primary and relevant secondary outcomes, stratified by enrolment in a patient support programme (PSP) whilst receiving carfilzomib treatment.

- Estimation

  This study will describe the utilisation of carfilzomib in routine clinical practice, including estimating average dose administered in the overall study population with an expected precision of ± 1 mg/m$^2$. Formal hypotheses will not be tested.

- Study Design/Type

  Single arm cohort study in which data will be collected through serial review of patient charts.

- Study Population

  Subjects with MM who received at least 1 prior line of treatment and are treated with carfilzomib per routine practice in a European country where reimbursement for carfilzomib is in place (anticipated participation in study: 9 countries [Austria, Belgium, France, Greece, Israel, Italy, the Netherlands, Portugal, and **the United Kingdom**] and 2 regions [Central and Eastern Europe (CEE); Nordics & Baltics]) between 2016 and 2020. **However, the final list of countries will depend on reimbursement and feasibility.**

- Summary of Subject Eligibility Criteria
  - age 18 years or older at the time of carfilzomib initiation
  - at least 1 prior line of MM treatment has been received
  - carfilzomib treatment has been initiated per routine practice and is currently ongoing
  - at least 1 administration of carfilzomib in a combination regimen (ie, not monotherapy) has been received
  - subjects who are enrolled in a carfilzomib clinical trial will not be eligible to take part in this observational study
  - **Subjects who are receiving carfilzomib treatment within a compassionate use program will not be eligible to take part in this observational study.**
  - provided written informed consent prior to abstraction of any data, in countries where written informed consent is required

- Follow-up

  The follow-up period for a subject is defined as the period from day 1 of cycle 1 of carfilzomib **regimen** until 30 days after the final carfilzomib dose (end of study, EOS) or until 18 months after initiation of carfilzomib treatment, death, withdrawal of consent, 31 March 2020, or loss to follow-up (whichever occurs earliest). Follow-up data will be collected through serial review of subjects' charts.

- Variables

Outcome Variables:

- carfilzomib dose, regimen, dosing frequency, administration schedule, and duration of treatment
- carfilzomib dose and frequency changes, interruptions, or delays
- reasons for discontinuation of carfilzomib treatment
- changes in dose and frequency of concomitant MM therapies given as part of the carfilzomib regimen
- baseline demographic characteristics (age at MM initial diagnosis, **and age,** sex, height, weight, body surface area [BSA] **at carfilzomib regimen initiation**)
- baseline MM disease characteristics
- treatment history
- safety profile of carfilzomib in routine clinical practice
- response to carfilzomib treatment as assessed by the physician
- Eastern Cooperative Oncology Group (ECOG) performance status (Appendix G) category at MM diagnosis and **carfilzomib regimen initiation**
- number of unplanned hospitalisations, for any reason
- reason for choosing carfilzomib treatment, dose, and regimen
- **specific** concomitant therapy that is not part of the carfilzomib regimen
- cardiovascular assessment as conducted per routine practice at carfilzomib **regimen** initiation **and at occurrence of cardiac adverse events**
- planned subsequent treatment regimen category

Exposure Variable:

- All subjects enrolled in the study will be exposed to carfilzomib. A subject's exposure status will be assessed from their medical records.

Other Covariates:

- Where relevant and appropriate, analyses will be presented by subgroups of interest including: country, line of treatment, age group, transplantation status, cytogenetic risk group as assessed at diagnosis, frailty score, and enrolment in a PSP.

- Study Sample Size

  The analyses for this study are intended to be descriptive in nature, and consequently, the sample size is assessed in terms of the expected levels of precision for estimating the mean average dose per administration of carfilzomib. In the ASPIRE trial, the mean (standard deviation [SD]) average dose per administration of carfilzomib was 26.1 (1.76) mg/m$^2$. Given the expected increased heterogeneity in the patient population to be enrolled in this observational study, SDs ranging from 5 to 15 mg/m$^2$ have been assumed for the sample size calculations. A sample size of approximately **8**00 subjects **has been** selected for this observational study to permit individual countries (or regions, where applicable) to enrol between 100 and 200 subjects. The expected half-widths of the 95% confidence interval (CI) for the mean average dose per administration of carfilzomib that would be observed for 1000 subjects is within 1 mg/m$^2$. If an individual country enrolled 100 subjects, the half width of the 95% CI would be no wider than 3 mg/m$^2$. If an individual country enrolled as many as 200 subjects, this would decrease to 2.08 mg/m$^2$. However if an individual country enrolled 50 subjects only, the half width of the CI would be 4.16 mg/m$^2$.

- Data Analysis

  The approach to the statistical analysis will be generally descriptive, no formal hypotheses will be tested. Categorical data will be summarised by the number and percentage of subjects in each category. Two-sided 95% CIs will be presented, calculated using Wilson's method where appropriate. Continuous data will be summarised by mean, SD, median, lower and upper quartiles, and minimum and maximum values. Time-to-event endpoints (DOR and time to progression) will be summarised using Kaplan-Meier methodology. Analyses will be presented overall and by country/region.

## 5. Amendments and Updates

| Amendment or Update No. | Date | Section of Study Protocol | Amendment or Update | Reason |
|---|---|---|---|---|
| 1 | 10 November 2016 | See summary of changes | | |
| 2 | 24 May 2017 | See summary of changes | | |
| **3** | **12 March 2018** | **See summary of changes** | | |

## 6. Milestones

| Milestone | Planned date |
|---|---|
| Start of data collection | Q1 2017 |
| Interim analysis 1 | Q4 2017 |
| Interim analysis 2 | Q4 2018 |
| End of data collection | Q1 2020 |
| Final report of study results | Q1 2021 |

Q = quarter

## 7. Rationale and Background

### 7.1 Diseases and Therapeutic Area

Multiple myeloma (MM) is a neoplasm of plasma cells. Patients with MM typically have high levels of serum and/or urinary M protein and clonal bone marrow plasma cells. Myeloma symptoms are listed as "CRAB" features; hyperCalcaemia, Renal dysfunction, Anaemia, and lytic Bone lesions. The natural history of MM is characterized by progressive bone destruction (Raje and Roodman, 2011; Christoulas et al, 2009; Kyle et al, 2003), cytopenia (Augustson et al, 2005; Kyle et al, 2003), and renal dysfunction (Hutchison et al, 2012; Dimopoulos et al, 2010; Kyle et al, 2003). Immunodeficiency results from deficits in the humoral immune system, antimyeloma therapies, and progressive leukopenia, and places patients at increased risk for infections (Blimark et al, 2015; Nucci and Anaissie, 2009; Schütt et al, 2006; Augustson et al, 2005). Furthermore, cardiac events have been observed to occur more frequently in MM compared to age- and sex-matched non-MM patients (Kistler et al, 2014).

The estimated incidence and age-standardized incidence rate of MM in Europe in 2012 was 38,900 persons and 3.8 per 100,000 persons, respectively, using the European standard population (Ferlay et al, 2013). By European country, the age-standardized incidence rate of MM ranges from 0.5 per 100,000 persons to 7.0 per 100,000 persons (Ferlay et al, 2013). The 2012 worldwide age-standardized mortality due to MM was 1.0 per 100,000 men and women, with an estimated age-standardized 2012 mortality

rate in Europe of 2.2 per 100,000 men and women (Ferlay et al, 2013). By European country, mortality rates range from 0.4 to 3.5 per 100,000 persons (Ferlay et al, 2013).

Multiple myeloma is a disease of older adults, with a median age at diagnosis of 70 years (Howlader et al, 2012). Worldwide, the incidence of MM is greater among men than women (Ferlay et al, 2013).

In the last decade, numerous new therapeutic agents have been approved globally for the treatment of relapsed myeloma including: immunomodulatory drugs (ImiD) (lenalidomide, pomalidomide); bortezomib, a proteasome inhibitor (PI); liposomal doxorubicin (in combination with bortezomib), and panobinostat (a histone deacetylase inhibitor). More recently, elotuzumab (an immunostimulatory monoclonal antibody) in combination with lenalidomide and dexamethasone, and daratumumab (a novel CD38-targeted monoclonal antibody) as single agent, have been approved by the United States (US) Food and Drug Administration (FDA) and, in the first half of 2016, by the European Medicines Agency (EMA). Newer therapies currently under clinical investigation or review by the EMA include ixazomib (an oral PI) and immune checkpoint inhibitors. These new drugs pose significant additions to the older treatment options for MM (including relapsed MM) such as melphalan and cyclophosphamide. In addition, thalidomide and dexamethasone, although not approved specifically for relapsed myeloma by health authorities, are used in combination as salvage therapy in advanced stage disease, or in frail patients with cytopenias (Palumbo and Anderson, 2011).

Carfilzomib is a second generation PI. It acts by inhibiting the ubiquitin-proteasome pathway, which plays a key role in intracellular protein degradation. Malignant cells, particularly those of certain haematologic malignancies including MM, have been shown to be more sensitive to the cytotoxic effects of proteasome inhibition than normal cells. Proteasome inhibitors affect multiple processes within the tumour cell and their microenvironment, including increased apoptosis and inhibition of angiogenesis (Crawford et al, 2011). Carfilzomib use has been studied in adult MM subjects who have failed at least 1 prior therapy. Specifically, in the ASPIRE study it was shown that adding carfilzomib to a backbone of lenalidomide and dexamethasone significantly improved progression free survival compared to lenalidomide and dexamethasone alone, among subjects with relapsed MM (Stewart et al, 2015). In addition, in the head-to-head study ENDEAVOR, comparing the first in class PI bortezomib (combined with dexamethasone) to carfilzomib (also combined with dexamethasone) among subjects with relapsed or refractory MM, again a significant improvement in progression

free survival was seen in the carfilzomib arm (Dimopoulos et al, 2016). A development programme is also underway among subjects with newly diagnosed MM, including the CLARION study. Carfilzomib received its initial approval on the European market in November 2015, in combination with either lenalidomide and dexamethasone or dexamethasone alone for use in MM patients with at least 1 prior line of treatment. Further approval was obtained thereafter, for carfilzomib in combination with dexamethasone alone.

### 7.2 Rationale

With the recent addition of carfilzomib as an important treatment option for MM, no data is available yet on how the drug is being used outside of the clinical trial setting. This study will therefore provide essential data to demonstrate the real-world utilization of carfilzomib to patients, prescribers, and payers in Europe in terms of profile of patients receiving carfilzomib and whether carfilzomib is being used per the summary of product characteristics (SmPC) in these patients, including dosing. Results of this study are aimed at meeting anticipated requests and/or requirements from local reimbursement agencies in a number of European countries. Data collected will also be used to inform real-world cost effectiveness evaluation of carfilzomib.

### 7.3 Statistical Inference (Estimation)

This study will describe the utilisation of carfilzomib in routine clinical practice, including estimating average dose administered in the overall study population with an expected precision of ± 1 mg/m$^2$. Formal hypotheses will not be tested.

## 8. Research Question and Objectives

### 8.1 Primary

To describe carfilzomib utilisation in routine clinical practice, including dosage, administration schedule, regimen, duration of treatment, and reason for discontinuation.

### 8.2 Secondary

- Describe the population treated with carfilzomib in terms of demographics, MM disease characteristics, treatment history, and comorbidities.
- Describe the safety profile of carfilzomib in routine clinical practice.
- Describe response to treatment as assessed by the physician and recorded in the medical file.
- Describe healthcare resource utilisation of subjects treated with carfilzomib, in terms of unplanned hospitalisations.
- Describe the reasons for choosing carfilzomib as the MM treatment of choice.

- Describe specific concomitant therapy (bisphosphonates, thromboprophylaxis, antihypertensive treatment, anti-infective treatment) and whether these therapies were used as prophylaxis or as treatment.
- Describe a cardiovascular assessment at carfilzomib **regimen** initiation **and at occurrence of cardiac adverse events,** where available per routine care (electrocardiogram [ECG], echocardiography, left ventricular ejection fraction [LVEF]).

### 8.3 Exploratory

- Describe treatment response as assessed by physician and per International Myeloma Working Group (IMWG) criteria, where recorded per routine practice: duration of response (DOR), time to response, time to best response.
- Describe time to progression.
- Describe primary and relevant secondary outcomes by patient frailty level as recorded by the physician at end of treatment (EOT).
- Describe primary and relevant secondary outcomes, stratified by enrolment in a patient support programme (PSP) whilst receiving carfilzomib treatment.

