Title	An Observational Study to Estimate Incidence Rates of Heart Failure Among US Racial and Ethnic Minority Patients With Multiple Myeloma Treated or Not Treated With Carfilzomib
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Research Question and Objectives	The primary and secondary objectives were to: • Estimate the incidence rate of cardiac failure in United States racial and ethnic populations of patients with multiple myeloma treated or not treated with carfilzomib • Describe demographics, clinical characteristics, and cardiac failure risk factors in patients with multiple myeloma treated or not treated with carfilzomib
Country of Study	United States
Author	Christopher Kim Center for Observational Research, Amgen Inc. +1 (805) 447-6946 chrkim@amgen.com

Marketing Authorization Holder

Marketing Authorization Holder	Amgen Inc.
MAH Contact Person	Amgen Inc. Global Development Leader One Amgen Center Drive Thousand Oaks, CA 91320 USA +1 (805) 447-3505 medinfo@amgen.com

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1. ABSTRACT

- **Title**

An Observational Study to Estimate Incidence Rates of Heart Failure Among US Racial and Ethnic Minority Patients With Multiple Myeloma Treated or Not Treated With Carfilzomib

- **Keywords**

Carfilzomib, cardiac failure, multiple myeloma

- **Rationale and Background**

This study was conducted to fulfill a postmarketing requirement to understand the potential differential risk of cardiac failure among racial and ethnic minorities.

- **Research Question and Objectives**
  - Primary objectives:
    - Estimate the incidence rates of cardiac failure in United States (US) racial and ethnic populations of patients with multiple myeloma treated with carfilzomib
    - Estimate the incidence rates of cardiac failure in US racial and ethnic populations of patients with multiple myeloma not treated with carfilzomib
  - Secondary objectives:
    - Describe demographic, clinical characteristics, and cardiac failure risk factors in US racial and ethnic populations of patients with multiple myeloma treated with carfilzomib
    - Describe demographic, clinical characteristics, and cardiac failure risk factors in US racial and ethnic populations of patients with multiple myeloma not treated with carfilzomib
  - Exploratory objectives:
    - Assess comparability between patients with multiple myeloma of black race treated with carfilzomib and those treated with other treatments for multiple myeloma, after propensity score matching, using standardized mean differences
    - Compare the risk of cardiac failure between patients with multiple myeloma of black race treated with carfilzomib and those treated with other treatments for multiple myeloma If the assessment indicates sufficient post-matching comparability
    - Assess comparability between patients with multiple myeloma of White race treated with carfilzomib and those treated with other treatments for multiple myeloma, after propensity score matching, using standardized mean differences
    - Compare the risk of cardiac failure between patients with multiple myeloma of White race treated with carfilzomib and those treated with other treatments for multiple myeloma If the assessment indicates sufficient post-matching comparability

- **Study Design**

This was a retrospective observational study conducted in 3 administrative claims databases to examine patients with multiple myeloma of specific racial/ethnic identifications using existing administrative databases.

- **Setting**

The data sources for this study included US fee-for-service (FFS) Medicare (01 January 2013 through 31 December 2017), and Optum research database and the Humana integrated databases (both 01 January 2013 through 31 December 2018).

- **Subjects**

Eligible patients were ≥ 18 years, had a multiple myeloma diagnosis, received carfilzomib or other multiple myeloma treatments in at least 1 line of therapy (LOT), and were continuously enrolled in medical and pharmacy insurance coverage for 12 months before the treatment index.

A full list of eligibility criteria is provided in Protocol Section 8.2.2.1 (Annex 2 of this report).

Patients with missing or unknown race/ethnicity variable or with evidence of renal transplant or dialysis were excluded.

- **Variables and Data Sources**

The exposure in this study was the use of carfilzomib-based regimens or non-carfilzomib-based regimens. Exposure was assessed for each LOT. Within each LOT, patients were considered as exposed from the treatment start date until 30 days after treatment end date or until initiation of a new LOT. Patients could contribute exposure to more than 1 LOT during the study period. Carfilzomib and other drug treatments were identified using National Drug Codes and Healthcare Common Procedure Coding System codes.

Treatment episodes were further classified as belonging to 1 of the following exposure cohorts:

Carfilzomib-treated: Treatment episodes in which patients initiated a carfilzomib-containing treatment regimen.

Non-carfilzomib-treated: Treatment episodes in which patients initiated a multiple myeloma regimen not containing carfilzomib.

