Summary Table of Study Protocol

Title	Risk factors for cardiac events in carfilzomib-treated patients in the Marketscan database
Protocol version identifier	*20160186*
Date of last version of the protocol	*5/2/2016*
EU Post Authorisation Study (PAS) Register No	*N/A*
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Procedure Number	
Marketing Authorisation Holder(s)	
Joint PASS	*N/A*
Research Question and Objectives	Descriptive analysis comparing the characteristics of carfilzomib-treated patients who do and do not have claims for any cardiac event in the Marketscan administrative claims database. Exploratory objectives will compare incidence of any cardiac events in carfilzomib-treated patients to multiple myeloma patients not treated with carfilzomib
Country(-ies) of Study	USA
Authors	Megan Braunlin Christopher Kim Winifred Werther

Marketing Authorisation Holder

Marketing authorisation holder(s)	
MAH Contact	

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Investigator's Agreement

I have read the attached protocol entitled "Risk factors for cardiac events in carfilzomib-treated patients in the Marketscan database", dated May 2, 2016, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

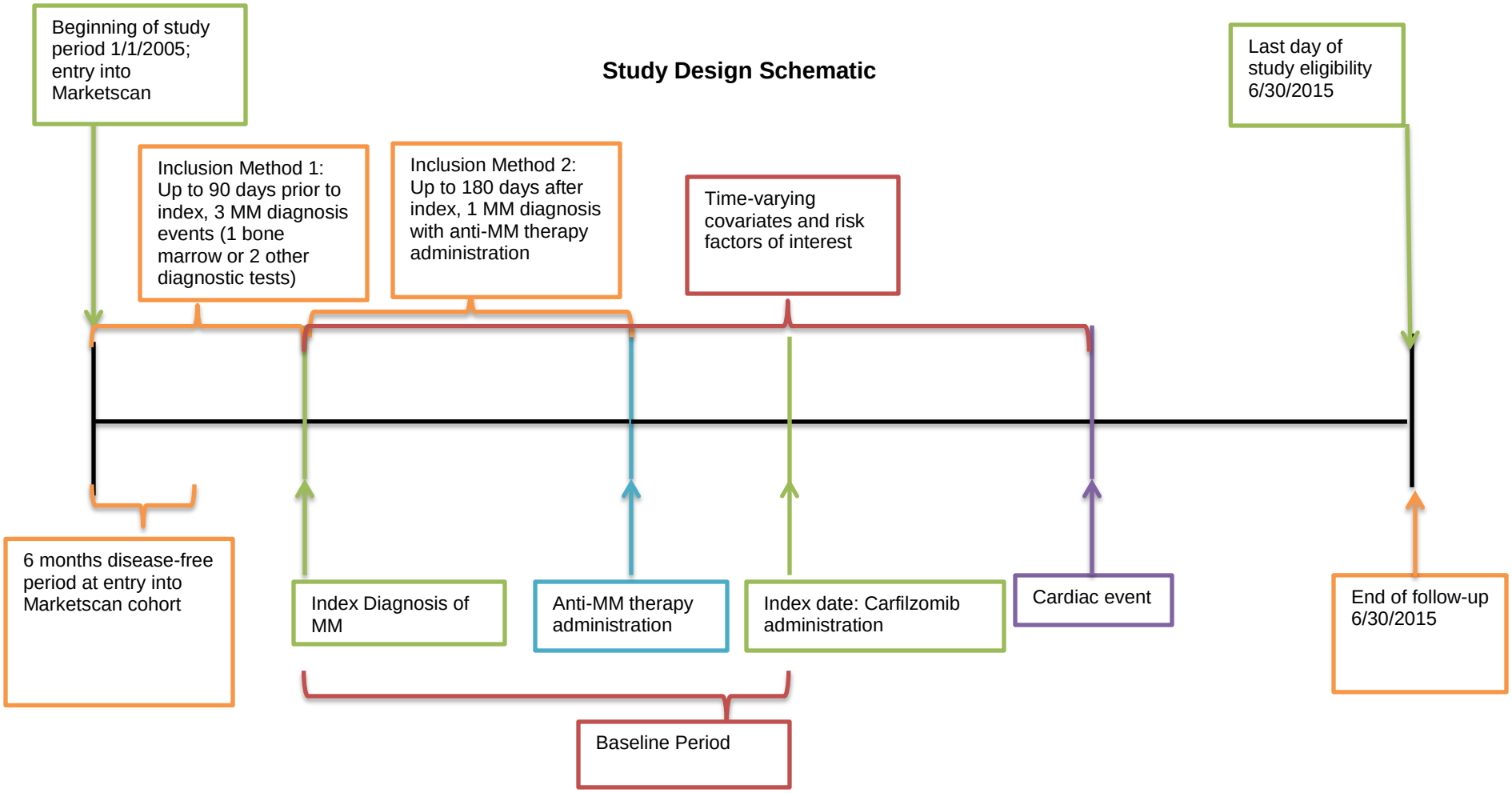
at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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 Principal Investigator Date (DD Month YYYY)