## 9. Research Methods

### 9.1 Study Design

This is a noninterventional observational study of a single arm cohort of adult subjects with MM **who have receive at least 1 prior therapy** receiving carfilzomib in routine clinical practice. Subjects who have received at least 1 administration of carfilzomib as prescribed by their physician will be considered for enrolment into the study. Each subject will have baseline data collected and all details on their MM treatment from their first dose of carfilzomib **regimen** until 30 days after their final carfilzomib administration (end of study [EOS]) or until 18 months after carfilzomib treatment initiation (whichever occurs earlier). Because subjects are only eligible to enrol after they have already received at least 1 administration of carfilzomib, some of the carfilzomib treatment data (as well as all baseline data) will be collected retrospectively. See Appendix F for the Schedule of Assessments.

The data required for this study are expected to be routinely recorded on subjects' charts as per local clinical practice. Relevant data will be abstracted from the subject charts on a quarterly basis (rather than wait for eg, 18 months to have passed before abstracting all information from the charts in one go).

### 9.2 Setting and Study Population

#### 9.2.1 Study Period

The study period within each country participating in the study varies, depending on the date on which reimbursement is granted for the use of carfilzomib in MM patients who

have received at least 1 prior line of treatment. Once reimbursement of carfilzomib has been granted in a country, sites within that country will be initiated for participation in the study. For countries in which carfilzomib is already reimbursed on the initial approval date of this study protocol, the study period is anticipated to start in the first quarter of 2017. Should enrolment be slower than expected within a country, it may be necessary to add additional sites within a country, or if that is not possible, to extend the enrolment window. Whilst a potential extension of the enrolment window could lead to a lengthening of the duration of the study period at a site (and potentially country) level, the overall LSLV for the entire study will be no later than 31 March 2020. We expect that the vast majority of subjects will have completed their observation period by that date.

### 9.2.2 Selection and Number of Sites

All treatment centres with a focus on treating subjects with MM in participating countries will be prospectively defined as sites for potential inclusion in the study. To ensure representativeness of sites compared to the types of treatment centres within a country, a range of centre types will be selected to take part in the study (including academic, local, and, where relevant, private offices). In addition, sites will be selected to ensure a good geographical spread within each country.

### 9.2.3 Subject Eligibility

Sites will be required to enrol eligible subjects in a sequential manner based on the subjects' visit schedules.

#### 9.2.3.1 Inclusion Criteria

Subjects are eligible to take part in the study when meeting the following criteria:

- age 18 years or older at the time of carfilzomib initiation
- at least 1 prior line of MM treatment has been received
- carfilzomib treatment has been initiated per routine practice and is currently ongoing
- at least 1 administration of carfilzomib in a combination regimen (ie, not monotherapy) has been received
- provided written informed consent prior to abstraction of any data, in countries where written informed consent is required

Subjects who previously **completed** treatment with carfilzomib in a clinical trial, **a compassionate use program,** or through routine practice, are eligible to take part in the study.

Subjects who receive radiotherapy concurrently with carfilzomib treatment are also eligible to take part in the study.

Subjects who initiate carfilzomib treatment on a combination regimen, subsequently discontinue all concomitant medications but remain on carfilzomib monotherapy in later cycles, remain eligible for participation in the study.

**Subjects who are also enrolled in other observational studies in which standard of care is not altered are eligible to take part in the study.**

#### 9.2.3.2 Exclusion Criteria

Subjects who are enrolled in a carfilzomib clinical trial will not be eligible to additionally take part in this observational study. **Subjects who are receiving carfilzomib treatment within a compassionate use program will not be eligible to take part in this observational study.** If a subject who has enrolled into this observational study, also enrolls in a clinical trial in which MM treatment and/or disease management is protocol-specified, the subject becomes ineligible and the subject's data will be censored from the time the subject enrolled in the clinical trial.

### 9.2.4 Baseline Period

The baseline period is defined as the period from a subject's initial MM diagnosis date until day 0 of cycle 1 of carfilzomib treatment. Entries recorded during this baseline period on a subject's medical chart will be reviewed to obtain information on demographic factors, disease and MM treatment history, relevant comorbidities, and relevant concomitant therapies.

### 9.2.5 Study Follow-up

The follow-up period for a subject is defined as the period from day 1 of cycle 1 of carfilzomib **regimen** until 30 days after the final dose of carfilzomib (EOS) or until 18 months after initiation of carfilzomib treatment, death, withdrawal of consent, 31 March 2020, or loss to follow-up (whichever occurs earliest). Follow-up data will be collected through serial review of subjects' charts. End of treatment is defined as the day on which the final dose of carfilzomib was administered.

## 9.3 Variables

### 9.3.1 Exposure Assessment

All subjects enrolled in the study will be exposed to carfilzomib. A subject's exposure status will be assessed from their medical records. If a subject ends carfilzomib treatment, their treatment period will end on the day of the final administration of carfilzomib (EOT). Their follow-up will, however, end 30 days after their final dose of carfilzomib as described in Section 9.2.5 above (EOS). Data collected during these

30 days after end of carfilzomib treatment will be no different from the normal follow-up data collection, with the exception that fields to enter carfilzomib treatment data will be left blank.

### 9.3.2 Outcome Assessment

Primary outcome measures:

- Carfilzomib dose, regimen, dosing frequency, administration schedule, and duration of treatment:
  - carfilzomib dose per administration (in mg/m$^2$ and in mg)
  - number of carfilzomib doses administered
  - starting carfilzomib dose of 20 mg/m$^2$ (and, where applicable, other dose levels as specified in the SmPC)
  - cumulative carfilzomib dose (in mg/m$^2$ and in mg)
  - duration of carfilzomib treatment
  - number of cycles started
  - carfilzomib dose of 20 mg/m$^2$ administered on days 1 and 2 of cycle 1 and 27 mg/m$^2$ for every administration thereafter with 6 administrations of carfilzomib in each cycle (specifically days 1, 2, 8, 9, 15, and 16 for cycles 1 through 12 and days 1, 2, 15, and 16 for cycle 13 onwards)
  - carfilzomib dose of 20 mg/m$^2$ administered on days 1 and 2 of cycle 1 and 56 mg/m$^2$ for every administration thereafter with 6 administrations of carfilzomib in each cycle (specifically days 1, 2, 8, 9, 15, and 16)
  - starting carfilzomib treatment in combination with 25 mg lenalidomide (days 1 through 21) and 40 mg dexamethasone (days 1, 8, 15, and 22)
  - starting carfilzomib treatment in combination with 20 mg dexamethasone (days 1, 2, 8, 9, 15, 16, 22, and 23)
  - starting dose of lenalidomide (cycle 1)
  - starting dose and administration schedule of dexamethasone (cycle 1)
- Carfilzomib dose and frequency changes, interruptions, or delays:
  - at least 1 carfilzomib dose modification
  - at least 1 carfilzomib dose escalation
  - at least 1 carfilzomib dose reduction
  - at least 1 change in frequency of carfilzomib administration
  - time from initiation of carfilzomib treatment to carfilzomib dose modification (in days and in cycles)
  - at least 1 missed dose of carfilzomib
  - at least 1 delay between cycles of more than 1 week after day 28 of the previous cycle
  - at least 1 delay of carfilzomib treatment within a cycle of 3 days or more after the planned day of injection
  - reason for dose modification or delay
  - reason for change in frequency of administration

- Reasons for discontinuation of carfilzomib treatment
- Changes in dose and frequency of concomitant MM therapies given as part of the carfilzomib regimen:
  - for lenalidomide: a modification in dose or frequency of administration compared to the start of cycle 1.
  - for dexamethasone: a modification in dexamethasone dose or frequency compared to the start of cycle 1.
  - for subjects with a lenalidomide or dexamethasone dose modification: time from initiation of carfilzomib treatment to dose modification (in days and in cycles).
  - reason for change in frequency of administration.

Secondary outcome measures:

- Baseline demographic characteristics (age at MM initial diagnosis, **and age,** sex, height, weight, body surface area [BSA] **at carfilzomib regimen initiation**)
- Baseline MM disease characteristics:
  - type of monoclonal protein (heavy and light chain)
  - presence of CRAB features **at MM diagnosis**
  - International Staging System (ISS) and revised ISS stage at diagnosis (I, II, III, or unknown) **and carfilzomib regimen initiation**
  - ECOG performance status category at MM diagnosis **and carfilzomib regimen initiation** (0, 1, 2, 3, 4, or unknown; Appendix G)
  - cytogenetic analysis performed (yes/no)
  - cytogenetic risk at diagnosis (high risk/unfavourable, intermediate, normal/favourable, unknown, no cytogenetic analysis performed)
  - cytogenetic profile
  - number of lines of prior treatment (1, 2, 3, 4, or more)
  - timing of relapse after first-line treatment (relapse less than 1 year versus 1 year or more after front-line therapy discontinuation)
  - magnetic resonance imaging (MRI)**, positron emission tomography-computed tomography (PET-CT), computed tomography (CT), and X-ray** performed at **MM** diagnosis **and carfilzomib regimen initiation** (yes/no)
  - **myeloma/osteolytic lesions detected by** MRI**, PET-CT, CT, and X-ray at MM diagnosis and carfilzomib regimen initiation**
  - presence of comorbidities, diagnosed at any point in time before **carfilzomib regimen initiation**
  - measurement of serum M-component (in g/100 ml), urine M-component (in mg per 24h), percent of bone marrow plasma cells, serum creatinine, creatinine clearance (mL/min), serum albumin and serum beta-2-microglobulin (mg/L), **at MM diagnosis and carfilzomib regimen initiation**
  - baseline measurement of lactate dehydrogenase (LDH) **at MM diagnosis and carfilzomib regimen initiation**

- Treatment history:
  - type of prior therapy (PI in general, bortezomib in specific, ImiD in general (thalidomide, pomalidomide, lenalidomide), lenalidomide in specific, anthracycline, dexamethasone, cyclophosphamide, melphalan, daratumumab, elotuzumab, izaxomib
  - response to prior treatment regimen received before initiation of carfilzomib
  - previous hematopoietic stem cell transplantation transplant(s) (HSCT)
  - proportion of subjects previously treated for their MM in a clinical trial
- Safety profile of carfilzomib in routine clinical practice:
  - adverse event (grade 3 or above) following initiation of carfilzomib
  - onset of adverse event (grade 3 or above) in days from treatment initiation
  - LVEF decrease as recorded in tests performed per routine practice
  - adverse events (grade 3 or above) requiring administration of a blood transfusion or dialysis
  - management of cardiotoxicity:
    - dose reduction of MM treatment due to cardiotoxicity
    - MM treatment withheld due to cardiotoxicity
    - initiation or a dose increase of existing antihypertensive treatment
    - initiation or a dose increase of existing heart failure treatment
- Response to carfilzomib treatment as assessed by the physician:
  - best response (stringent complete response [sCR], complete response [CR], very good partial response [VGPR], partial response [PR], minimal response [MR], stable disease [SD] or progressive disease [PD]; see Appendix E)
  - overall response (PR or better)
- For subjects who relapsed: type of relapse (molecular, hematologic, or symptomatic)
- ECOG performance status (Appendix G) category at MM diagnosis and **carfilzomib regimen initiation**
- Number of unplanned hospitalisations, for any reason
- Reason for choosing carfilzomib treatment, dose, and regimen
- **Specific c**oncomitant therapy that is not part of the carfilzomib regimen (thromboprophylaxis/ anticoagulants, antihypertensive and heart failure treatment, antiviral treatment, antibiotic treatment, bone targeting agents, hematopoietic growth factors, pain control)
- Cardiovascular assessment as conducted per routine practice at carfilzomib **regimen** initiation **and occurrence of cardiac adverse events**:
  - ECG category (normal, prolonged QT, abnormal clinically significant, abnormal not clinically significant)
  - echocardiography performed (yes, no, unknown)
  - LVEF (%)

- **blood pressure**
- **heart rate**

- Planned subsequent treatment regimen category (PI in general, bortezomib in specific, ImiD (thalidomide, pomalidomide, lenalidomide), anthracycline, dexamethasone, cyclophosphamide, melphalan, daratumumab, elotuzumab, izaxomib, transplant)

Exploratory outcome measures:

- duration of response during carfilzomib exposure (ie, during the treatment period), defined as duration in months from the start date of physician-assessed sCR, CR, VGPR, or PR (whichever response is achieved first) to the earlier of disease progression as recorded in the medical chart or death due to any cause (response assessed by physician, and also per the updated IMWG criteria where available; see Appendix E)
- time to response, defined as duration in months from the start date of carfilzomib treatment until sCR, CR, VGPR, or PR is reached (whichever response is achieved first), as assessed by physician, and also per the updated IMWG criteria where available
- time to best response defined as duration in months from the start date of carfilzomib treatment until the best achieved response (sCR, CR, VGPR, or PR, with sCR being the best possible and PR being the lowest possible response level), as assessed by physician, and also per the updated IMWG criteria where available
- response status at EOT
- time to progression whilst on carfilzomib treatment, defined as duration in months from start of carfilzomib treatment until disease progression as recorded in the medical chart per routine clinical practice by the physician
- frailty score category as assessed by the physician (fit, intermediate fitness, frail) at EOT
- enrolment in a PSP (yes/no)
- receipt of carfilzomib infusion at home at any point during carfilzomib treatment

### 9.3.3 Validity and Reliability

The data collected for this study will derive from medical records that are kept per routine clinical practice for the documentation and decision-making for a subject's care. Abstractors will be trained on the electronic abstraction form (electronic case report form [eCRF]) to ensure that data entered are accurate.