The outcome in this study was a hospitalization for cardiac failure events requiring an overnight stay at an inpatient facility. These events were defined as any inpatient claim

in the top 3 diagnostic positions in the study database after the index date (initiation of a LOT) for a particular treatment episode carrying a relevant diagnosis for cardiac failure. The primary summary measure was reported as the incidence rate of cardiac failure hospitalization (units in per 100 patient-years).

Baseline patient characteristics and comorbidities were determined from claims in the 12-month baseline period for each treatment episode.

- **Results**

Results for the primary objective were:

Medicare

For white patients, the incidence rate (95% CI) of cardiac failure was 14.47 (12.20, 17.04) per 100 patient-years for patients treated with carfilzomib-containing regimens and 10.73 (10.25, 11.22) per 100 patient-years for patients treated with non-carfilzomib-containing regimens. For black patients, the incidence rate (95% CI) of cardiac failure was 15.79 (10.12, 23.50) per 100 patient-years for patients treated with carfilzomib-containing regimens and 12.13 (10.94, 13.42) per 100 patient-years for patients treated with non-carfilzomib-containing regimens. Reporting the incidence rate in Asian, Hispanic, and North American native patients treated with carfilzomib-containing regimens was not done because of event counts of < 11 being suppressed as required by Centers for Medicare & Medicaid Services.

Optum

For white patients, the incidence rate (95% CI) of cardiac failure was 7.28 (4.17, 11.89) per 100 patient-years for patients treated with carfilzomib-containing regimens and 8.43 (7.54, 9.38) per 100 patient-years for patients treated with non-carfilzomib-containing regimens. For black patients, the incidence rate (95% CI) of cardiac failure was 8.9 (2.46, 23.76) per 100 patient-years for patients treated with carfilzomib-containing regimens and 11.52 (9.47, 13.88) per 100 patient-years for patients treated with non-carfilzomib-containing regimens.

Humana

For white patients, the incidence rate (95% CI) of cardiac failure was 8.74 (4.99, 14.19) per 100 patient-years for patients treated with carfilzomib-containing regimens and 8.10 (7.07, 9.23) per 100 patient-years for patients treated with non-carfilzomib-containing regimens. For black patients, the incidence rate (95% CI) of cardiac failure was 9.90 (3.97, 20.40) per 100 patient-years for patients treated with

carfilzomib-containing regimens and 11.20 (9.34, 13.33) per 100 patient-years for patients treated with non-carfilzomib-containing regimens.

- **Discussion**

Overall, the results of this study, which characterized the incidence rates of cardiac failure in patients with multiple myeloma treated with a carfilzomib-containing or non-carfilzomib-containing regimen, do not suggest a significant differential race/ethnicity effect for cardiac failure between white and black patients. Because of the small sample size of Asian, Hispanic, and North American native patients with multiple myeloma treated with a carfilzomib-containing regimen, no specific conclusions regarding the incidence of cardiac failure among Asian, Hispanic, and North American native patients compared with other race/ethnicities could be drawn. Cardiac failure events were slightly higher in carfilzomib-containing regimens compared with non-carfilzomib-containing regimens, yet no significant differential effect by race within whites and blacks was observed.

The benefit:risk profile of carfilzomib remains favourable in the currently approved indications. No new safety signal was identified from this study.

- **Marketing Authorization Holder**

Amgen Inc.

- **Names and Affiliations of Principal Investigators**

Not applicable.

2. LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
ARR	apparent relative risk
CDM	Clinformatics® Data Mart
CMS	Centers for Medicare and Medicaid Services
EHR	electronic health record
FFS	fee-for-service
HR	hazard ratio
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
LOT	line of therapy
OR_{EC}	the association between the unknown confounder and the exposure
P_C	the prevalence of the confounder
P_E	the prevalence of the exposure
RR_{CD}	the association between the confounder and the disease outcome
SAP	statistical analysis plan
US	United States

3. INVESTIGATORS

Not applicable.

4. OTHER RESPONSIBLE PARTIES

Sponsor:

- Alan Fu, PhD
  Manager, Observational Research
  Amgen Inc.
  Thousand Oaks, CA
  +1 (805) 490-3575
- Zandra Klippel, MD
  Medical Director, Global Development
  Amgen Inc.
  Thousand Oaks, CA
  +1 (805) 447-4897

Chronic Disease Research Group:

- Shuling Li, PhD
  Chronic Disease Research Group
  Minneapolis, MN
  +1 (612) 873-6253
- Jiannong Liu
  Chronic Disease Research Group
  Minneapolis, MN
  +1 (612) 873-6256

Humana:

- Brandon Suehs, PharmD, PhD
  Humana Healthcare Research
  Louisville, KY
  +1 (502) 301-2461