Study Design Schematic



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2. List of Abbreviations

Abbreviation	Definition
MM	Multiple Myeloma

3. Responsible Parties

Megan Braunlin

Christopher Kim

Winifred Werther

4. Abstract

The purpose of this study is to identify and describe patient characteristics associated with any cardiac events in multiple myeloma (MM) patients who receive treatment with carfilzomib (Kyprolis®). To identify any cardiac events (hypertension including malignant hypertension, heart failure, ischemic heart disease including acute myocardial infarction, cardiac arrhythmias and conduction disorders, and cardiomyopathy), the Marketscan administrative claims database will be used to construct an incident MM cohort using a validated algorithm. Logistic regression will be used to estimate covariates associated with any cardiac events. Additionally, an exploratory objective will be to construct a comparison group that will be matched to the characteristics of the carfilzomib-treated patients. Treatment regimens and lines of therapy will be used to identify carfilzomib- and non-carfilzomib-treated cohorts. The characteristics of the carfilzomib-treated and non-carfilzomib treated MM patients will be compared between those who have and do not have a cardiac event.

- **Title:** Risk factors for cardiac events in carfilzomib-treated patients in the Marketscan database
- **Objectives:** The aim of this observational study is to describe the differences between carfilzomib-treated Multiple Myeloma (MM) patients who do and do not have cardiac events in the Marketscan administrative database in the United States.

Primary Objectives:

- Aim 1: Identify and estimate the incidence rate of any cardiac events in carfilzomib-treated MM patients during the treatment period and 30 day period after termination of treatment.
- Aim 2: Compare the demographic and clinical characteristics of carfilzomib-treated patients with and without the occurrence of any cardiac events

Secondary Objectives:

- Aim 1: Assess cardiac event incidence and association by cumulative duration of carfilzomib treatment and by line of treatment that carfilzomib is administered.

Exploratory Objectives:

- Aim 1: Compare the incidence rates of any cardiac event from the carfilzomib-treated cohort to non-carfilzomib-treated cohort.

- **Study Design/Type:** Retrospective cohort study
- **Study Population or Data Resource:** Multiple myeloma patients in the Marketscan administrative database (January 1, 2005-June 30, 2015).
- **Summary of *Study* Eligibility Criteria**
  - ***MM eligibility criteria:*** A published algorithm for identifying MM patients in claims data was used to create the cohort as part of previous work completed by Amgen's Center for Observational Research (DAC #335). (ref: Princic et al. Blood 2015 126:4521) Briefly, patients were required to have 4 MM diagnoses, and 1 bone marrow or 2 other diagnostic tests within 90 days; or 1 MM diagnosis and evidence of treatment for MM within 180 days of diagnosis.
  - ***Carfilzomib eligibility criteria:*** Treatment with carfilzomib (HCPCS: C9295 or J9047)
  - ***Non-carfilzomib treated criteria (exploratory objective)***: not treated with carfilzomib and treated with anti-myeloma therapy as defined in the lines of therapy algorithm (DAC #335)
- **Variables**
- The covariates/comorbidities, exposure, and outcome variables will be defined by the presence of a claim on the patient record.
- **Study Sample Size**
- As of February 2016, there were approximately 23,000 MM patients diagnosed in Marketscan. Assuming 350 patients will be treated with carfilzomib in this time span, and 5.7% (n=20) of the patients have an event; the confidence interval around this estimate will be 3.3%-8.1%. See section 9.5 for further information.
- **Data Analysis**
- Primary Objectives
  - Aim 1: Incidence rate of any cardiac event. Incidence of individual types of cardiac events will be calculated. Count incident cardiac events in the carfilzomib-treated population (numerator). Count total person-years of eligible event time in the carfilzomib-treated population who do not have the event during baseline (denominator). Identify any cardiac events during carfilzomib treatment period. Treatment period includes 30-days after termination (last dose in the line of therapy). Separately identify the any cardiac events that occur during the post treatment period. Calculate separate incidence rate in each time period and combined.
  - Aim 2: Compare the demographic and clinical characteristics of carfilzomib-treated patients with and without the occurrence of any cardiac events. Descriptive tables detailing differences between covariates of patients during the baseline period (after MM diagnosis, prior to carfilzomib treatment). Logistic regression model to estimate association of cardiac event with baseline covariates.
- Secondary Objectives
  - Aim 1: Stratified analysis by cumulative duration and by line of therapy of carfilzomib treatment. Assess cumulative months carfilzomib is administered.

Assess during which line of therapy carfilzomib is administered. Compare incidence and associations by each grouping to identify differences in cardiac event rate.

- Exploratory Objectives
  - Aim 1: A non-carfilzomib-treated MM comparison group will be constructed using the same MM eligibility criteria listed above. The same analyses for the primary objectives will be conducted on the comparison group. These patients will be matched on age at diagnosis index date, index year, sex. In addition, the non-carfilzomib-treated group will be matched on the line of therapy (e.g., 1st, 2nd, 3rd) that the carfilzomib-treated patient received carfilzomib. For example, a patient who received carfilzomib in third line will be matched to a MM patient who received a non-carfilzomib containing regimen in line 3. The primary objectives will then be assessed for this comparison group.