## 9.4 Data Sources

Data will be obtained from routine clinical records at **3**-monthly intervals and transcribed onto an anonymous eCRF which will be in 3 parts:

I. Baseline information, collected upon enrolment into the study.

II. **During treatment** – for the time period between starting carfilzomib treatment and enrolling into the study, the initial set of follow-up data will be collected retrospectively as collection of baseline information. Thereafter, follow**-**up data will be collected every **3** months.

III. End of study – **data will be documented in the eCRF up to** 30 days after the final carfilzomib administration (unless preceded by 18 months of follow-up, subject death, loss to follow up, withdrawal of consent, or 31 March 2020).

The vast majority of data for this study will be abstracted from medical records through chart reviews. The data from these chart reviews will be merged to form a longitudinal cohort for analysis. Since these are data that are collected per routine practice for patient care, information on carfilzomib administration and adverse events are expected to be reasonably complete, although some missing data can be expected. Evaluations of concomitant medications, demographic details, medical and treatment history, and response to treatment are also important for patient care and are expected to routinely be available in the medical record. At the end of a subject's follow-up, the treating physician will be contacted directly to request detail on a couple of data points which are not likely to be captured in a subject's records, namely: whether the physician followed the IMWG criteria to assess response to MM treatment and whether the subject was enrolled in a PSP. We anticipate this information will easily be recalled by the physician and what the planned next treatment regimen will be for the subject.

### 9.5 Study Size

The primary objective of this study is to describe utilisation of carfilzomib in routine clinical practice for subjects with MM who have received at least 1 prior line of treatment. A total of 9 countries and 2 regions are anticipated to take part in the study, provided that reimbursement for the use of carfilzomib is obtained on a local level. Specifically, we plan to conduct the study in Austria, Belgium, France, Greece, Israel, Italy, the Netherlands, Portugal, and **the United Kingdom** as well as the Central and Eastern Europe (CEE) and Nordics & Baltics regions, given that these countries have either a requirement (Portugal, Bulgaria, and France) or a strong need to provide real-world evidence of how carfilzomib is used within a limited time period after obtaining reimbursement. **However, the final list of countries will depend on reimbursement and feasibility.**

A sample size of approximately **8**00 subjects **has been** selected for this observational study to permit individual countries (or regions, where applicable) to enrol between 100

and 200 subjects. The analysis is intended to be descriptive in nature, and consequently, the sample size is assessed in terms of the expected levels of precision for estimating the mean average dose per administration of carfilzomib.

In the ASPIRE trial, the mean (standard deviation [SD]) average dose per administration of carfilzomib was 26.1 (1.76) mg/m$^2$ . Given the expected increased heterogeneity in the patient population to be enrolled in this study, SDs ranging from 5 to 15 mg/m$^2$ have been assumed for the sample size calculations presented below. Table 1 presents the expected half-widths of the 95% CI for the mean average dose per administration of carfilzomib that would be observed for 1000 subjects. Estimates are also provided for smaller sample sizes that may be applicable to country and subgroup analyses.

**Table 1. Expected Precision for Estimating Mean Average Dose per Administration**

| Sample size | 95% Confidence Interval Half-Width (mg/m$^2$) | | |
|---|---|---|---|
| | SD = 5 | SD = 10 | SD = 15 |
| 50 | 1.39 | 2.77 | 4.16 |
| 100 | 0.98 | 1.96 | 2.94 |
| 150 | 0.80 | 1.60 | 2.40 |
| 200 | 0.69 | 1.39 | 2.08 |
| 1000 | 0.31 | 0.62 | 0.93 |

For example, a sample size of 1000 subjects would ensure that the half width of the 95% CI for mean average dose per administration of carfilzomib is within 1 mg/m$^2$. If an individual country enrolled 100 subjects, the half width of the 95% CI would be no wider than 3 mg/m$^2$. If an individual country enrolled as many as 200 subjects, this would decrease to 2.08 mg/m$^2$. If an individual country enrolled 50 subjects only, the half width of the CI would be 4.16 mg/m$^2$.

### 9.6 Data Management

Data are abstracted by site staff from subject notes into an electronic database provided by the sponsor. The sponsor provides protocol-specific training to all site staff delegated to abstract subject data. An eCRF Completion Guideline is provided.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, case report forms [CRFs] and other pertinent data) provided that subject confidentiality is respected.

The Clinical Monitor or designee is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of research. The Clinical Monitor or designee is to have access to subject medical records and other study-related records needed to verify the entries on the CRFs in accordance with the local laws and regulations.

The investigator agrees to cooperate with the Clinical Monitor, or designee to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Review of study-related records will occur to evaluate the study conduct and compliance with the protocol, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the eCRFs must be maintained and available upon request.
- Updates to eCRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data is checked for consistency, omissions, and any apparent discrepancies. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications are created in the electronic data capture (EDC) system database for site resolution and closed by Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this EDC study. This signature indicates that the investigator inspected or reviewed the data on the eCRF, the data queries, and site notifications, and agrees with the content.

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit – week 4 and early termination) and clarifying "other, specify" if data are provided (eg, race, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the study and at study closeout.

#### 9.6.1 Review and Verification of Data Quality

Automatic edit checks within the database and further manual review by the sponsor help to ensure quality and completeness of the data. Data queries are sent to site for clarification and resolution of discrepancies.

### 9.7 Data Analysis

#### 9.7.1 Planned Analyses

##### 9.7.1.1 Interim Analysis/Analyses

A limited number of interim analyses may be performed to meet requirements from local reimbursement agencies of the countries participating in the study and/or for publication purposes. These analyses will be described in the statistical analysis plan; the results of interim analyses are not expected to alter the conduct of the study.

##### 9.7.1.2 Primary Analysis

The primary analysis will be conducted when the last subject has ended study follow-up, as described in Section 9.2.5.

#### 9.7.2 Planned Method of Analysis

##### 9.7.2.1 General Considerations

The approach to the statistical analysis will be generally descriptive, no formal hypotheses will be tested.

Categorical data will be summarised by the number and percentage of subjects in each category. Two-sided 95% CIs will be presented, calculated using Wilson's method where appropriate. Continuous data will be summarised by mean, SD, median, lower and upper quartiles, and minimum and maximum values. Time-to-event endpoints (DOR and time to progression) will be summarised using Kaplan-Meier methodology.

Analyses will be presented overall and by country/region.

##### 9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

The eCRFs will be designed to minimise missing data and to optimise the integrity of collected data. Subjects' records will not be excluded because of missing data and missing data will not be imputed. For categorical variables, missing responses will be shown as a separate category in the analysis. For numeric variables, the number of nonmissing observations will be presented.

#### 9.7.2.3 Descriptive Analysis

##### 9.7.2.3.1 Description of Study Enrollment

The number of subjects enrolled and the number within each analysis set will be summarised. Subjects that were not enrolled but who met the eligibility criteria will be listed in a nonparticipant log, along with reason for nonenrolment, by country. Subject enrolment by country and investigator will be summarised.

##### 9.7.2.3.2 Description of Subject Characteristics

Baseline demographic and disease characteristics will be summarised descriptively as outlined in Section 9.7.2.1.

#### 9.7.2.4 Analysis of the Primary, Secondary and Exploratory Endpoint(s)

##### 9.7.2.4.1 Primary Outcome Measures

The primary outcome measures will be analysed descriptively as outlined in Section 9.7.2.1.

The average carfilzomib dose per subject will be summarised (in mg and in mg/$m^2$), overall, and by cycle (and separately for days 1 and 2 of cycle 1). Cumulative dose, number of cycles, and duration of carfilzomib treatment will also be summarised.

The proportion of subjects receiving 20 mg/$m^2$ on days 1 and 2 of cycle 1 and 27 mg/$m^2$ for every administration thereafter, and receiving 6 doses of carfilzomib in each cycle (specifically days 1, 2, 8, 9, 15, and 16 for cycles 1 through 12 and days 1, 2, 15, and 16 for cycle 13 onwards) will be presented. The proportion of subjects starting carfilzomib treatment in combination with lenalidomide and dexamethasone will be presented, as well as the proportion of subjects starting carfilzomib treatment in combination with dexamethasone alone. These summaries will be accompanied by summaries of the starting doses of lenalidomide (where given) and dexamethasone. Furthermore, the treatment schedule of dexamethasone will be summarized. Changes from the starting doses of lenalidomide and dexamethasone will also be described.

The proportion of subjects experiencing at least 1 carfilzomib dose modification, (escalations and reductions), missed dose, and delay between or within cycle, will be presented, overall and by cycle. The timing and reasons for dose modification or delay and reason for change in frequency of administration will also be summarised, as well as the reason for discontinuation of carfilzomib.

#### 9.7.2.4.2 Secondary Outcome Measures

The secondary outcome measures will be analysed descriptively as outlined in Section 9.7.2.1.

Best response to carfilzomib treatment will be summarised, along with the proportion of subjects with an overall response. This analysis will be repeated for those subjects whose disease was assessed according to IMWG criteria.

#### 9.7.2.4.3 Exploratory Outcome Measures

Duration of response and time to progression, as described in Section 9.3.2, will be summarised descriptively using the Kaplan-Meier method. Details of censoring will be provided in the statistical analysis plan. The median, lower, and upper quartiles will be estimated along with 95% CIs, and Kaplan-Meier estimates at relevant timepoints will be presented.

Other exploratory outcomes will be analysed descriptively as outlined in Section 9.7.2.1.

### 9.7.2.5 Sensitivity Analysis

Baseline demographic and disease characteristics will be summarised for subjects enrolled within 3 months following reimbursement approval in their respective country, in order to assess potential differences as compared to the overall country-level study population.

#### 9.7.2.5.1 Subgroup Analysis

Where relevant and appropriate, analyses will be presented by subgroups of interest including **but not limited to**:

- country
- line of treatment
- age group
- transplantation status
- cytogenetic risk group as assessed at diagnosis
- frailty score
- enrolment in a PSP

### 9.7.3 Analysis of Safety Outcomes

The Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 or later will be used to code all adverse events to a system organ class and a preferred term.

The subject incidence of adverse events will be summarized for all, serious, and fatal events. Adverse events will be tabulated by system organ class and preferred term in descending order of frequency.

### 9.8 Quality Control

Source data verification will be performed at the study site, in accordance with Amgen standard operating procedures (SOPs).

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Documents to be maintained for the study are as follows:

- subject files containing the completed eCRF, informed consent forms, as applicable, and subject identification list
- study files containing the protocol with all amendments, copies of prestudy documentation, and all correspondence to and from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or other relevant ethical review board and Amgen

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available. Retention of study documents will be governed by the contractual agreement with Amgen.

Amgen retains all data, programs, and outputs generated for the study. At study close, data are uploaded from the Medidata Rave database and stored in accordance with Amgen SOPs. Statistical programming and outputs are locked in the analysis environment and no updates are permitted; standard programming procedures will apply.

## 9.9 Limitations of the Research Methods

### 9.9.1 Internal Validity of Study Design

#### 9.9.1.1 Measurement Error(s)/Misclassification(s)

It is plausible that different countries (or sites) use different criteria to assess eg, response to treatment, potentially resulting in systematic differences between countries in terms of response to treatment measurements.

Due to retrospective (quarterly) chunks of data abstraction, there is a risk of measurement error when data that were entered in the past were unclear or incomplete. This would lead to bias if the information was not missing at random.