5. MILESTONES

Milestone	Planned Date	Actual Date
Start of data collection	Q3 2019	01 September 2019
End of data collection	Q1 2020	01 March 2020
Final report of study results	Q2 2020	15 June 2020

6. RATIONALE AND BACKGROUND

6.1 Disease and Therapeutic Area

Carfilzomib is a second-generation proteasome inhibitor that irreversibly binds to the proteasome (McBride et al, 2015). In the United States (US), carfilzomib is approved in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received 1 to 3 lines of therapy. Carfilzomib is also indicated for use as a single agent for the treatment of multiple myeloma inpatients with relapsed or refractory disease who have received 1 or more lines of therapy.

Additional information about multiple myeloma is provided in Protocol Section 6 (Annex 2 of this report).

6.2 Rationale

This study was conducted to fulfill a postmarketing requirement to understand the potential differential risk of cardiac failure among racial and ethnic minorities.

7. RESEARCH QUESTION AND OBJECTIVES

- Primary objectives:
  - Estimate the incidence rates of cardiac failure in US racial and ethnic populations of patients with multiple myeloma treated with carfilzomib
  - Estimate the incidence rates of cardiac failure in US racial and ethnic populations of patients with multiple myeloma not treated with carfilzomib
- Secondary objectives:
  - Describe demographic, clinical characteristics, and cardiac failure risk factors in US racial and ethnic populations of patients with multiple myeloma treated with carfilzomib
  - Describe demographic, clinical characteristics, and cardiac failure risk factors in US racial and ethnic populations of patients with multiple myeloma not treated with carfilzomib
- Exploratory objectives:
  - Assess comparability between patients with multiple myeloma of black race treated with carfilzomib and those treated with other treatments for multiple myeloma, after propensity score matching, using standardized mean differences
  - Compare the risk of cardiac failure between patients with multiple myeloma of black race treated with carfilzomib and those treated with other treatments for multiple myeloma If the assessment indicates sufficient post-matching comparability
  - Assess comparability between patients with multiple myeloma of White race treated with carfilzomib and those treated with other treatments for multiple myeloma, after propensity score matching, using standardized mean differences
  - Compare the risk of cardiac failure between patients with multiple myeloma of White race treated with carfilzomib and those treated with other treatments for multiple myeloma If the assessment indicates sufficient post-matching comparability

8. AMENDMENTS AND UPDATES

None

9. RESEARCH METHODS

9.1 Study Design

This was a retrospective cohort study of patients with multiple myeloma of specific racial/ethnic identifications using existing administrative databases. The data sources for this study included:

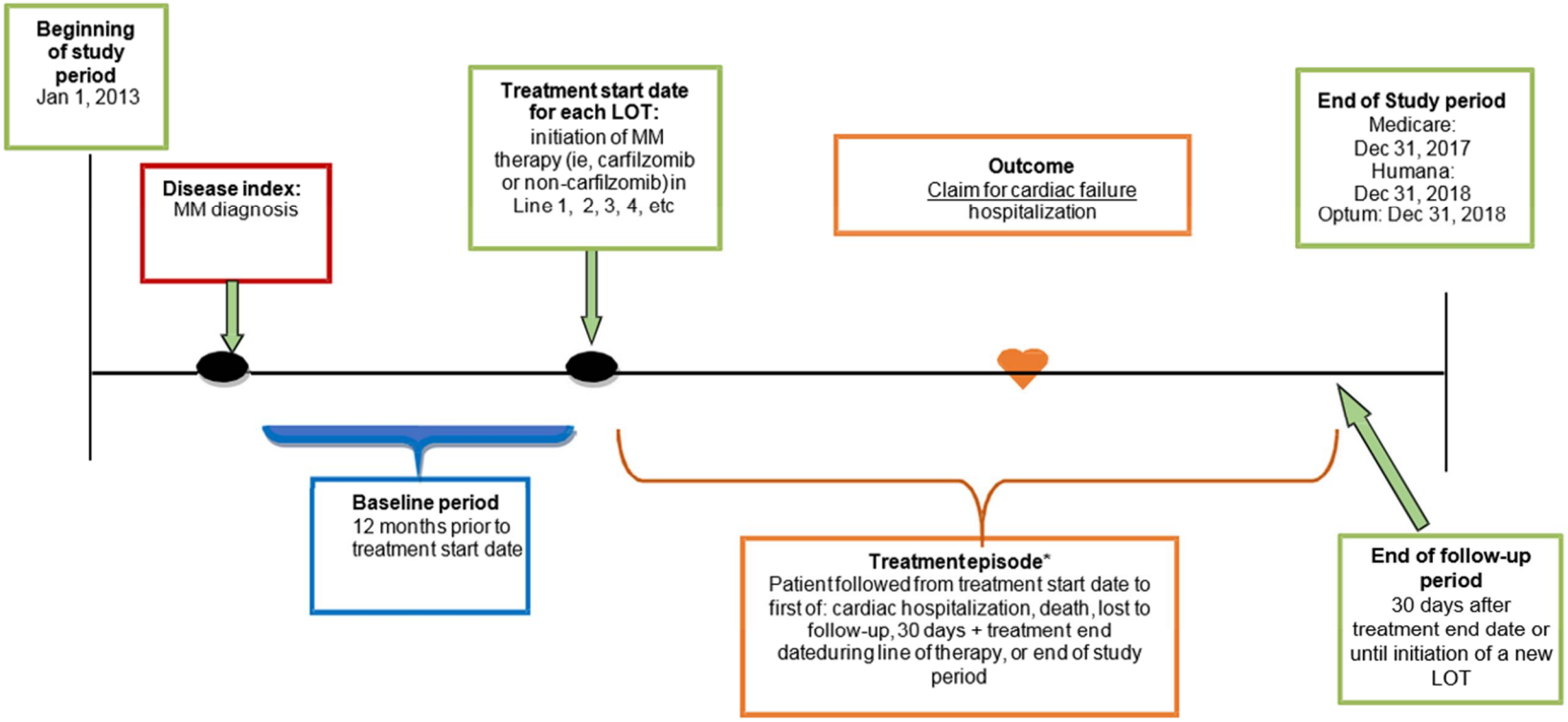
- US fee-for-service (FFS) Medicare, including Parts A, B, and D (100% data to ensure maximum coverage)
- Optum Clinformatics Data Mart (administrative claims)
- Humana integrated databases