5. Amendments and Updates

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
First version	5/2/2016	Initial	-	-

6. Milestones

Milestone	Planned date
Start of data collection and analysis	*May 2016*
Finish data analysis	*June 2016*
Abstract to ASH conference	*August 2016*
Final report of study results	*May 2017*

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Multiple myeloma (MM) is a common hematological cancer in the US and accounts for approximately 1% of all incident cases in the US [1]. MM is an incurable but treatment-responsive disease, and many patients achieve long-term asymptomatic remission[2]. MM is a cancer of the bone marrow that affects approximately 26,850 newly diagnosed patients a year in the US, and there are currently a total of approximately 89,000 patients in US. MM is most commonly diagnosed in the 65+ years old population. The prognosis of MM patients has improved in the last two decades with almost 47% of diagnosed patients surviving 5-years or longer[3]. The improved prognosis is due to the introduction of high-dose chemotherapy with stem cell support in the early 1990s, and later the introduction of targeted treatments such as thalidomide, bortezomib and lenalidomide[4] However, patients with MM can have different clinical outcomes, and disease-and treatment-related toxicities. Managing MM is thus a complex process and decisions on the course of therapy are typically tailored to each patient based on several factors.

The median age at MM diagnosis is approximately 70 years, and the incidence increases with age[3]. The prevalence of MM is also increasing due to increasing life expectancy in the population. MM occurs slightly more often in men than in women, but the sex ratio is close to one, and is more common in African-Americans than in Caucasians.

Carfilzomib is approved when combined with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory MM who have received one to three lines of therapy. Carfilzomib is also indicated for use as a single agent for the treatment of MM patients who have received at least 2 prior therapies including bortezomib and an immunomodulatory agent and who have demonstrated disease progression on or within 60 days of completion of the last therapy. Carfilzomib has demonstrated efficacy and tolerability in combination regimens in patients with MM in phase 3 studies[5, 6]. Carfilzomib safety profile has been characterized by a low incidence of peripheral neuropathy, a common adverse event in bortezomib-based regimens. However, recent studies suggest that proteasome inhibitors, including carfilzomib, are associated with cardiac events[7]. In the ASPIRE trial[6] and ENDEAVOR trial[5], some elevation of cardiac events were observed. In registration trials of carfilzomib cardiac failure events (*e.g.* CHF, pulmonary edema, ejection fraction decreased) were reported in 7% of patients[7]. In the phase 3 ASPIRE study comparing carfilzomib-lenalidomide dexamethasone to lenalidomide and dexamethasone alone, the rates of grade ≥3 cardiac failure were 3.8% vs 1.8%, respectively[6].

With the increasing emergence of therapies and improvements in patient survival, understanding any cardiac events in carfilzomib-treated MM patients will be important in the management of MM patients and inform clinical decision making.

7.2 Rationale

During the ASPIRE[6] and ENDEAVOR[5] clinical trials more cardiac events were observed in carfilzomib arms relative to the control arms. The purpose of this study is to investigate the incidence rate of any cardiac events in the carfilzomib treated population in a real world data source and the demographic and clinical differences in patients who do and do not have a cardiac event.

7.3 Statistical Inference (Estimation or Hypothesis[es])

This study is observational and descriptive. No hypothesis is being tested. The purpose of the study is to estimate the incidence rate of any cardiac events in carfilzomib-treated MM patients. The total number of events in the carfilzomib treated (primary objective) and the non- carfilzomib treated (exploratory objective) populations are the numerators and the number of person-years will be the denominator.
Logistic regression will be used to estimate the association between any covariates and any cardiac events in the MM patients.

8. Research Question and Objectives

8.1 Primary

Aim 1: Identify and estimate the incidence rate of any cardiac events in carfilzomib-treated MM patients during the treatment period and 30 day period after termination of treatment.

Aim 2: Compare the demographic and clinical characteristics of carfilzomib-treated patients with and without the occurrence of any cardiac events

8.2 Secondary

Aim 1: Assess cardiac event incidence and associations by cumulative duration of carfilzomib treatment and by line of treatment that carfilzomib is administered.

8.3 Exploratory

Aim 1: Compare the incidence rates of any cardiac event from the carfilzomib-treated cohort to non-carfilzomib-treated cohort.

9. Research Methods

9.1 Study Design

Retrospective cohort design is being used to estimate rates of cardiac events in the MM population treated with carfilzomib. A retrospective design provides an efficient method, with regard to time and cost, to describe population-based disease outcomes.

9.2 Setting and Study Population

9.2.1 Study Period

All newly diagnosed MM patients treated with carfilzomib beginning in January 1, 2005 through June 30, 2015 are eligible for inclusion in this study population.

9.2.2 Subject/Patient/Healthcare Professional Eligibility

9.2.2.1 Inclusion Criteria

- 1.) Marketscan Inclusion Criteria (MM cohort from DAC 335)
  - This algorithm requires a combination of ICD-9-CM code 203.0X and diagnosis tests or treatment. To meet this algorithm a patient must have a MM diagnosis (index diagnosis) and 1 of:
  - 3 additional MM diagnoses during the 90 days prior to the index diagnosis AND bone marrow or 2 other diagnostic tests during the 90 days prior to the index diagnosis. Index diagnosis is the 4th diagnosis.