#### 9.9.1.2 Information Bias

Information bias is another possible bias if, for example, the information for subjects with more complications and/or more complex disease manifestation was recorded with more or less detail. Hospital medical charts of patients receiving carfilzomib infusion at home may be less complete than charts of patients receiving carfilzomib at the hospital. Subjects who are enrolled in a PSP have the potential to be better informed about their disease and its management. This is a form of information bias and it is an exploratory objective of this study to assess whether this affects patient outcomes. Furthermore, it is plausible that adverse event reporting rates are different between subjects enrolled in a PSP versus those who are not, eg, due to closer monitoring of their treating physician (who may also be receiving additional support and educational material through the PSP).

#### 9.9.1.3 Selection Bias

In countries where subject informed consent is required to access medical records, selection/volunteer bias could be an issue if, for example, sicker subjects are less likely to consent.

Physicians prescribing carfilzomib treatment immediately after reimbursement has been obtained in their country may have been waiting for this treatment to become available for patients who have no alternative treatment options, for example, following failure of all previous MM therapies. Therefore, there is a risk that the patient population enrolled in the study has more severe disease than the general MM population within that country. Sensitivity analyses will be conducted to better understand if there is a difference in disease characteristics for subjects enrolled early (ie, within 3 months after gaining reimbursement) to assess whether selection bias has affected enrolment within each country participating in the study.

To minimise bias, eligibility criteria have been kept broad, and each site will document any eligible subjects that are not subsequently enrolled to the study.

#### 9.9.1.4 Confounding

No formal comparisons of outcomes between subgroups are planned for this study, thereby eliminating the risk of confounding bias.

### 9.9.2 External Validity of Study Design

To ensure representativeness of sites compared to the types of treatment centres within a country, a range of centre types will be selected to take part in the study (including academic, local hospitals and, where relevant, private offices). In addition, sites will be selected to ensure a good geographical spread within each country. Lastly, to ensure a representative set of subjects is enrolled at each site, sites will be required to enrol eligible subjects in a sequential manner based on their visit schedules.

Healthcare resource use is likely to depend on country-specific requirements within the healthcare system and on how MM care is arranged in a country. Therefore, the overall summary of healthcare resource use will be biased towards the countries included in the study.

Healthcare systems and reimbursement decisions may vary between the countries anticipated to take part in the study. Therefore, some of the outcomes may not be informative to summarise across the entire study due to inherent biases (eg, if a country imposes a cap on the maximum number of reimbursed cycles of treatment).

### 9.9.3 Analysis Limitations

The precision of estimates will depend on the number of subjects enrolled in each country or subgroup. The precision of time to event analyses will depend on the number of events observed during the study follow-up.

### *9.9.4* Limitations Due to Missing Data and/or Incomplete Data

An important limitation will relate to missing information since the data for this study will be abstracted from medical charts. The eCRF will prompt recording of any information that is available, but the data being abstracted were recorded for patient care and not research purposes. Therefore, information that is not deemed relevant to the care of that subject might not be captured in the chart, resulting in missing or incomplete data. For categorical data, missing responses will impact the resulting proportions of subjects with nonmissing values.

Furthermore, the study aims to describe the safety profile of carfilzomib. As the study-specific eCRF only captures adverse events of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 and above, it is important to note that it will not be possible to describe the safety profile of carfilzomib as it relates to lower grade adverse events.

### 9.10 Other Aspects

A list of stand-alone documents are provided in Appendix A.

## 10. Protection of Human Subjects

This study will comply will all relevant ethical and regulatory requirements in each country, and will not be used for the conduct of marketing surveys or other marketing purposes. The study will comply with Amgen adverse event reporting SOPs. This study and data collection will be conducted in accordance with the relevant local laws.

The responsible physician is also responsible for forwarding the following documents to Amgen or its representative for review before study initiation occurs:

- signed and dated protocol signature page (Responsible Physician's Agreement)
- copy of the Central Ethics Board approval of the protocol, waiver for requirement of informed consent
- subject or subject's legally acceptable representative has provided informed consent (for countries where required per local regulations)
- up-to-date curriculum vitae of responsible physician and all co/sub-physicians
- signed confidentiality agreement
- signed study contract

The responsible physician will be charged with maintaining correct and comprehensive documentation, while the Amgen monitor/designee is tasked to ensure that the responsible physician is following the correct study protocol.

### 10.1 Informed Consent

For countries where written informed consent is required, an initial sample informed consent form will be provided by Amgen for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Regional Clinical Trial Manager (RCTM) to the investigator. The written informed consent document is to be prepared in the language of the potential subject population. Where required by participating clinical sites for the collection of anonymized medical chart data, and before a subject's participation in the study, the investigator is responsible for obtaining written informed

consent, where applicable by local regulations, from the subject or legally acceptable representative. The acquisition of informed consent is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject or legally acceptable representative. If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

### 10.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC or other relevant ethical review board for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before study can be executed.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC or other relevant ethical review board for all subsequent protocol amendments and changes to the informed consent document, as applicable. The investigator is to notify the IRB/IEC or other relevant ethical review board of deviations from the protocol or serious adverse event(s) occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB/IEC or other relevant ethical review board approval/renewal throughout the duration of the study. Copies of the investigator's reports, where applicable by local regulations and the IRB/IEC or other relevant ethical review board continuance of approval must be sent to Amgen.

### 10.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

## 11. Collection of Safety Information and Product Complaints

All grade 3 or above **safety** events (adverse drug reactions, serious adverse drug reactions, product complaints, and other safety findings [eg, pregnancy, lactation]) in routine clinical practice will be documented in accordance with Amgen requirement documents (eg, SOPs).

### 11.1 Definition of Safety Events

#### 11.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an adverse event includes:

- worsening of a pre-existing condition or underlying disease
- events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)

It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen.

#### 11.1.2 Serious Adverse Events

A serious adverse event is any adverse event as defined above that meets at least 1 of the following serious criteria:

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an "other significant medical hazard" that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

"Other significant medical hazards" refer to important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm,

convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

### 11.1.3 Other Safety Findings

Other safety findings (regardless of association with an adverse event) include:

- medication errors, overdose, whether accidental or intentional, misuse, or abuse, involving an Amgen product,
- pregnancy and lactation exposure,
- transmission of infectious agents,
- reports of uses outside the terms for authorized use of the product including off-label use,
- occupational exposure,
- any lack or loss of intended effect of the product(s).

### 11.1.4 Product Complaints

Product complaints include any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product or device after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s) or device(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

The products for which product complaints are to be collected as part of this study are: carfilzomib and all other Amgen products to which eligible subjects are exposed during their observation time on study.

## 11.2 Safety Reporting Requirements

The investigator is responsible for ensuring that **all grade 3 or above** safety events (adverse events, product complaints, and other safety findings) observed by the investigator or reported by the subject that occur after initiation of carfilzomib through the final study contact are recorded in the subject's appropriate study documentation. All safety events that are grade 3 or above must be submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (electronic form) within 1 business day of investigator awareness. Lower grade safety events are out of scope for this study as per the study outcomes.

In large phase 3 randomized-controlled trials of Kyprolis for the treatment of subjects with relapsed or refractory MM, nearly all subjects experienced at least

1 treatment-emergent adverse event (Dimopoulos et al, 2016; Stewart et al, 2015). Additionally, in these studies, the majority of subjects also experience grade 3 or higher treatment-emergent adverse events. The high incidence of treatment-emergent adverse events in these populations, reflects not only the potential effects of treatment but also co-morbidities associated with age as well as the complications associated with MM. Higher grade (or more severe) adverse events are more likely to impact tolerability of carfilzomib and the decision to modify treatment. Thus, this study will only collect grade 3 or higher **safety** events.

If the EDC system is unavailable to the site staff to report the adverse event, the information is to be reported to Amgen via a paper Adverse Event Contingency Report Form within 1 business day of the investigator's awareness.

For EDC studies where the first notification of an Adverse Event is reported to Amgen via the Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

See Appendix B for sample Adverse Event Contingency Report Form, Appendix C for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and Appendix D for sample Pregnancy and Lactation Notification Worksheets.

The investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded on study eCRFs where safety data may also be recorded (eg, safety report form, event form).

### 11.2.1 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required to regulatory authorities, investigators/institutions, IRBs/IECs, or other relevant ethical review board(s) in accordance with pharmacovigilance guidelines and in compliance with local regulations. The investigator is to notify the appropriate IRB/IEC or other relevant ethical review board of serious adverse events in accordance with local procedures and statutes.

## 12. Administrative and Legal Obligations

### 12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the investigator must be obtained where applicable per local governing

law and/or regulations. The IEC must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IEC to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the contractual agreement. The investigator is to notify the IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

## 13. Plans for Disseminating and Communicating Study Results

Final results of the study will be disseminated in the form of a manuscript in the peer-reviewed literature. In addition, where relevant, data from potential interim analyses will be presented at (a) relevant congress(es).

### 13.1 Publication Policy

The results of the study will be submitted for publication.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published, and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3, and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

## 14. Compensation

Not applicable

## 15. References

Augustson B, Begum G, Dunn J, et al. Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United Kingdom Medical Research Council Trials between 1980 and 2002—Medical Research Council Adult Leukaemia Working Party. *J Clin Oncol*. 2005;23:9219-9226.

Blimark C, Holmberg E, Mellqvist UH, et al. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. *Haematologica*. 2015 Jan;100(1):107-13.

Christoulas D, Terpos E, Dimopoulos M. Pathogenesis and management of myeloma bone disease. *Expert Rev Hematol*. 2009;2(4):385-398.

Crawford LJ, Walker B and Irvine AE. Proteasome inhibitors in cancer therapy. *J Cell Commun Signal*. 2011;5:101-110.

Dimopoulos M, Terpos E, Chanan-Khan A, et al. Renal impairment in patients with multiple myeloma: a consensus statement on behalf of the International Myeloma Working Group. *J Clin Oncol*. 2010;28 :4976-4984.

Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicenter study. *Lancet Oncol*. 2016;17(1):27-38.

Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*. 2013;49:1374-1403.

Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations), National Cancer Institute. 2012. Available from: http://seer.cancer.gov/csr/1975_2009_pops09

Hutchison C, Batuman V, Behrens J, et al. The pathogenesis and diagnosis of acute kidney injury in multiple myeloma. *Nat Rev Nephrol*. 2012;8(1):43-51.

Kistler K, Murphy B, Kalman J, et al. A comparison of cardiac event rates in patients with or without multiple myeloma in the US. *J Clin Oncol.* 2014;32(suppl; abstr e19563).

Kyle R, Gertz M, Witzig T, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc*. 2003;78:21-33.

Nucci M and Anaissie E. Infections in patients with multiple myeloma in the era of high-dose therapy and novel agents. *Clin Infect Dis*. 2009 Oct 15;49(8):1211-25.

Palumbo A and Anderson K. Multiple myeloma. *N Engl J Med*. 2011;364:1046-60.

Raje N, Roodman G. Advances in the biology and treatment of bone disease in multiple myeloma. *Clin Cancer Res*. 2011;17:1278-1286.

Schütt P, Brandhorst D, Stellberg W et al. Immune parameters in multiple myeloma patients: influence of treatment and correlation with opportunistic infections. *Leuk Lymphoma*. 2006 Aug;47(8):1570-82.

Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Eng J Med*. 2015;372(2):142-152.