The analysis focused on cardiac failure in US racial and ethnic groupings of patients with multiple myeloma treated or not treated with carfilzomib (see Section 9.9.2 for details on racial and ethnic groups summarized in this study). Cardiac failure was identified using an adapted validated algorithm based on International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and 10th Revision (ICD-10-CM) diagnosis codes. The study period included up to 5 years of follow-up in Medicare FFS database and up to 6 years in the Optum and Humana databases.

Occurrence of the study outcome (defined as hospitalization for cardiac failure events requiring an overnight stay at an inpatient facility in the top 3 diagnostic positions) was assessed during treatment episodes delineated by line of therapy (LOT). Each patient could contribute multiple exposures corresponding to the number of observed LOT in the data source during the study period.

The study schema is provided in Figure 9-1.

Figure 9-1. Study Schema



* Only one treatment episode is shown in this study design schema. Each patient can contribute multiple treatment episodes.

LOT = line of therapy; MM = multiple myeloma

9.2 Setting

For Medicare FFS database, the study period was 01 January 2013 through 31 December 2017. For Optum and Humana databases, the study period was 01 January 2013 through 31 December 2018.

9.3 Subjects

9.3.1 Inclusion Criteria

Patients who satisfied the following key criteria were eligible:

- Multiple myeloma diagnosis, as determined utilizing an algorithm based upon presence of a combination of ICD-9-CM and ICD-10-CM diagnosis codes, Current Procedural Terminology codes for diagnosis tests or National Drug Codes and Healthcare Common Procedure Coding System codes for treatments (see Protocol Appendix C [Annex 2 of this report]).
- Age ≥ 18 years.
- Receipt of carfilzomib or other multiple myeloma treatments in at least 1 LOT (see Protocol Appendix D [Annex 2 of this report]).
- Continuously enrolled in medical and pharmacy insurance coverage for 12 months before the treatment index.

A full list of eligibility criteria is provided in Protocol Section 8.2.2.1 (Annex 2 of this report).

9.3.2 Exclusion Criteria

Patients with missing or unknown race/ethnicity variable or evidence of renal transplant or dialysis were excluded.

9.4 Variables

9.4.1 Exposure Assessment

The exposure in this study was the use of carfilzomib-based regimens or non-carfilzomib-based regimens. Exposure was assessed for each LOT. Within each LOT, patients were considered as exposed from the treatment start date until 30 days after treatment end date or until initiation of a new LOT. Patients could contribute exposures to more than 1 LOT during the study period. Carfilzomib and other drug treatments were identified using National Drug Codes and Healthcare Common Procedure Coding System codes (see Protocol Appendix A [Annex 2 of this report]).