    OR
  - Anti-MM therapy within 180 days after one MM diagnosis; Drug codes must be on a claim with a chemotherapy administration code. Index diagnosis is the first diagnosis to meet treatment criteria.
- 2.) Carfilzomib eligibility criteria (primary objective): treatment with carfilzomib (HCPCS: C9295 or J9047)
- 3.) Non-carfilzomib treated criteria (exploratory objective**)**: not treated with carfilzomib and treated with anti-myeloma therapy as defined in the lines of therapy algorithm (DAC #335)
-

9.2.2.2 Exclusion Criteria

9.2.3 Baseline Period

The baseline period is defined as the 12 months prior to diagnosis of MM to treatment with carfilzomib (or matched line of therapy for comparison group). Baseline

characteristics will be derived from claims rendered during the baseline period. Comorbid conditions will be identified using 1 inpatient or outpatient claim in the baseline period, with the exception of cerebrovascular disease; which will be identified using inpatient claims only. Covariates and comorbid conditions are outlined in section 9.3.3.

9.2.4 Study Follow-up

From study index date, patients are followed through death, or end of study period.

9.3 Variables

9.3.1 Exposure Assessment

The baseline covariates/comorbidities will be defined by the presence of a claim on the patient record. The baseline covariates will be assessed in the logistic model. The diagnostic codes for these covariates are outlined in the appendix .

Carfilzomib exposure will be characterized by duration of treatment (months) and line of therapy. Patients treated with carfilzomib in more than one line of therapy (e.g. discontinuation, re-continuation) will be assessed in a separate stratified analysis.

The non-carfilzomib-treated group will be matched on the line of therapy (e.g., 1st, 2nd, 3rd) that the carfilzomib-treated patient received carfilzomib. Exposure in the non-carfilzomib-treated group will be defined by the treatments given in the matched line of therapy.

9.3.2 Outcome Assessment

The primary outcomes of interest in this study will be any cardiac events.

Events to be analyzed separately:

- Hypertension including malignant hypertension
- Heart failure,
- Ischemic heart disease including acute myocardial infarction,
- Cardiac arrhythmias and conduction disorders,
- Cardiomyopathy
- Any cardiac event (defined by all above outcomes combined)
- Any cardiac event excluding hypertension (Heart failure, ischemic heart disease, cardiac arrhythmias and conduction disorders, and cardiomyopathy)

These outcomes will be defined by specified diagnosis codes outlined in Appendix 14.1 and specific in-patient, out-patient logic for particular outcomes.

9.3.3 Covariate Assessment

See section 9.2.3 and 9.3.1 for details of baseline period and exposure assessment for defining covariates. Covariates include demographic characteristics and comorbidities that are associated with exposures and outcomes (CVD and MM treatments).

The following baseline characteristics will be determined:

- Age at study index date
- Sex
- Calendar year of study index date
- Geographic region

Comorbidities:

- Charlson comorbidity index

- Cardiac outcomes (9.3.2)
- COPD
- Cancer
- Liver disease
- Gastrointestinal disease
- Inflammatory diseases
- Independent covariates associated with CVD

Disease and treatment related comorbidities

- Infections
- Renal disease
- Skeletal Related Events (SRE)
- Hypercalcemia
- Anemia
- Amyloidosis
- Osteoporosis
- Thrombocytopenia
- GI Bleed
- Anthracycline use
- Stem cell transplantation
- Deep vein thrombosis
- Thromboembolism
- Pulmonary hypertension

See Appendix 14.2 for the full list of covariates and a description of the ICD-9 codes.

9.3.4 Validity and Reliability

9.4 Data Sources

Administrative claims data from Truven Marketscan will be used to identify patients with MM treated with carfilzomib. MarketScan is compliant with the Healthcare Information Portability and Accountability Act (HIPAA), and is a fully integrated patient-level database containing inpatient, outpatient, drug, lab, health risk assessment, and benefit design information from commercial and Medicare supplemental insurance. This database is considered a real-world reflection of treatment patterns and costs of treatment in more than 36 million patients across the US, and is considered representative of the privately insured population in the US.

9.5 Study Size

This is an estimation study. As of February 2016, there were approximately 23,000 MM patients diagnosed in Marketscan. Assuming 350 patients will be treated with carfilzomib in this time span, the estimated confidence interval of the event proportion in this population will be as follows (Wald statistic):

Estimated Events	Estimate	Lower, Upper 95%
10	2.9%	1.1%-4.6%
20	5.7%	3.3%-8.1%
35	10%	6.9%-13%
50	14%	10.6%-18%

EpiTools: http://epitools.ausvet.com.au/content.php?page=home

9.6 Data Management

9.6.1 Obtaining Data Files

Marketscan data is stored in-house at Amgen and is refreshed on a monthly basis.