## 16. Appendices

## Appendix A. List of Stand-alone Documents

| No. | Document Reference Number. | Date | Title |
|---|---|---|---|
| 1 | Number | Not applicable; living document; updated when new countries/sites start study participation | Contact details of principal investigator and country-coordinating investigators |

## Appendix B. Sample Adverse Event Contingency Report Form

| AMGEN<br>Study # 20150262<br>Carfilzomib | Electronic Adverse Event Contingency Report Form<br>For Restricted Use |
|---|---|

**Reason for reporting this event via fax**

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

*<<For completion by COM/Study manager/Author prior to providing to sites: SELECT OR TYPE IN A FAX#>>*

**1. SITE INFORMATION**

| Site Number | Investigator | Country |
|---|---|---|
| | | |

| Reporter | Phone Number | Fax Number |
|---|---|---|
| | ( ) | ( ) |

**2. SUBJECT INFORMATION**

| Subject ID Number | Age at event onset | Sex | Race | If applicable, provide End of Study date |
|---|---|---|---|---|
| | | ☐F ☐M | | |

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term:
and start date: Day ____ Month ____ Year ____

**3. ADVERSE EVENT**

Provide the date the Investigator became aware of this information: Day ____ Month ____ Year ____

| Adverse Event diagnosis or syndrome<br>If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report<br>*List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.* | Date Started<br>Day Month Year | Date Ended<br>Day Month Year | Check only if event occurred before first dose of drug under study | Is event serious? | If serious, enter Serious Criteria code (See codes below) | Relationship<br>Is there a reasonable possibility that the Event may have been caused by Amgen drug under study or an Amgen device used to administer the Amgen drug under study? <drug> No✓ Yes✓ | Outcome of Event<br>Resolved<br>Not resolved<br>Fatal<br>Unknown | Check only if event is related to study procedure<br>eg, biopsy |
|---|---|---|---|---|---|---|---|---|
| | | | | ☐ Yes ☐ No | | | | |
| | | | | ☐ Yes ☐ No | | | | |
| | | | | ☐ Yes ☐ No | | | | |

**Serious Criteria:** 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

**4. Was subject hospitalized or was a hospitalization prolonged due this event?** ☐No ☐Yes If yes, please complete all of Section 4

| Date Admitted<br>Day Month Year | Date Discharged<br>Day Month Year |
|---|---|
| | |

| Site Number | Subject ID Number |
|---|---|
| | |

**5. Was drug under study administered/taken prior to this event?** ☐No ☐Yes If yes, please complete all of Section 5

| Amgen Drug: | | Prior to, or at time of Event: Date of Initial Dose<br>Day Month Year | Date of Dose<br>Day Month Year | Dose | Route | Frequency | Action Taken with Product<br>01 Still being Administered<br>02 Permanently discontinued<br>03 Withheld | Lot # and Serial # |
|---|---|---|---|---|---|---|---|---|
| <<Drug >> | ☐Blinded ☐open label | | | | | | | Lot # ____<br>☐ Unknown<br>Serial # ____ |

*FORM-000346* *Version 1.0 Effective Date: 1 February 2016*

Page 1 of 3

| AMGEN<br>Study # 20150262<br>Carfilzomib | Electronic Adverse Event Contingency Report Form<br>For Restricted Use |
|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | ☐ Unavailable / Unknown |
| << Drug >> | ☐blinded ☐open label | | | | | | | Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown |

**6. CONCOMITANT MEDICATIONS (eg, chemotherapy)** Any Medications? ☐ No ☐ Yes If yes, please complete:

| Medication Name(s) | Start Date (Day Month Year) | Stop Date (Day Month Year) | Co-suspect No✓ | Co-suspect Yes✓ | Continuing No✓ | Continuing Yes✓ | Dose | Route | Freq. | Treatment Med No✓ | Treatment Med Yes✓ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |

**7. RELEVANT MEDICAL HISTORY** *(include dates, allergies and any relevant prior therapy)*

**8. RELEVANT LABORATORY VALUES** *(include baseline values)* Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

| Date (Day Month Year) | Test / Unit | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Test | | | | | | | | | | | |
| | Unit | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |

**9. OTHER RELEVANT TESTS** *(diagnostics and procedures)* Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

| Date (Day Month Year) | Additional Tests | Results | Units |
|---|---|---|---|
| | | | |
| | | | |

| Site Number | Subject ID Number |
|---|---|
| | |

**10. CASE DESCRIPTION** *(Provide narrative details of events listed in section 3)* Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

| AMGEN<br>Study # 20150262<br>Carfilzomib | Electronic Adverse Event Contingency Report Form<br>For Restricted Use |
|---|---|

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| | | |
| Signature of Investigator or Designee -<br>*I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.* | Title | Date |

## Appendix C. Additional Safety Reporting Information

Adverse Event Severity Scoring System

For oncology studies, the CTCAE is to be used. The CTCAE is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

## Appendix D. Pregnancy and Lactation Notification Worksheets

**AMGEN™ Pregnancy Notification Worksheet**

***Fax Completed Form to the Country-respective Safety Fax Line***

**1. Case Administrative Information**

**Protocol/Study Number:** _____

**Study Design:** ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

**2. Contact Information**

**Investigator Name** _____ **Site #** _____

**Phone** (____)_____ **Fax** (____)_____ **Email** _____

**Institution** _____

**Address** _____

**3. Subject Information**

**Subject ID #** _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm____/ dd____/ yyyy____

**4. Amgen Product Exposure**

| Amgen Product | Dose at time of conception | Frequency | Route | Start Date |
|---|---|---|---|---|
| | | | | mm____/dd____/yyyy____ |

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

**5. Pregnancy Information**

Pregnant female's LMP mm_____ / dd_____/ yyyy_____ ☐ Unknown

Estimated date of delivery mm_____ / dd_____/ yyyy_____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm_____ / dd_____/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

**Form Completed by:**

**Print Name:** _____ **Title:** _____

**Signature:** _____ **Date:** _____

Effective Date: March 27, 2011 Page 1 of 1

## AMGEN® Lactation Notification Worksheet

***Fax Completed Form to the Country-respective Safety Fax Line***
SELECT OR TYPE IN A FAX#

### 1. Case Administrative Information

**Protocol/Study Number:** _____

**Study Design:** ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

### 2. Contact Information

**Investigator Name** _____ **Site #** _____

**Phone (____)**_____ **Fax (____)**_____ **Email** _____

**Institution** _____

**Address** _____

### 3. Subject Information

**Subject ID #** _____ **Subject Date of Birth:** mm_____ / dd_____/ yyyy_____

### 4. Amgen Product Exposure

| Amgen Product | Dose at time of breast feeding | Frequency | Route | Start Date |
|---|---|---|---|---|
| | | | | mm____/dd____/yyyy____ |

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

### 5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

**Form Completed by:**

**Print Name:** _____ **Title:** _____

**Signature:** _____ **Date:** _____

Effective Date: 03 April 2012, version 2. Page 1 of 1

## Appendix E. IMWG Response Definitions

| International Myeloma Working Group Uniform Response Criteria | |
|---|---|
| **Response subcategory** | **Response Criteria[a]** |
| sCR | CR as defined below, plus normal FLC ratio and absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c] |
| CR | Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow[b] |
| VGPR | Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24 h |
| PR | ≥ 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥ 90% or to < 200 mg per 24 h<br>If the serum and urine M-protein are unmeasurable, [d]a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria<br>If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%<br>In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required |
| SD (not recommended for us as an indicator of response; stability of disease is best described by providing the time to progression estimates) | Not meeting criteria for CR, VGPR, PR or PD |

CR = complete response; FLC = free light chain; PD = progressive disease; PR = partial response; SD = stable disease; sCR = stringent complete response; VGPR = very good partial response

[a] All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

[b] Confirmation of with repeat bone marrow biopsy not needed.

[c] Presence/absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ 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 κ/λ of > 4:1 or < 1:2.

[d] Measurable disease defined by at least 1 of the following three measurements:
Serum M-protein X 1 g/dl (X 10 g/l)[10 g/l]
Urine M-protein X 200 mg/24 h
Serum FLC assay: Involved FLC level X10 mg/dl (X100 mg/l) provided serum FLC ratio is abnormal.

## Appendix F. Schedule of Assessments

| | | Observational Period | | |
|---|---|---|---|---|
| Data to be collected | Baseline[a] | **During Treatment**[b] | EOT | EOS[c] |
| **Site characteristics** | **X** | - | - | - |
| **Subject log for nonparticipants** | **X** | - | - | - |
| Demographics | X | - | - | - |
| Medical history | X | - | - | - |
| **MM history and disease** | **X** | - | - | - |
| **Physical measurements** | **X** | - | - | - |
| **Vitals (BP)** | **X** | - | - | - |
| **Echocardiogram** | **X** | **X** | - | - |
| **ECG** | **X** | - | - | - |
| **ECOG performance status (at MM diagnosis)** | **X** | - | - | - |
| **ECOG performance status** | **X** | - | - | - |
| **MRI (at diagnosis)** | **X** | - | - | - |
| **MRI** | **X** | - | - | - |
| **PET-CT, CT, X-ray (at MM diagnosis)** | **X** | - | - | - |
| **PET-CT, CT, X-ray** | **X** | - | - | - |
| **Chemistry (at MM diagnosis)** | **X** | - | - | - |
| **Chemistry** | **X** | - | - | - |
| **Haematology (at MM diagnosis)** | **X** | - | - | - |
| **Haematology** | **X** | - | - | - |
| **Bone marrow aspirate (at MM diagnosis)** | **X** | - | - | - |
| **Bone marrow aspirate** | **X** | - | - | - |
| **FISH/cytogenetics (at MM diagnosis)** | **X** | - | - | - |
| **Serum electrophoresis (at MM diagnosis)** | **X** | - | - | - |
| **Serum electrophoresis** | **X** | - | - | - |
| **Urine electrophoresis (at MM diagnosis)** | **X** | - | - | - |
| **Urine electrophoresis** | **X** | - | - | - |
| **Serum free light chains (at MM diagnosis)** | **X** | - | - | - |
| **Serum free light chains** | **X** | - | - | - |
| **Prior MM therapy** | **X** | - | - | - |

**Page 1 of 2**

**Footnotes are on the last page of table.**

| | | Observational Period | | |
|---|---|---|---|---|
| **Data to be collected** | **Baseline[a]** | **During Treatment[b]** | **EOT** | **EOS[c]** |
| **Prior radiotherapy** | **X** | **-** | **-** | **-** |
| **Planned regimen (at baseline)** | **X** | **-** | **-** | **-** |
| **Radiotherapy for current malignancy** | **-** | X | **-** | **-** |
| **Myeloma response assessment** | **-** | X | **-** | **-** |
| **Myeloma response assessment (EOT)** | **-** | **-** | **X** | **-** |
| **Myeloma assessment** | **-** | X | X | **-** |
| **E**vents | **-** | X | **-** | X |
| Hospitalizations | **-** | X | **-** | X |
| Concomitant medication**s** | **-** | X | **-** | X |
| **Carfilzomib administration** | **-** | **X** | **-** | **-** |
| **Dexamethasone administration** | **-** | **X** | **-** | **-** |
| **Lenalidomide administration** | **-** | **X** | **-** | **-** |
| **Last carfilzomib dose** | **-** | **X** | **-** | **-** |
| **Last lenalidomide dose** | **-** | **X** | **-** | **-** |
| **Last dexamethasone dose** | **-** | **X** | **-** | **-** |
| **EOS** | **-** | **-** | **-** | **X** |
| Planned **MM** subsequent treatment**s** | **-** | **-** | **-** | X |
| **P**atient support program | **-** | **-** | **-** | X |
| Cardi**ac** assessment**s** | **-** | X | **-** | X |

**Page 2 of 2**

**BP = blood pressure; CT = computed tomography; ECG = electrocardiogram;** ECOG = Eastern Cooperative Oncology Group; EOS = end of study; EOT = end of treatment; **FISH = fluorescent in situ hybridization;** MM = multiple myeloma**; MRI = magnetic resonance imaging; PET = positron emission tomography-computed tomography**

[a] Baseline period – initial MM diagnosis date until day 0 of cycle 1 of carfilzomib treatment.

[b] **During treatment** – for the time period between starting carfilzomib treatment and enrolling into the study, the initial set of follow-up data will be collected retrospectively as collection of baseline information. Thereafter, follow-up data will be collected every **3** months.

[c] EOS – **data will be documented in the eCRF up to** 30 days after the final dose of carfilzomib (unless preceded by 18 months of follow-up, subject death, loss to follow**-**up, withdrawal of consent, or 31 March 2020).

## Appendix G. Eastern Cooperative Oncology Group Performance Status Scale

| Grade | Description |
|---|---|
| 0 | Fully active, able to carry on all predisease performance without restriction. |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, ie, light housework or office work. |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours. |
| 3 | Capable of only limited self-care, confined to a bed or chair > 50% of waking hours. |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead |

**Amendment 3**

**Protocol Title: Real-world Evidence of the Use of Carfilzomib Among Patients With Relapsed Multiple Myeloma in Europe**

Amgen Protocol Number 20150262

Amendment Date: 12 March 2018

**Rationale:**

This is Amendment 3 for carfilzomib Study 20150262. The primary change to the protocol is to remove the relapse inclusion criteria to allow all on-label multiple myeloma subjects to be eligible for the study, not just those who have relapsed.