Treatment episodes were further classified as belonging to 1 of the following exposure cohorts:

Carfilzomib-treated: Treatment episodes in which patients initiated a carfilzomib-containing treatment regimen.

Non-carfilzomib-treated: Treatment episodes in which patients initiated a multiple myeloma regimen not containing carfilzomib.

9.4.2 Outcome Assessment

The outcome in this study was a hospitalization for cardiac failure events requiring an overnight stay at an inpatient facility. These events were defined as any inpatient claim in the study database carrying a relevant ICD-9-CM or ICD-10-CM diagnosis for cardiac failure in the top 3 diagnosis positions after the index date for a particular treatment episode. The diagnosis codes used to identify cardiac failure from claims are listed in Protocol Appendix E (Annex 2 of this report). These codes are widely used to define cardiac failure from medical claims in literature and their performance for this purpose have been validated in several databases and health systems and then adapted to this study (Sarczynski et al, 2012).

9.4.3 Covariate Assessment

Baseline patient characteristics and comorbidities were determined from claims in the 12-month baseline period for each treatment episode and are provided in Protocol Section 8.3.3 (Annex 2 of this report).

See Protocol Appendix A (Annex 2 of this report) for the list of ICD-9-CM, ICD-10-CM, Current Procedural Terminology codes, Healthcare Common Procedure Coding System codes, and case identification algorithms for identifying these variables in the study database.

9.4.4 Validity and Reliability

Diagnosis of multiple myeloma

Because ICD-9-CM diagnosis codes alone may contain many false positive patients without multiple myeloma, patients with multiple myeloma were identified in this study using a claims-based algorithm (Princic et al, 2016). As described in Protocol Appendix C (Annex 2 of this report), this algorithm included the use of diagnosis codes, Current Procedural Terminology codes for certain tests and procedures, and presence of claims for myeloma treatments. In the validation study for this algorithm, MarketScan claims data were compared with electronic medical records in a study of 2179 patients, and the algorithm yielded sensitivity of 83%, specificity of 94%, and positive predictive value of 93%.

Validation information for cardiac failure

In this study, cardiac failure was ascertained from any claim that was submitted by an inpatient facility and includes ICD-9-CM diagnosis code 428.xx (cardiac failure) and ICD-10-CM diagnosis code I50.xx (cardiac failure) in the top 3 diagnostic code positions. The ICD-10-CM diagnosis codes were mapped from the corresponding ICD-9-CM diagnosis codes.

Among codes designating cardiac failure, these were the codes generally reported to have the highest positive predictive value in a systematic review of studies that evaluated the validity of diagnosis codes and algorithms developed using administrative health plan data to identify cardiac failure (Saczynski et al, 2012). This review was conducted as part of the US Food and Drug Administration's Mini-Sentinel program.

Accuracy of racial and ethnicity information variable

The Medicare program obtained information on beneficiaries' race and ethnicity for its administrative record from the Social Security Administration. The Social Security Administration collected this data at a time of application for a social security number and then transferred it to the Medicare Program's enrollment database upon enrollees' eligibility.

Zaslavsky et al investigated the relationships between race/ethnicity as reported in the Medicare enrollment database and self-reported race information from the 2010 Medicare Consumer Assessments of Healthcare Providers and Systems surveys (Zaslavsky et al, 2012). Sensitivity, specificities, and positive predictive values of Medicare enrollment database identification for white and black patients were high (exceeding 90%). Specificities and positive predictive values for Hispanics and Asians were also high, but sensitivities were moderate.

9.5 Data Sources and Measurement

9.5.1 US Fee-for-service Medicare

United States Medicare is a comprehensive, nationally representative, population-based data system of US patients ≥ 65 years of age, persons with certain disabilities, or receiving dialysis (or kidney transplant) for permanent kidney damage. Patients included in the US Medicare data system for this study are those with full FFS (traditional) Medicare. Patient information is documented from initial enrollment in Medicare until the date of death with minimal loss to follow-up. Essentially all billable medical transactions

were captured in the Medicare data system. Because these were subject to federal audit, data quality for these variables is generally high.

The 100% Medicare multiple myeloma files from 2013 through 2017 were used in this study. Data were from the Centers for Medicare and Medicaid Services (CMS) Chronic Conditions Data Warehouse. The 100% multiple myeloma data files include the annual denominator file and the annual claims-based standard analytic files from 2013 through 2017 for all Medicare beneficiaries with at least 1 ICD-9/10-CM diagnosis code for multiple myeloma in any position from Part A or Part B claims between 2013 and 2017.