9.6.2 Linking Data Files

N/A

9.6.3 Review and Verification of Data Quality

Marketscan data have been used extensively at Amgen, and the quality of the data is high with a very low frequency of patients with missing values or with values out of range for core clinical and demographic variables. Edit, range, and logic checks will nonetheless be performed on each variable of interest by the study programmer to ensure quality and completeness.

9.7 Data Analysis

9.7.1 Planned Analyses

9.7.1.1 Primary Analysis

- Primary Objectives
    - Aim 1: Incidence rate of any cardiac event. Incidence of individual types of cardiac events will be calculated. Count incident cardiac events in the carfilzomib-treated population (numerator). Count total person-years of eligible event time in the carfilzomib-treated population who do not have the event during baseline (denominator). Identify any cardiac events during carfilzomib treatment period. Treatment period includes 30-days after termination (last dose in the line of therapy). Separately identify the any cardiac events that occur during the post treatment period. Calculate separate incidence rate in each time period and combined.
    - Aim 2: Compare the demographic and clinical characteristics of carfilzomib-treated patients with and without the occurrence of any cardiac events. Descriptive tables detailing differences between covariates of patients during the baseline period (after MM diagnosis, prior to carfilzomib treatment). Logistic regression model to estimate association of cardiac event with baseline covariates.
- Secondary Objectives
    - Aim 1: Stratified analysis by cumulative duration and by line of therapy of carfilzomib treatment. Assess cumulative months carfilzomib is administered. Assess during which line of therapy carfilzomib is administered. Compare incidence and associations with covariates by each grouping to identify differences in cardiac event rate.
- Exploratory Objectives
    - Aim 1: A non-carfilzomib-treated MM comparison group will be constructed using the same MM eligibility criteria listed above. The same analyses for the primary objectives will be conducted on the comparison group. These patients will be matched on age at diagnosis index date, index year, sex. In addition, the non-carfilzomib-treated group will be matched on the line of therapy (e.g., 1st, 2nd, 3rd) that the carfilzomib-treated patient received carfilzomib. For example, a patient

who received carfilzomib in third line, will be matched to a MM patient who received a non-carfilzomib containing regimen in line 3.

9.7.2 Planned Method of Analysis

9.7.2.1 General Considerations

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Variables with missing or incomplete fields will be coded as missing but kept in analyses. The expected missing rate is low (<1%) and as such, should not have a large impact upon the results of the study. If selected patients do not have at least 6 months of follow-up, it is expected that these patients will be excluded, unless noted by death.

9.7.2.3 Descriptive Analysis

The total number of MM patients treated with carfilzomib by cardiac event will be described and compared with a t-test statistic. The demographic and clinical characteristics will be described as outlined in section 9.3.1 and the full codes and covariates in the appendix.

9.7.2.3.1 Description of Study Enrollment

Study subjects are enrolled from the established Marketscan database which is an adjudicated health insurance claims system. This study begins in January 1, 2005 and runs through the end of follow-up in June 30, 2015.

9.7.2.3.2 Description of Subject/Patient Characteristics

All members of the Marketscan insurance plan are enrolled in the database.

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

Incidence rates for each type of cardiac event will be estimated using traditional methods (eliminating those with prevalent cardiac events at treatment start date from the numerator and denominator; prevalent cardiac conditions is defined by occurrence of a claim for the cardiac events in the baseline period). A patient will be counted in the numerator of the incidence rate at the time of the first diagnosis. Patient follow up begins at treatment index and continues until first occurrence of the outcome for those experiencing an event of interest. For event-free patients, follow-up begins at treatment index and ends 30 days after the end of active carfilzomib-treatment. Exploratory analyses may access time through the end of enrollment or the end of the study time period. The timing of the cardiac event will be observed: events within 30-days and (exploratory) more than 30-days of termination of carfilzomib treatment. Incidence rates will be calculated together and separately for the time windows.

Secondary analyses will be by cumulative duration of treatment and by line of therapy that carfilzomib is administered will be conducted. The duration of treatment is determined by the first day of administration until the final administration of drug.

The demographic and clinical demographics will be summarized in tables and compared with a t-test statistic to identify differences between carfilzomib-treated MM patients who do and do not experience a cardiac event.

The risk of any cardiac events in the carfilzomib-treated MM patients will be compared using logistic regression, which will include the baseline demographics and comorbidity covariates as previously specified. Each of the covariates will first be examined in a univariate analysis.

The models will be checked to ensure they meet all model assumptions. Multivariate logistic regression will use stepwise methods for selecting covariates. Stepwise criteria will be p<0.1 for inclusion and p<0.05 to stay in the model. The initial model will be run with the exhaustive covariate list which will include all demographic characteristics (age at diagnosis, age at carfilzomib treatment, sex, geographic region, year of index date) from the insurer and comorbidities (Charlson score; yes/no of all comorbidities) outlined in the appendix.

Exploratory analyses of incidence rates and comparisons of demographic/clinical covariates will be calculated for a non-carfilzomib-treated comparison group. The group will be matched 3:1 and using the following criteria: age at diagnosis index date (+/- 5 years, index year, sex, and lines of therapy. The primary objectives will be assessed for this comparison group.