Additional changes to the protocol are to:

- Remove the 1-year enrollment duration limit for the sites and the language around site specific caps for subject enrollment
- Clarify that subjects who are receiving carfilzomib treatment within a compassionate use program will not be eligible for the study
- Clarify when specific outcome measures will be collected
- Remove electrocardiogram (ECG) changes and left ventricular ejection fraction (LVEF) decrease as recorded in test performed per routine practice as part of the safety profile of carfilzomib
- Clarify that blood pressure and heart rate will be collected as part of the cardiovascular assessments conducted
- Update the counries involved in the study
- Update the schedule of assessments to provide clarity on the data to be collected from the sites

**Description of Changes**

**Section:** Global

**Change:** Updated protocol date from 24 May 2017 to **12 March 2018**.

**Section:** Global

**Chage:** Updated the protocol title from "Real-world Evidence of the Use of Carfilzomib Among Patients With Relapsed Multiple Myeloma in Europe" to "Real-world Evidence of the Use of Carfilzomib Among Multiple Myeloma **Patients** in Europe **Who Have Received at Least One Prior Therapy**".

**Section:** Global

**Change:** Editorial changes (including typographical, grammatical, and formatting) have been made throughout the document.

**Section:** Title Page

**Replace:**

| | |
|---|---|
| Protocol version identifier | 20150262 |
| Date of last version of the protocol | 10 November 2016 |
| Countries/Regions of Study | Austria, Belgium, Central and Eastern Europe (CEE) region, France, Greece, Israel, Italy, the Netherlands, the Nordics & Baltics region, Portugal, and Switzerland (provided that reimbursement granted at local level) |
| Author | PPD [redacted] |

**With:**

| | |
|---|---|
| Protocol version identifier | **Amendment 3** |
| Date of last version of the protocol | **24 May 2017** |
| Countries/Regions of Study | Austria, Belgium, Central and Eastern Europe (CEE) region, France, Greece, Israel, Italy, the Netherlands, the Nordics & Baltics region, Portugal, and **the United Kingdom** (provided that reimbursement granted at local level) |
| Author | PPD [redacted] |

**Section:** Title Page

**Add:**

| | |
|---|---|
| **NCT Number** | **NCT03091127** |

**Section:** Title Page, Marketing Authorisation Holder

**Replace:**

| | |
|---|---|
| MAH Contact | PPD<br>1 Uxbridge Business Park<br>Sanderson Road<br>Uxbridge, UB8 1DH<br>United Kingdom<br>PPD |

**With:**

| | |
|---|---|
| MAH Contact | PPD<br>1 Uxbridge Business Park<br>Sanderson Road<br>Uxbridge, UB8 1DH<br>United Kingdom<br>PPD |

**Section:** Title Page

**Replace:**

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: Austria (CEE Headquarters), +43 1 531 40 – 0; Belgium, +32 2 775 27 11; France, +33 1 70289000; Greece, +30 210 344 7000; Italy, +39 02 624 112 1; Netherlands, +31 76 5 732500; Norway, +47 23 30 80 00; Portugal, +351 21 422 05 50; Sweden, +46 8 695 11 00; Switzerland, +41 41 3690 300. Amgen's general number in the United States (1 805 447 1000).

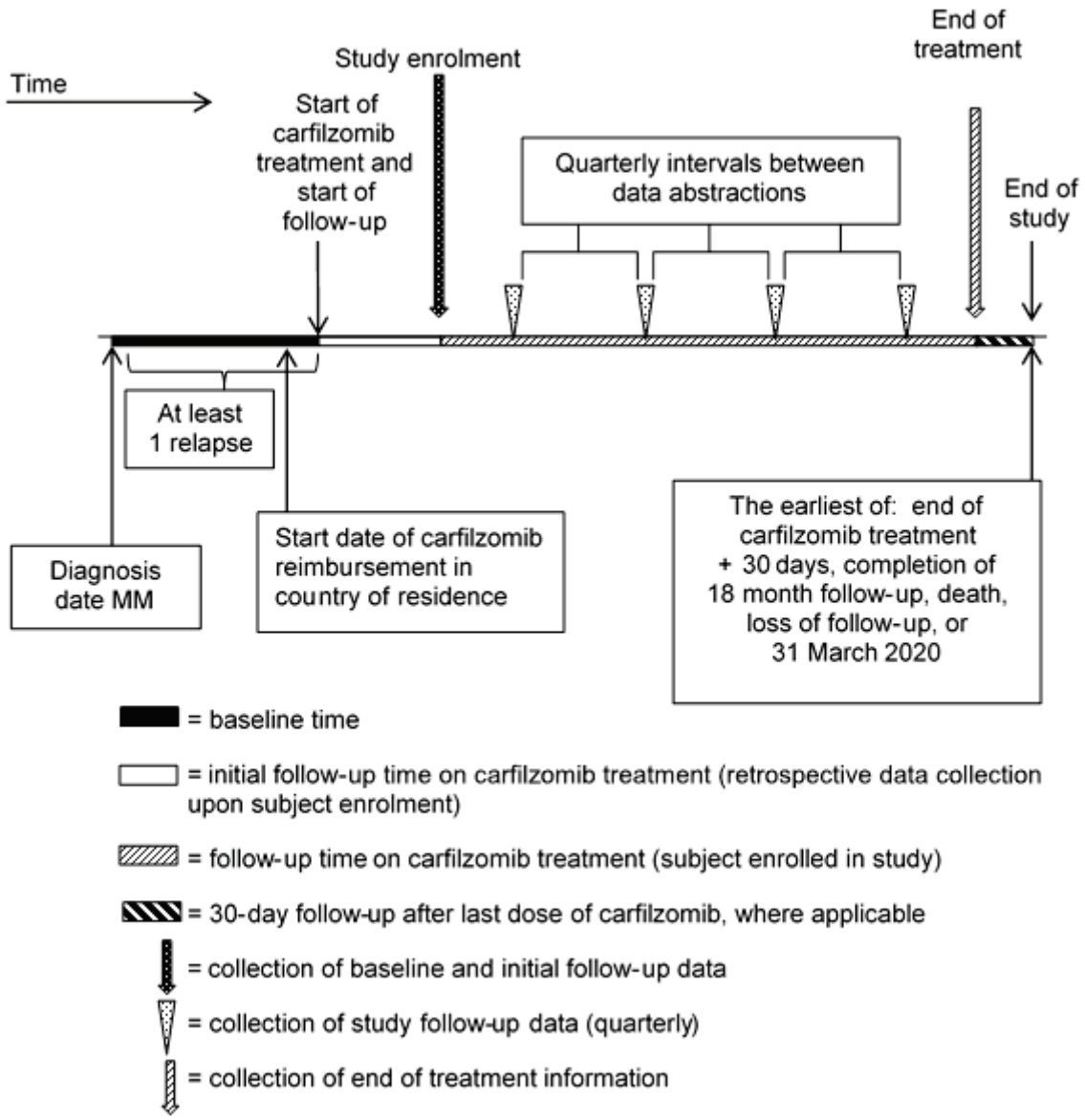
**With:**

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: Austria (CEE Headquarters), +43 1 531 40 – 0; Belgium, +32 2 775 27 11; **Czech Republic, +420 221 773 500;**

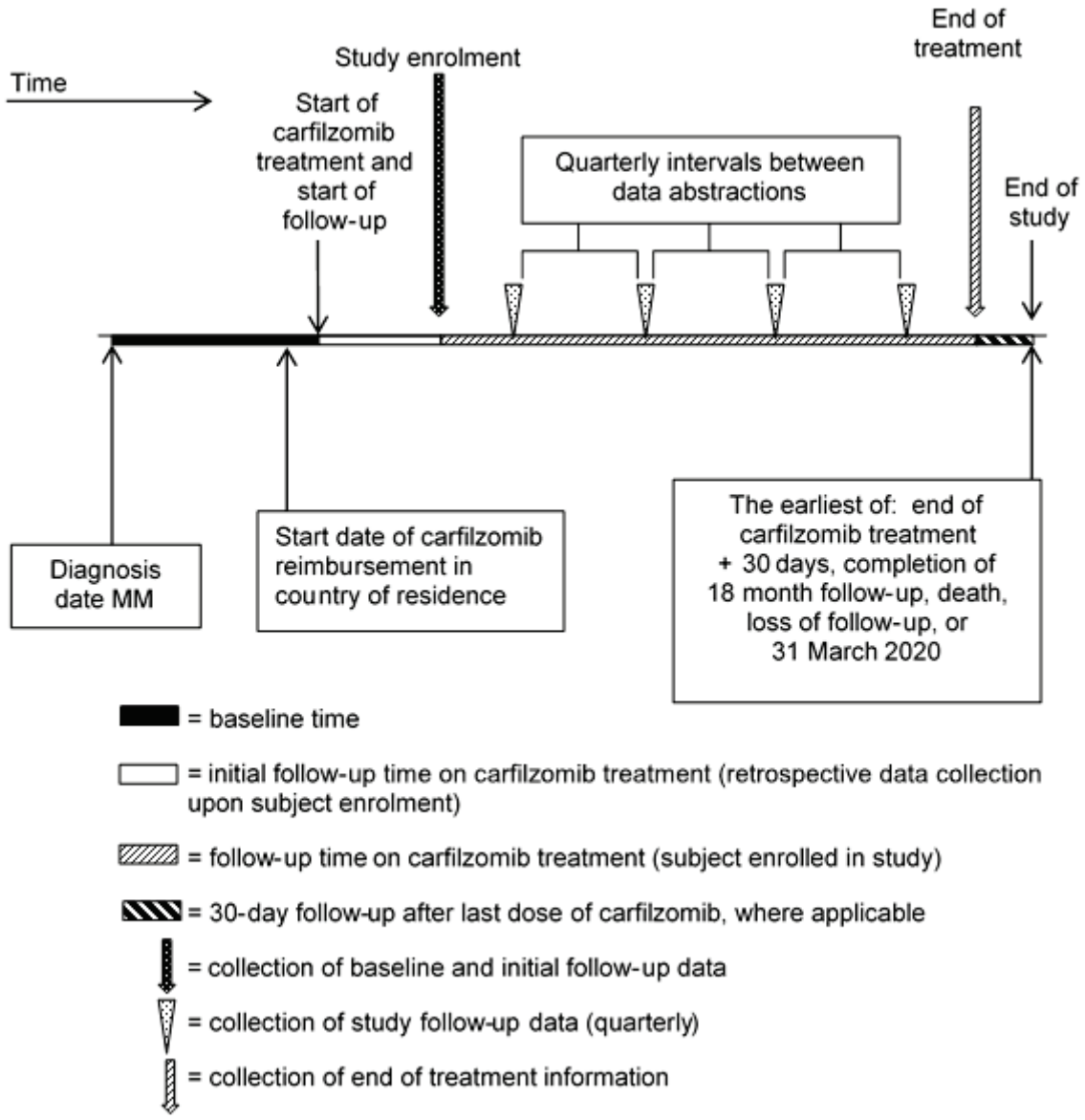
France, +33 1 70289000; Greece, +30 210 344 7000; Italy, +39 02 624 112 1; Netherlands, +31 76 5 732500; Norway, +47 23 30 80 00; Portugal, +351 21 422 05 50; **Romania, +40 21 527 3000; United Kingdom +44 12 2342 0305**. Amgen's general number in the United States (1-805-447-1000).

**Section:** Study Design Schema

**Replace:**



**With:**




**Section:** 2 List of Abbreviations/Definitions

**Add:**

| Abbreviation | Definition |
|---|---|
| **CT** | **computed tomography** |

## Section: 2 List of Abbreviations/Definitions

**Replace:**

| | |
|---|---|
| Follow-up period | The period from day 1 of cycle 1 of carfilzomib treatment 30 days after the final carfilzomib administration (EOS) or until 18 months after initiation of carfilzomib treatment, death, withdrawal of consent, 31 March 2020, or loss to follow-up (whichever occurs earliest). |

**With:**

| | |
|---|---|
| Follow-up period | The period from day 1 of cycle 1 of carfilzomib **regimen until** 30 days after the final carfilzomib administration (EOS) or until 18 months after initiation of carfilzomib treatment, death, withdrawal of consent, 31 March 2020, or loss to follow-up (whichever occurs earliest). |

## Section: 3 Responsible Parties

**Replace:**

PPD

Senior Manager, Center for Observational Research

Amgen Limited, 1 Uxbridge Business Park

Sanderson Road, Uxbridge, UB8 1DH, UK

PPD

PPD

Head, Global Clinical Program Management – Observational Research

Amgen Inc.

1 Amgen Center Drive

Thousand Oaks, CA 91320, US

PPD

Details on principal investigator and coordinating investigator for each country in which the study is to be performed are available upon request.

**With:**

| | |
|---|---|
| **Sponsor** | **Amgen Limited**<br>**1 Uxbridge Business Park**<br>**Sanderson Rd**<br>**Uxbridge UB8 1DH** |

Details on principal investigator and coordinating investigator for each country in which the study is to be performed are available upon request.