Medicare racial and ethnic groups in this study included whites, blacks, Asians, Hispanics, and North American natives.

Event counts of < 11 are suppressed as required by Centers for Medicare & Medicaid Services

9.5.2 Optum Clinformatics® Data Mart (CDM)

Optum Clinformatics® Data Mart (CDM) is a medical claims database which represents the medical experience of insured employees and their dependents from both affiliated commercial and Medicare Advantage plans. Patients must have had both medical and pharmacy coverage to be included in the database. The underlying insured population from which the data were drawn spans across all 50 states and is racially/ethnically diverse. The database contained fully adjudicated eligibility, pharmacy, procedure, and medical claims data for patients enrolled in a large US health plan (UnitedHealth Group). The health plan provided coverage for physician, hospital, and prescription drug services, and captured medical claims or encounter data from all available health care sites (eg, inpatient hospital, outpatient hospital, emergency room, physician's office, surgery center) for virtually all types of provided services. Each facility inpatient admission record contained information on diagnoses (recorded using ICD-9-CM and ICD-10-CM diagnosis codes), procedures (recorded with ICD-9-CM and ICD-10-CM procedure codes, Current Procedural Terminology codes, or Healthcare Common Procedure Coding System codes), and Present on Admission codes. Data were linked at the patient level by a unique identifier that was consistent across services, health plans, and time, so patients could be tracked over multiple years even if they switched health plans.

Optum racial and ethnic groups in this study included whites, blacks, Asians, and Hispanics (when reporting incidence rates of cardiac failure, Asian and Hispanic patients were combined to add statistical stability).

The Optum electronic health record (EHR) consisted of electronic medical records of patients receiving care at health care partners who are major health systems and integrated delivery networks. Optum EHR data could be deterministically linked at the patient level to a subset of Optum CDM. However, very few patients that received carfilzomib treatment were available for analysis, and as such, the results are not presented (white patients: N = 67; 14% linkage; black patients: N = 17; 22% linkage).

9.5.3 Humana Integrated Databases

The Humana Integrated Research Database contained claims data for Humana's research eligible fully-insured commercial and Medicare membership. Humana Inc is a large US health insurance company; most members reside in the Midwestern and Southern regions of the United States; the West and Northeast regions are sparsely represented. The data sources for this study generally included Humana member enrollment, medical, and pharmacy data from Humana's claims database. Information from these different data sources could be linked reliably for each member using a unique member identifier which is included in all data sources. Race/ethnicity information was available for Medicare members and was based on information provided directly by the CMS.

Humana racial and ethnic groups in this study included whites, blacks, and others.

9.6 Bias

As with all observational studies, there was a potential for bias and unmeasured confounding to limit the interpretation of results. The primary and secondary objectives were descriptive in nature. Bias was addressed through the study design and statistical analysis in the comparative exploratory objective. Potential effect of unmeasured confounding was assessed through quantitative bias analysis by the rule-out method to assess the extent of unmeasured confounding that would be required to refute an observed difference in outcome incidence between cohorts (see Section 9.9.4.1).

Details on information and selection bias are provided in Protocol Section 8.9.1 (Annex 2 of this report).

9.7 Study Size

For the Medicare FFS database, estimated patient-years of observation among patients with multiple myeloma of different race and ethnicities treated and not treated with carfilzomib that was available for calculation of cardiac failure incidence rates were extrapolated form an analysis covering 3 years of Medicare FFS data (2013 through 2015). For the Humana and Optum databases, patient-years of observation were estimated from preliminary patient counts (for the years 2013 through 2018) and assuming a follow-up of 2 years. A cardiac failure incidence of 5 to 20 per 100 patient-years was estimated along with the number of events and 90% CI for the incidence rates for each racial/ethnic group among patients with multiple myeloma treated with and not treated with carfilzomib in each database. The actual numbers of events and cardiac failure incidence depended on the true patient-years accrued for each racial/ethnic group in the databases.

9.8 Data Transformation

This study used the Medicare FFS data, Optum Clinformatics Data Mart, and the Humana research database. Chronic Disease Research Group obtained the Medicare FFS data under a data use agreement. Comprehensive Health Insights Inc., a Humana company, had direct access to the Humana Research Database, which contains all claims data for Humana's fully-insured commercial and Medicare membership. The data sources for this study included Humana member enrollment, as well as medical and pharmacy claims data, from the Humana Research Database. Amgen had access to the Optum research database, which includes enrollment data, demographics, pharmacy claims, all medical and facility claims, and data on services, procedures, and their accompanying diagnosis. Data were received from Optum CDM by download using Amazon WorkSpace S3 buckets. A manifest detailing contents (list of tables, fields, and number of rows) was included in the transfer to enable Amgen to verify that the transfer completed successfully.