9.7.2.5 Sensitivity Analysis

9.7.2.5.1 Subgroup Analysis

N/A

9.7.2.5.2 Stratified Analysis

Cumulative duration of treatment: cumulative duration will be calculated for all patients. Depending on the distribution of duration, analyses will be stratified by median, quartiles, or larger groupings. Incidence and associations will be calculated within each group.

Treatment by line of therapy: the line in which carfilzomib is administered will be determined from a previous CfOR project (DAC project 335). Incidence and associations will be calculated by line of therapy.

9.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

Analyses will be tested for the any outcomes limited to the primary and secondary positions (rather than all positions) in a diagnosis claim to see if the initial results are inconsistent or do not make logical sense with regard to cardiac events.

9.7.2.5.4 Other Sensitivity Analysis

N/A

9.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

Primary study objectives are related to cardiac safety events.

9.8 Quality Control

CfOR DAC programmers will write and execute the analytics. A programmer will be assigned to QC and verify the results from the analysis.

9.9 Limitations of the Research Methods

9.9.1 Internal Validity of Study Design

9.9.1.1 Measurement Error(s)/Misclassification(s)

Our use of routine data is advantageous since the study itself does not affect the diagnostic process and thus does not introduce bias due to surveillance in follow-up studies. The vast majority of the data coming from this study are part of the routine, Marketscan data. Misclassification of data is likely in a claims database such as

Marketscan, but is unlikely to be differential in nature and will likely only bias any analyses towards the null.

9.9.1.2 Information Bias

Marketscan data is most likely to be missing data points that are random and nondifferential.

9.9.1.3 Selection Bias

As the Marketscan cohort is the population from which the MM patients treated with carfilzomib are drawn, there should be no selection bias. All carfilzomib-treated patients with MM diagnoses will be included in the study.

9.9.1.4 Confounding

9.9.2 External Validity of Study Design

Study is likely to be representative to the entire US population of MM patients that are general commercially insured population. Results may not be generalizable to a Medicare insured population that is $\geq$65 years old.

9.9.3 Analysis Limitations

This study is subject to the limitations of the accuracy and completeness of the Marketscan systems. Some limitations may exist in regional differences of treatment, coverage lapses and differential treatment sequencing that may differ from treatment in regions of the country where Marketscan does not cover.

9.9.4 Limitations Due to Missing Data and/or Incomplete Data

Previous experience with Marketscan data indicates a low degree of missing or incomplete data. However, some information could be missing. Some test results of labs are not captured in Marketscan, so algorithms will be used where necessary. For individuals with missing information on critical variables to define the patient population or outcome measures, these individuals will not be included in analyses.

9.10 Other Aspects

10. Protection of Human Subjects

Marketscan data have been de-identified prior to delivery to Amgen. No study subjects will be contacted for this study.

10.1 Informed Consent

Informed consent from patients is not required.

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

Institutional Review Board approval is not applicable for this study.

10.3 Subject Confidentiality

Only anonymized data will be used in analyses. Study results will only be presented in aggregate form so that individuals cannot be identified, and individual data will not be shared with the study sponsor.

11. Collection of Safety Information and Product Complaints

Reporting of individual adverse events is not applicable for secondary data collection studies.

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. Amgen must be informed of all amendments and give approval. The Investigator **must** send a copy of the approval letter 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 Amgen 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

13.1 Publication Policy

The intent is to publish the results of this study as both an abstract at a scientific meeting and as a manuscript. 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, and 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.

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14. Appendices

14.1 Outcomes Table

Outcome	ICD-9	Details	Source
Hypertension	401.XX, 402.XX, 403.XX, 404.XX, 405.XX, 437.2X	1 In-patient, 2 out-patient, hypertensive medication	Kyprolis hypertension study
Malignant hypertension	402.0X, 403.0X, 404.0X, 405.0X, 437.2X	1 In-patient, 2 out-patient, hypertensive medication	Kyprolis hypertension study
Cardiac Heart Failure	428.X	Primary hospital discharge	Mini-Sentinal (Saczynski 2012)
Ischemic heart disease	410.xx, 411.xx, 413.xx, 414.xx		Kistler study
Acute Myocardial infarction (subset of IHD)	410.x		Kyprolis hypertension study
Cardiac arrhythmias	427.xx and 798.xx	Any position	Mini-Sentinal (Tamariz 2011)
Conduction disorders	426.xx		Kistler study
Cardiomyopathy	425.x		hypertension study

(Saczynski 2012) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3808171/
(Tamariz 2011) http://www.mini-sentinel.org/work_products/HealthOutcomes/MS_HOI_CardiacArrhythmiasReport.pdf