**Section:** 4 Abstract, Study Population

**Replace:**

Subjects with MM who received at least 1 prior line of treatment and are treated with carfilzomib per routine practice in a European country where reimbursement for carfilzomib is in place (anticipated participation in study: 9 countries [Austria, Belgium, France, Greece, Israel, Italy, the Netherlands, Portugal, and Switzerland] and 2 regions [Central and Eastern Europe (CEE); Nordics & Baltics]) between 2016 and 2020.

**With:**

Subjects with MM who received at least 1 prior line of treatment and are treated with carfilzomib per routine practice in a European country where reimbursement for carfilzomib is in place (anticipated participation in study: 9 countries [Austria, Belgium, France, Greece, Israel, Italy, the Netherlands, Portugal, and **the United Kingdom**] and 2 regions [Central and Eastern Europe (CEE); Nordics & Baltics]) between 2016 and 2020.

**Section:** 4 Abstract, Secondary Objectives

**Add:**

- Describe a cardiovascular assessment at carfilzomib **regimen** initiation **and at occurrence of cardiac adverse events,** where available per routine care (electrocardiogram [ECG], echocardiography, left ventricular ejection fraction [LVEF]).

**Section:** 4 Abstract, Study Population

**Replace:**

Subjects with MM who received at least 1 prior line of treatment and are treated with carfilzomib per routine practice in a European country where reimbursement for carfilzomib is in place (anticipated participation in study: 9 countries [Austria, Belgium, France, Greece, Israel, Italy, the Netherlands, Portugal, and Switzerland] and 2 regions [Central and Eastern Europe (CEE); Nordics & Baltics]) between 2016 and 2020.

**With:**

Subjects with MM who received at least 1 prior line of treatment and are treated with carfilzomib per routine practice in a European country where reimbursement for carfilzomib is in place (anticipated participation in study: 9 countries [Austria, Belgium, France, Greece, Israel, Italy, the Netherlands, Portugal, and **the United Kingdom**] and

2 regions [Central and Eastern Europe (CEE); Nordics & Baltics]) between 2016 and 2020.

**Section:** 4 Abstract, Study Population

**Add:**

**However, the final list of countries will depend on reimbursement and feasibility.**

**Section:** 4 Abstract, Summary of Subject Eligibility Criteria, sub-bullet 2

**Delete:**

- ~~experienced a relapse (eligible regardless of the type of relapse experienced; molecular, hematologic, or symptomatic)~~

**Section:** 4 Abstract, Summary of Subject Eligibility Criteria, sub-bullet 7

**Add:**

- subjects who are enrolled in a carfilzomib clinical trial will not be eligible to take part in this observational study**.**
- **Subjects who are receiving carfilzomib treatment within a compassionate use program will not be eligible to take part in this observational study.**

**Section:** 4 Abstract, Follow-up

**Replace:**

The follow-up period for a subject is defined as the period from day 1 of cycle 1 of carfilzomib treatment until 30 days after the final carfilzomib dose (end of study, EOS) or until 18 months after initiation of carfilzomib treatment, death, withdrawal of consent, 31 March 2020, or loss to follow-up (whichever occurs earliest).

**With:**

The follow-up period for a subject is defined as the period from day 1 of cycle 1 of carfilzomib **regimen** until 30 days after the final carfilzomib dose (end of study, EOS) or until 18 months after initiation of carfilzomib treatment, death, withdrawal of consent, 31 March 2020, or loss to follow-up (whichever occurs earliest).

**Section:** 4 Abstract, Variables, Outcome Variables, sub-bullet 5

**Replace:**

- baseline demographic characteristics (age at baseline, age at MM initial diagnosis, sex, height, weight, body surface area [BSA])

**With:**

- baseline demographic characteristics (age at MM initial diagnosis, **and age,** sex, height, weight, body surface area [BSA] **at carfilzomib regimen initiation**)

**Section:** 4 Abstract, Variables, Outcome Variables, sub-bullet 10

**Delete:**

- ~~for subjects who relapsed: type of relapse (molecular, hematologic, or symptomatic)~~

**Section:** 4 Abstract, Variables, Outcome Variables, sub-bullet 11

**Replace:**

- Eastern Cooperative Oncology Group (ECOG) performance status (Appendix G) category at MM diagnosis and during follow-up

**With:**

- Eastern Cooperative Oncology Group (ECOG) performance status (Appendix G) category at MM diagnosis and **carfilzomib regimen initiation**

**Section:** 4 Abstract, Variables, Outcome Variables, sub-bullets 14 and 15

**Add:**

- **specific** concomitant therapy that is not part of the carfilzomib regimen
- cardiovascular assessment as conducted per routine practice at carfilzomib **regimen** initiation **and at occurrence of cardiac adverse events**

**Section:** 4 Abstract, Sample Size

**Replace:**

A sample size of approximately 1000 subjects was selected for this observational study to permit individual countries (or regions, where applicable) to enrol between 100 and 200 subjects.

**With:**

A sample size of approximately **8**00 subjects **has been** selected for this observational study to permit individual countries (or regions, where applicable) to enrol between 100 and 200 subjects.

**Section:** 5 Amendments and Updates

**Add:**

| Amendment or Update No. | Date | Section of Study Protocol | Amendment or Update | Reason |
|---|---|---|---|---|
| 1 | 10 November 2016 | See summary of changes | | |
| 2 | 24 May 2017 | See summary of changes | | |
| **3** | **12 March 2018** | **See summary of changes** | | |

**Section:** 8.2 Secondary, Bullet 7

**Add:**

- Describe a cardiovascular assessment at carfilzomib **regimen** initiation **and at occurrence of cardiac adverse events,** where available per routine care (electrocardiogram [ECG], echocardiography, left ventricular ejection fraction [LVEF]).

**Section:** 9.1 Study Design, Paragraph 1

**Replace:**

This is a noninterventional observational study of a single arm cohort of adult subjects with relapsed MM receiving carfilzomib in routine clinical practice.

**With:**

This is a noninterventional observational study of a single arm cohort of adult subjects with MM **who have received at least 1 prior therapy** receiving carfilzomib in routine clinical practice.

**Section:** 9.1 Study Design, Paragraph 1

**Add:**

Each subject will have baseline data collected and all details on their MM treatment from their first dose of carfilzomib **regimen** until 30 days after their final carfilzomib administration (end of study [EOS]) or until 18 months after carfilzomib treatment initiation (whichever occurs earlier).

**Section:** 9.2.1 Study Period

**Delete:**

~~Upon site initiation, each site has a one year enrolment window, with each enrolled subject being followed for a maximum of 18 months. Therefore, the maximum study~~

~~duration at the site level will be 30 months.~~ For countries in which carfilzomib is already reimbursed on the initial approval date of this study protocol, the study period is anticipated to start in the first quarter of 2017~~; in these first wave countries it is thus anticipated that the last subject last visit (LSLV) will occur no later than quarter (Q)3 of 2019~~. Should enrolment be slower than expected within a country, it may be necessary to add additional sites within a country, or if that is not possible, to extend the enrolment window ~~at some (or all) sites of that country in order to meet the minimum required sample size~~.

**Section:** 9.2.2 Selection and Number of Sites

**Delete:**

~~The total number of sites within each country will range depending on the number of subjects to be enrolled within each country, assuming between 5 to 15 subjects will be enrolled at each site. To ensure that the total subject quota for the study is not filled by countries in which reimbursement for carfilzomib is obtained early, a site-specific cap will be applied to define the maximum number of subjects that can be enrolled at each site. Should a site in one country (or region) have difficulty enrolling, the subject cap at other sites may be lifted, provided that the number of subjects of one type of site (eg, academic) will not be overrepresented in the overall patient population enrolled in the study for that country (or region).~~

**Section:** 9.2.3.1 Inclusion Criteria, Bullet 2

**Delete:**

- ~~experienced a relapse (regardless of the type of relapse experienced; molecular, hematologic, or symptomatic)~~

**Section:** 9.2.3.1 Inclusion Criteria, Paragraph 2

**Replace:**

Subjects who previously received treatment with carfilzomib, either through participation in a clinical trial, or through routine practice, are eligible to take part in the study.

**With:**

Subjects who previously **completed** treatment with carfilzomib in a clinical trial, **a compassionate use program,** or through routine practice, are eligible to take part in the study.

**Section:** 9.2.3.1 Inclusion Criteria, Paragraph 5

**Subjects who are also enrolled in other observational studies in which standard of care is not altered are eligible to take part in the study.**

**Section:** 9.2.3.2 Exclusion Criteria

**Add:**

**Subjects who are receiving carfilzomib treatment within a compassionate use program will not be eligible to take part in this observational study.**

**Section:** 9.2.5 Study Follow-up

**Replace:**

The follow-up period for a subject is defined as the period from day 1 of cycle 1 of carfilzomib treatment until 30 days after the final dose of carfilzomib (EOS) or until 18 months after initiation of carfilzomib treatment, death, withdrawal of consent, 31 March 2020, or loss to follow-up (whichever occurs earliest).

**With:**

The follow-up period for a subject is defined as the period from day 1 of cycle 1 of carfilzomib **regimen** until 30 days after the final dose of carfilzomib (EOS) or until 18 months after initiation of carfilzomib treatment, death, withdrawal of consent, 31 March 2020, or loss to follow-up (whichever occurs earliest).

**Section:** 9.3.2 Outcome Assessment, primary outcome measures, Bullet 1 Sub-bullet 9

**Delete:**

- ~~carfilzomib dosing per label (ie, allowing for dose reductions for adverse events)~~

**Section:** 9.3.2 Outcome Assessment, secondary outcome measures, Bullets 1 and 2

**Replace:**

- Baseline demographic characteristics (age at baseline, age at MM initial diagnosis, sex, height, weight, body surface area [BSA])
- Baseline MM disease characteristics:
  - type of monoclonal protein (heavy [A, G, E, M] and light chain [kappa, lambda])
  - presence of CRAB features (yes/no)
  - International Staging System (ISS) and revised ISS stage at diagnosis (I, II, III, or unknown)

- ECOG performance status category at MM diagnosis (0, 1, 2, 3, 4, or unknown; Appendix G)
- cytogenetic analysis performed (yes/no)
- cytogenetic risk at diagnosis (high risk/unfavourable, intermediate, normal/favourable, unknown, no cytogenetic analysis performed)
- cytogenetic profile (del(17p), t(4:14), t(14;16) or other)
- number of lines of prior treatment (1, 2, 3, 4, or more)
- timing of relapse after first-line treatment (relapse less than 1 year versus 1 year or more after front-line therapy discontinuation)
- magnetic resonance imaging (MRI) performed at diagnosis (yes/no)
- abnormal MRI results (yes, no, unknown)
- positron emission tomography–computed tomography (PET-CT) performed at diagnosis (yes/no)
- abnormal PET-CT results (yes, no, unknown)
- presence of comorbidities, diagnosed at any point in time before baseline
- baseline measurement of serum M-component (in g/100 ml), urine M-component (in mg per 24h), percent of bone marrow plasma cells, serum creatinine, creatinine clearance (mL/min), serum albumin and serum beta-2-microglobulin (mg/L), based on the diagnostic test performed closest before initiation of carfilzomib treatment
- baseline measurement of lactate dehydrogenase (LDH)

**With:**

- Baseline demographic characteristics (age at MM initial diagnosis, **and age,** sex, height, weight, body surface area [BSA] **at carfilzomib regimen initiation**)
- Baseline MM disease characteristics:
  - type of monoclonal protein (heavy and light chain)
  - presence of CRAB features **at MM diagnosis**
  - International Staging System (ISS) and revised ISS stage at diagnosis (I, II, III, or unknown) **and carfilzomib regimen initiation**
  - ECOG performance status category at MM diagnosis **and carfilzomib regimen initiation** (0, 1, 2, 3, 4, or unknown; Appendix G)
  - cytogenetic analysis performed (yes/no)
  - cytogenetic risk at diagnosis (high risk/unfavourable, intermediate, normal/favourable, unknown, no cytogenetic analysis performed)
  - cytogenetic profile
  - number of lines of prior treatment (1, 2, 3, 4, or more)
  - timing of relapse after first-line treatment (relapse less than 1 year versus 1 year or more after front-line therapy discontinuation)
  - magnetic resonance imaging (MRI)**, positron emission tomography-computed tomography (PET-CT), computed tomography (CT), and X-ray** performed at **MM** diagnosis **and carfilzomib regimen initiation** (yes/no)