For more information, see Protocol Section 8.6 (Annex 2 of this report).

9.9 Statistical Methods

9.9.1 Main Summary Measures

The number of patients included in each database were reported. Results from the primary and secondary objectives were summarized using descriptive statistics.

9.9.2 Main Statistical Methods

For the primary objectives, the incidence rate of cardiac failure hospitalization (units in per 100 patient-years) was summarized for patients with multiple myeloma treated with carfilzomib-containing or non-carfilzomib-containing therapies by race/ethnicity (white, black, Asian, Hispanic, and North American native patients [Medicare FFS only]). The unit of measurement was the carfilzomib-containing or non-carfilzomib-containing treatment episode/LOT and each patient could contribute in multiple LOTs for event rate calculations. Results were reported across all LOTs/by combining all LOTs and individually by LOT (first line, second line, third line, ≥ fourth line) when there was sufficient data. Ninety-five percent confidence intervals were calculated using Byar's formula (Breslow and Day, 1987). Values were suppressed where there were < 11 patients/events per category as required by Centers for Medicare & Medicaid Services.

For the secondary objectives, baseline patient characteristics were summarized.

Details of statistical methods for the exploratory objectives are provided in Statistical Analysis Plan (SAP) Section VI (Annex 4 of this report).

9.9.3 Missing Values

Patients may have had missing insurance claims for medical or pharmacy encounters for which they did not use their insurance. This was not expected to be a common issue for this study population. International Classification of Disease, 9th Revision, Clinical Modification and ICD-10-CM diagnosis codes for lifestyle factors (smoking, obesity, and alcohol consumption) were known to be under-used. Thus, underestimation of the number of patients with these factors was expected.

9.9.4 Sensitivity Analyses

Sensitivity analyses were conducted to identify cardiac failure in the first 2 and first 5 diagnostic positions. Results for the first 2 positions resulted in many suppressed cells because of < 11 events and 5 positions were similar as the primary analysis. However, to keep the definition more sensitive than the first 2 and more specific than the first 5, the first 3 were used.

9.9.4.1 Quantitative Bias Analysis

Quantitative bias analysis was performed on the comparative exploratory objectives. To assess unmeasured confounding, the rule-out method was used to assess how strong a confounder (or set of confounders) needed to be to fully explain the observed

association between an exposure and the outcome. Details are provided in SAP Section VI (Annex 4 of this report).

9.9.5 Amendments to the Statistical Analysis Plan

Details of amendments made to the SAP are provided in Annex 4.

9.10 Quality Control

Medicare had its own quality control process and accuracy assessment programs. Chronic Disease Research Group had an existing quality assurance protocol that is routinely implemented with Medicare data they received. Each file was examined in detail, and consistency across years was assessed to evaluate data completeness and accuracy and to identify any change in variable names or addition of new variables.

Comprehensive Health Insights Data Offerings team performed quality checks on the Humana Research Database. The research scientist performed quality data checks at certain stages of the research process (eg, data extraction, programming). All datasets, including the analytical file, were quality-checked to ensure that data appear to be correct. This involved checking for missing values, ensuring that minimum and maximum values were within acceptable ranges, and that frequency counts, means, and other quantitative results were reasonable.

The Optum CDM was a de-identified, Health Insurance Portability and Accountability compliant, closed system of claims, which underwent audits and quality control procedures by the insurer at regular intervals. The coding of medical claims confirmed to insurance industry standards, including the use of designated claims forms (eg, physicians used the Health Care Financing Agency-1500 format and hospitals used the UB-92 forma). Data received from Optum CDM are checked against the vendor-provided manifest to verify that every table, field, and row was received by Amgen. Amgen ran additional data quality checks, including custom data checks comparing prior versions to the current data.

10. RESULTS

10.1 Participants

Details of cohort attrition for the Medicare, Optum, and Humana databases are provided in Table 15-1.1, Table 15-1.2, and Table 15-1.3, respectively.

10.2 Descriptive Data

10.2.1 Medicare

For the Medicare database, 128 patients (87.7%) were white, 15 patients (10.3%) were black, and 0 patients were North American native who were treated with a carfilzomib-containing regimen in LOT 1 (Table 15-2.1); data for other race/ethnicities were suppressed because of event counts of < 11 being suppressed as required by Centers for Medicare & Medicaid Services. Overall, the mean (SD) age of patients treated with a carfilzomib-containing regimen in LOT 1 was 71.1 (6.8) years; 56.9% of patients were men, the most common medical history was hypertension (70.6%), and 19.9% of patients were obese.