14.2 Co-morbidities, Charlson, and other baseline conditions

Appendix. ICD-9 codes for comorbid conditions

	ICD 9/ CPT Code	Details
Comorbid Conditions		
Cardiac outcomes included from above table		
Cerebrovascular disease (stroke)	430, 431, 432	Hemorrhagic stroke
	433.x1, 434.x1	Ischemic

		stroke
	435.x	Transient cerebral ischemia (inpatient only)
Peripheral vascular disease (PVD)	440-444; 447; 451-453; 557	
Any CV event	Any of the above events	
Chronic obstructive pulmonary disease (COPD)	491.xx – 494.xx, 496.xx, 510.xx	
Chronic liver disease and cirrhosis	570.xx, 571.xx, 572.1, 572.4, 573.1 – 573.3, V42.7,	
Rheumatoid arthritis and other inflammatory polyarthropathies	714.x	
Osteoarthritis and allied disorders	715.x	
Gastrointestinal disorders (GI)	456.0 - 456.2, 530.7, 531.xx – 534.xx, 569.84, 569.85, 578	
Clinical Characteristics		
Charlson Comorbidity Index		
Prior Cancer History		
Solid Tumor	140-199 (excluding 200-208)	excluding lymphoma, leukemia and multiple myeloma
Hematologic Cancer	200.xx-208.xx (excluding 203.0x for MM)	lymphoma and leukemia
Independent Covariates associated with CVD		
Diabetes mellitus	250.xx	
Hyperlipidemia	272.0-272.4	
Hypertension	401.XX	Essential hypertension
	402.XX	Hypertens

		ive heart disease
	403.XX	Hypertensive chronic kidney disease
	404.XX	Hypertensive heart and chronic kidney disease
	405.XX	Secondary hypertension
	437.2X	Hypertensive encephalopathy
Malignant hypertension / hypertensive encephalopathy	401.0X	Essential hypertension – malignant
	402.0X	Hypertensive heart disease – malignant
	403.0X	Hypertensive chronic kidney disease – malignant
	404.0X	Hypertensive heart and chronic kidney disease – malignant
	405.0X	Secondary hypertension – malignant
	437.2X	Hypertensive encephalopathy

Treatment and disease related complications		
Infections	001-139, 254.1, 320-326, 372.0-372.39, 373.0-373.2, 382-382.4, 383.xx, 386.33, 386.35, 388.60, 390, 391.x-392.0, 392.9, 393, 421.0-421.1, 422.0, 422.91-422.93, 460-466, 472.0-474.02, 475-476.1, 478.21-478.24,478.29, 480.x-490, 491.1, 494.x, 510.x-511.1, 513.x, 518.6, 519.01, 522.5, 522.7, 527.3, 528.3, 540-542, 566-567.9, 569.5, 572-572.1, 573.1-573.3, 575-575.12, 590-590.9, 595.x-595.4, 597.xx-597.89, 598.xx, 599.0, 601.x, 604.xx, 607.1-607.2, 608.0, 608.4, 616.1, 616.3-616.4, 616.8, , 611.0, 614-616.0, 670, 680-686.9, 706.0, 711-711.9, 790.7, 790.8, 730.x-730.2, 730.3, 730.8-730.9, 996.62, 996.60-996.61, 996.63-996,69, 997.62, 998.5x, 999.3	
Renal failure[8, 9]	403.xx, 404.xx 584.x 582.xx, 583.xx, 585.xx,586, 588.xx	Hypertensive chronic kidney disease Acute kidney failure Chronic kidney disease
Hypercalcemia	275.42	
Anemia	280-285	
Amyloidosis	277.3, 277.30, 277.39	
Osteoporosis	733.0x	
GI bleed	456.0, 456.20, 530.21, 530.7, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.x1, 537.83, 537.84, 562.x2, 562.x3, 569.84, 569.85, 569.86, 578.0	ICD 9/ CPT
Thrombocytopenia	287.3, 287.4, 287.5	
Deep vein thrombosis	451.1x 451.81	ICD-9

	451.83 451.89 453.4x 453.50 453.51 453.52 453.7x 453.8x	
Thromboembolism	415.1x, 416.2, 451.x,453.x (1 inpatient or 2 outpatient)	ICD-9
Pulmonary hypertension	416.1	ICD-9
Skeletal Related Events		
Spinal Cord Compression	3369 63050, 63051, 22551, 22552, 63064, 63066, 61343, s2348, 63075-8, s2350, s2351, 63195, 63197, 63199, 63001, 63003, 63005, 63011, 63015, 63016, 63017, 63170, 63012, 63045, 63046, 63047, 63048, 63040, 63042, 63043, 63044, 63020, 63030, 63035, 22224, 22222, 22214, 22212, 22207, 22206, 0274t, 0275t, c9729, 0202t, 22865, 0164t, 0094t, 0097t, 63057, 63056, 63055, 63081, 63082, 63087, 63088, 63101, 63102, 63103, 63090, 63091, 63086, and 63085	ICD 9/ HCPCS
Pathological fractures	7331, 73311, 73312, 73313, 73314, 73315, 73316, and 73319	ICD 9
Surgery to bone	7815, 7845, 7855, 7915, 7925, 7935, 7995, 7812, 7842, 7852, 7911, 7921, 7931, 7991, 7813, 7843, 7853, 7912, 7922, 7932, 7992, 7817, 7847, 7857, 7916, 7926, 7936, 7996, 0353, 8102, 8103, 8104, 8105, 8106, 8107, 8108, 7810, 7811, 7816, 7819, 7840, 7841, 7846, 7849, 7850, 7851, 7856, 7859, 7910, 7919, 7920, 7929, 7930, 7939, 7990, and 7999 27187, 27235, 27236, 27244, 27245, 27248, 27269, 27495, 27506, 27507, 27509, 27511, 27513, 27514, 23615, 23616, 23630, 24498, 24515, 24516, 24538, 24545, 24546, 24566, 24575, 24579, 24582, 24586, 24587, 24635, 24665, 24666, 24685, 25490, 25491, 25492, 25515, 25525, 25526, 25545, 25606, 25607, 25608, 25609, 27535, 27536, 27745, 27756, 27758, 27759, 27766, 27769, 27784, 27792, 27826, 27827, 22325, 22326, 22327, 22328, 22520, 22521, 22522, 22532, 22533, 22534, 22548, 22550, 22554, 22555, 22556, 22558, 22565, 22585, 22590, 22595, 22600, 22610, 22612, 22614, 22615, 22625, 22630, 22632, 20982, 23490, 23515, 23585, 27215, 27216, 27217,	ICD 9/ HCPCS