- **myeloma/osteolytic lesions detected by** MRI**, PET-CT, CT, and X-ray at MM diagnosis and carfilzomib regimen initiation**
- presence of comorbidities, diagnosed at any point in time before **carfilzomb regimen initiation**
- measurement of serum M-component (in g/100 ml), urine M-component (in mg per 24h), percent of bone marrow plasma cells, serum creatinine, creatinine clearance (mL/min), serum albumin and serum beta-2-microglobulin (mg/L), **at MM diagnosis and carfilzomib regimen initiation**
- baseline measurement of lactate dehydrogenase (LDH) **at MM diagnosis and carfilzomib regimen initiation**

**Section:** 9.3.2 Outcome Assessment, secondary outcome measures, Bullet 4, sub-bullet 3

**Delete:**

- ~~ECG changes as recorded in tests performed per routine practice~~

**Section:** 9.3.2 Outcome Assessment, secondary outcome measures, Bullet 7

**Replace:**

- ECOG performance status (Appendix G) category at MM diagnosis and during follow-up

**With:**

- ECOG performance status (Appendix G) category at MM diagnosis and **carfilzomib regimen initiation**

**Section:** 9.3.2 Outcome Assessment, secondary outcome measures, Bullet 10

**Replace:**

- Concomitant therapy that is not part of the carfilzomib regimen (thromboprophylaxis/ anticoagulants, antihypertensive and heart failure treatment, antiviral treatment, antibiotic treatment, bone targeting agents, hematopoietic growth factors, pain control)

**With:**

- **Specific c**oncomitant therapy that is not part of the carfilzomib regimen (thromboprophylaxis/ anticoagulants, antihypertensive and heart failure treatment, antiviral treatment, antibiotic treatment, bone targeting agents, hematopoietic growth factors, pain control)

**Section:** 9.3.2 Outcome Assessment, secondary outcome measures, Bullet 11

**Add:**

- Cardiovascular assessment as conducted per routine practice at carfilzomib **regimen** initiation **and occurrence of cardiac adverse events**:
  - ECG category (normal, prolonged QT, abnormal clinically significant, abnormal not clinically significant)
  - echocardiography performed (yes, no, unknown)
  - LVEF (%)
  - **blood pressure**
  - **heart rate**

**Section:** 9.4 Data Sources, Paragraphs 3 and 4

**Replace:**

II. Follow-up data – for the time period between starting carfilzomib treatment and enrolling into the study, the initial set of follow-up data will be collected retrospectively at the same time as collection of baseline information. Thereafter, follow-up data will be collected every three months.

III. End of study – collected 30 days after the final carfilzomib administration (unless preceded by 18 months of follow-up, subject death, loss to follow up, withdrawal of consent, or 31 March 2020).

**With:**

II. **During treatment** – for the time period between starting carfilzomib treatment and enrolling into the study, the initial set of follow-up data will be collected retrospectively as collection of baseline information. Thereafter, follow-up data will be collected every **3** months.

III. End of study – **data will be documented in the eCRF up to** 30 days after the final carfilzomib administration (unless preceded by 18 months of follow-up, subject death, loss to follow up, withdrawal of consent, or 31 March 2020).

**Section:** 9.5 Study Size, Paragraph 1

**Delete:**

The primary objective of this study is to describe utilisation of carfilzomib in routine clinical practice for subjects with ~~relapsed~~ MM who have received at least 1 prior line of treatment.

**Section:** 9.5 Study Size, Paragraph 1

**Replace:**

A total of 9 countries and 2 regions are anticipated to take part in the study, provided that reimbursement for the use of carfilzomib is obtained on a local level. Specifically, we plan to conduct the study in Austria, Belgium, France, Greece, Israel, Italy, the Netherlands, Portugal, and Switzerland as well as the Central and Eastern Europe (CEE) and Nordics & Baltics regions, given that these countries have either a requirement (Portugal, Bulgaria, and France) or a strong need to provide real-world evidence of how carfilzomib is used within a limited time period after obtaining reimbursement.

**With:**

A total of 9 countries and 2 regions are anticipated to take part in the study, provided that reimbursement for the use of carfilzomib is obtained on a local level. Specifically, we plan to conduct the study in Austria, Belgium, France, Greece, Israel, Italy, the Netherlands, Portugal, and **the United Kingdom** as well as the Central and Eastern Europe (CEE) and Nordics & Baltics regions, given that these countries have either a requirement (Portugal, Bulgaria, and France) or a strong need to provide real-world evidence of how carfilzomib is used within a limited time period after obtaining reimbursement.

**Section:** 9.5 Study Size, Paragraph 1

**Add:**

**However, the final list of countries will depend on reimbursement and feasibility.**

**Section:** 9.5 Study Size, Paragraph 2

**Replace:**

A sample size of approximately 1000 subjects was selected for this observational study to permit individual countries (or regions, where applicable) to enrol between 100 and 200 subjects.

**With:**

A sample size of approximately **8**00 subjects **has been** selected for this observational study to permit individual countries (or regions, where applicable) to enrol between 100 and 200 subjects.

**Section:** 9.7.2.5.1 Subgroup Analysis

**Add:**

Where relevant and appropriate, analyses will be presented by subgroups of interest including **but not limited to**:

**Section:** 9.9.1.1 Measurement Error(s)/Misclassification(s), Paragraph 1

**Delete:**

~~To mitigate this risk, this study also collects data to facilitate calculation of response to treatment ourselves, by using consistent methodology across all study sites and countries.~~

**Section:** 9.9.1.2 Information Bias

**Delete:**

~~Additionally, there may be missing information on adverse events as underreporting of less serious adverse events in the medical record may occur.~~

**Section:** 11 Collection of Safety Information and Product Complaints

**Replace:**

All grade 3 or above adverse events (adverse drug reactions, serious adverse drug reactions, product complaints, and other safety findings [eg, pregnancy, lactation]) in routine clinical practice will be documented in accordance with Amgen requirement documents (eg, SOPs).

**With:**

All grade 3 or above **safety** events (adverse drug reactions, serious adverse drug reactions, product complaints, and other safety findings [eg, pregnancy, lactation]) in routine clinical practice will be documented in accordance with Amgen requirement documents (eg, SOPs).

**Section:** 11.2 Safety Reporting Requirements, Paragraph 2

**Add:**

The investigator is responsible for ensuring that **all grade 3 or above** safety events (adverse events, product complaints, and other safety findings) observed by the investigator or reported by the subject that occur after initiation of carfilzomib through the final study contact are recorded in the subject's appropriate study documentation.

**Section:** 11.2 Safety Reporting Requirements, Paragraph 2

**Replace:**

Thus, this study will only collect grade 3 or higher adverse events.

**With:**

Thus, this study will only collect grade 3 or higher **safety** events.

**Section:** Appendix F Schedule of Assessments

**Replace:**

| | | Observational Period | | |
|---|---|---|---|---|
| Data to be collected | Baseline[a] | 3 monthly follow-up data[b] | EOT | EOS[c] |
| Demographics | X | | | |
| Medical history | X | | | |
| Treatment history | X | | | |
| Disease characteristics | X | X | | |
| Disease treatment | | X | | X |
| Concomitant medication | X | X | | X |
| Adverse events | | X | | X |
| Cardiovascular assessment | X | X | | X |
| Frailty score assessment | X | | X | |
| ECOG | X | X | | |
| Response to carfilzomib treatment | | X | X | |
| Relapse status and type | X[d] | | X[e] | |
| Hospitalizations | | X | | X |
| Enrolment in a patient support programme | | | | X |
| Planned subsequent treatment regimen | | | | X |

ECOG = Eastern Cooperative Oncology Group; EOS = end of study; EOT = end of treatment; MM = multiple myeloma

[a] Baseline period – initial MM diagnosis date until day 0 of cycle 1 of carfilzomib treatment.

[b] Follow-up data – for the time period between starting carfilzomib treatment and enrolling into the study, the initial set of follow-up data will be collected retrospectively at the same time as collection of baseline information. Thereafter, follow-up data will be collected every three months.

[c] EOS – collected 30 days after the final dose of carfilzomib (unless preceded by 18 months of follow-up, subject death, loss to follow up, withdrawal of consent, or 31 March 2020).

[d] At baseline, relapse status and type are captured in relation to receipt of prior therapies.

[e] At EOT, relapse status and type are captured in relation to carfilzomib treatment.

**With:**

| | | Observational Period | | |
|---|---|---|---|---|
| Data to be collected | Baseline[a] | **During Treatment**[b] | EOT | EOS[c] |
| **Site characteristics** | **X** | - | - | - |
| **Subject log for nonparticipants** | **X** | - | - | - |
| Demographics | X | - | - | - |
| Medical history | X | - | - | - |
| **MM history and disease** | **X** | - | - | - |
| **Physical measurements** | **X** | - | - | - |
| **Vitals (BP)** | **X** | - | - | - |
| **Echocardiogram** | **X** | **X** | - | - |
| **ECG** | **X** | - | - | - |
| **ECOG performance status (at MM diagnosis)** | **X** | - | - | - |
| **ECOG performance status** | **X** | - | - | - |
| **MRI (at diagnosis)** | **X** | - | - | - |
| **MRI** | **X** | - | - | - |
| **PET-CT, CT, X-ray (at MM diagnosis)** | **X** | - | - | - |
| **PET-CT, CT, X-ray** | **X** | - | - | - |
| **Chemistry (at MM diagnosis)** | **X** | - | - | - |
| **Chemistry** | **X** | - | - | - |
| **Haematology (at MM diagnosis)** | **X** | - | - | - |
| **Haematology** | **X** | - | - | - |
| **Bone marrow aspirate (at MM diagnosis)** | **X** | - | - | - |
| **Bone marrow aspirate** | **X** | - | - | - |
| **FISH/cytogenetics (at MM diagnosis)** | **X** | - | - | - |
| **Serum electrophoresis (at MM diagnosis)** | **X** | - | - | - |
| **Serum electrophoresis** | **X** | - | - | - |
| **Urine electrophoresis (at MM diagnosis)** | **X** | - | - | - |
| **Urine electrophoresis** | **X** | - | - | - |
| **Serum free light chains (at MM diagnosis)** | **X** | - | - | - |
| **Serum free light chains** | **X** | - | - | - |
| **Prior MM therapy** | **X** | - | - | - |

**Page 1 of 2**

**Footnotes are on the last page of table.**

| | | Observational Period | | |
|---|---|---|---|---|
| **Data to be collected** | **Baseline[a]** | **During Treatment[b]** | **EOT** | **EOS[c]** |
| **Prior radiotherapy** | **X** | - | - | - |
| **Planned regimen (at baseline)** | **X** | - | - | - |
| **Radiotherapy for current malignancy** | - | X | - | - |
| **Myeloma response assessment** | - | X | - | - |
| **Myeloma response assessment (EOT)** | - | - | **X** | - |
| **Myeloma assessment** | - | X | X | - |
| **E**vents | - | X | - | X |
| Hospitalizations | - | X | - | X |
| Concomitant medication**s** | - | X | - | X |
| **Carfilzomib administration** | - | **X** | - | - |
| **Dexamethasone administration** | - | **X** | - | - |
| **Lenalidomide administration** | - | **X** | - | - |
| **Last carfilzomib dose** | - | **X** | - | - |
| **Last lenalidomide dose** | - | **X** | - | - |
| **Last dexamethasone dose** | - | **X** | - | - |
| **EOS** | - | - | - | **X** |
| Planned **MM** subsequent treatment**s** | - | - | - | X |
| **P**atient support program | - | - | - | X |
| Cardi**ac** assessment**s** | - | X | - | X |

**Page 2 of 2**

**BP = blood pressure; CT = computed tomography; ECG = electrocardiogram;** ECOG = Eastern Cooperative Oncology Group; EOS = end of study; EOT = end of treatment; **FISH = fluorescent in situ hybridization;** MM = multiple myeloma**; MRI = magnetic resonance imaging; PET-CT = positron emission tomography-computed tomography**

[a] Baseline period – initial MM diagnosis date until day 0 of cycle 1 of carfilzomib treatment.

[b] **During treatment** – for the time period between starting carfilzomib treatment and enrolling into the study, the initial set of follow-up data will be collected retrospectively as collection of baseline information. Thereafter, follow-up data will be collected every **3** months.

[c] EOS – **data will be documented in the eCRF up to** 30 days after the final dose of carfilzomib (unless preceded by 18 months of follow-up, subject death, loss to follow-up, withdrawal of consent, or 31 March 2020).