	27218, 27226, 27227, 27228, 27524, 27540, 22523, 22524, 22525, 22526, 22527, 25574, and 25575	
Radiation to bone	9223, 9224, 9229 A9600, A9604, A9605, C9401, J3005, 77401, 77402, 77403, 77404, 77406, 77407, 77408, 77409, 77411, 77412, 77413, 77414, 77416, 77418, 79005, 79101, 79200, 79300, 79400, 79403, 79440, 79445, and 79999	ICD 9/ HCPCS

Any definitions for co-morbidities [8-10]

Appendix . Anti-hypertensive medication classification in MarketScan

Evo Treatment Group
AHBP_ACEI
AHBP_ANTIALDOSTERONE
AHBP_ARB
AHBP_BB_EB
AHBP_BETA_ALL
AHBP_CALCIUM
AHBP_DIURETICS

Appendix ICD-9, HCPCS, or NDC codes used for anti- cancer treatment with anthracyclines

Anthracyclines	Daunorubicin Doxorubicin Epirubicin Idarubicin Mitoxantrone	J9000, J9001, J9178, 00013100691, 00013101679, 00013107694, 00013108691, 00013109691, 00013109694, 00013110679, 00013111683, 00013113691, 00013114691, 00013114694, 00013115679, 00013116683, 00013117687,

		00013123691, 00013124691, 00013125679, 00013126683, 00013128683, 00015335122, 00015335222, 00015335322, 00069303020, 00069303120, 00069303220, 00069303320, 00069303420, 00186153013, 00186153101, 00186153231, 00186153241, 00186153261, 00186153281, 00186157512, 00469100161, 00469883020, 00469883130, 00469883250, 00702023110, 00702023206, 00702023301, 00702023510, 00702023606, 00702023701, 00703504001, 00703504303, 00703504601, 10019092001, 10019092102, 38779065206, 38779065209, 49452243701, 53905023206, 53905023606, 54868313100, 55390023110, 55390023210, 55390023301, 55390023510, 55390023610, 55390023701, 55390023801, 55390024110, 55390024210,

		55390024301, 55390024510, 55390024610, 55390024701, 55390024801, 63323010161, 63323088305, 63323088310, 63323088330, 17314960001, 17314960002, 59676096001, 59676096002, 61471029512, 00009509101, 00009509301, 00591346983, 00591347057, 00703306711, 00703306911, 10139006101, 10139006125, 10518010410, 10518010411, 25021020325, 25021020351, 55390020701, 55390020801, 59762509101, 59762509301, 61703034735, 61703034859, 61703035901, 61703035902, 61703035959, 61703035991, 61703035992, 61703035993, 63323015100, 63323015105, 63323015125, 63323015175, 66758004201, or 66758004202

Appendix.
Description Code

Description	Code
ICD-9 procedure codes	
Autologous bone marrow transplant without purging	41.01
Autologous hematopoietic stem cell transplant without purging	41.04
Autologous hematopoietic stem cell transplant with purging	41.07
Autologous bone marrow transplant with purging	41.09
Allogeneic hematopoietic stem cell transplant	
Allogeneic bone marrow transplant with purging	41.02
Allogeneic bone marrow transplant without purging	41.03
Allogeneic hematopoietic stem cell transplant without purging	41.05
Cord blood stem cell transplant	41.06
Allogeneic hematopoietic stem cell transplant with purging	41.08
Bone marrow transplant, not otherwise specified	41.00
ICD-9 diagnosis codes	
Complications of bone marrow transplant	996.85
Bone marrow replaced by transplant	V42.81
CPT codes	
Bone marrow or blood-derived peripheral stem cell transplantation	38240
Bone marrow or blood-derived peripheral stem cell transplantation	38241
Bone marrow or blood-derived peripheral stem cell transplantation	38242
HCPCS codes	
Cord blood-derived stem-cell transplantation, allogeneic	S2142
Bone marrow or blood-derived stem cells transplantation	S2150