For patients treated with a carfilzomib-containing regimen in LOT 2, 738 patients (81.8%) were white, 132 patients (14.6%) were black, and 17 patients (1.9%) were Hispanic (Table 15-2.1); data for other race/ethnicities were suppressed because of event counts of < 11. Overall, the mean (SD) age of patients treated with a carfilzomib-containing regimen in LOT 2 was 73.8 (7.2) years; 55.2% of patients were men, the most common medical history was hypertension (75.1%), and 19.1% of patients were obese.

For patients with a carfilzomib-containing regimen in LOT 3, 541 patients (84.8%) were white and 81 patients (12.7%) were black (Table 15-2.1); data for other race/ethnicities were suppressed because of event counts of < 11. Overall, the mean (SD) age of patients treated with a carfilzomib-containing regimen in LOT 3 was 74.8 (7.2) years; 54.2% of patients were men, the most common medical history was hypertension (76.0%), and 18.3% of patients were obese.

For patients treated with a non-carfilzomib-containing regimen in LOT 1, 15621 patients (81.0%) were white, 3013 patients (15.6%) were black, 326 patients (1.7%) were Hispanic, 253 patients (1.3%) were Asian, and 81 patients (0.4%) were North American native (Table 15-2.1). Overall, the mean (SD) age of patients treated with a non-carfilzomib-containing regimen in LOT 1 was 75.7 (8.3) years; 50.1% of patients

were women, the most common medical history was hypertension (79.0%), and 19.2% of patients were obese.

For patients treated with a non-carfilzomib-containing regimen in LOT 2, 6403 patients (82.5%) were white, 1110 patients (14.3%) were black, 116 patients (1.5%) were Hispanic, 103 patients (1.3%) were Asian, and 28 patients (0.4%) were North American native (Table 15-2.1). Overall, the mean (SD) age of patients treated with a non-carfilzomib-containing regimen in LOT 2 was 75.7 (8.0) years; 51.3% of patients were women, the most common medical history was hypertension (79.1%), and 19.2% of patients were obese.

For patients treated with a non-carfilzomib-containing regimen in LOT 3, 2645 patients (83.9%) were white, 419 patients (13.3%) were black, 46 patients (1.5%) were Hispanic, 31 patients (1.0%) were Asian, and 11 patients (0.4%) were North American native (Table 15-2.1). Overall, the mean (SD) age of patients treated with a non-carfilzomib-containing regimen in LOT 3 was 75.3 (7.9) years; 51.8% of patients were women, the most common medical history was hypertension (76.4%), and 19.3% of patients were obese.

10.2.2 Optum

For the Optum database, 70 patients (74.5%) were white, 11 patients (11.7%) were black, 9 patients (9.6%) were Hispanic, and 4 patients (4.3%) were Asian who were treated with a carfilzomib-containing regimen in LOT 1 (Table 15-2.7). Overall, the mean (SD) age of patients treated with a carfilzomib-containing regimen in LOT 1 was 65.1 (9.9) years; 57.5% of patients were men, the most common medical history was hypertension (47.9%), and 20.2% of patients were obese.

For patients treated with a carfilzomib-containing regimen in LOT 2, 107 (70.9%) of patients were white, 23 patients (15.2%) were black, 15 patients (9.9%) were Hispanic, and 6 patients were Asian (4.0%) (Table 15-2.7). Overall, the mean (SD) age of patients treated with a carfilzomib-containing regimen in LOT 2 was 68.0 (11.0) years; 57.0% of patients were men, the most common medical history was hypertension (63.6%), and 24.5% of patients were obese.

For patients treated with a carfilzomib-containing regimen in LOT 3, 88 (77.2%) of patients were white, 14 patients (12.3%) were black, 10 patients (8.8%) were Hispanic, and 2 patients were Asian (1.8%) (Table 15-2.7). Overall, the mean (SD) age of patients

treated with a carfilzomib-containing regimen in LOT 3 was 69.1 (10.8) years; 55.3% of patients were men, the most common medical history was hypertension (63.2%), and 21.1% of patients were obese.

For patients treated with a non-carfilzomib-containing regimen in LOT 1, 4053 patients (70.8%) were white, 959 patients (16.8%) were black, 570 patients (10.0%) were Hispanic, and 144 patients (2.5%) were Asian (Table 15-2.7). Overall, the mean (SD) age of patients treated with a non-carfilzomib-containing regimen in LOT 1 was 70.6 (10.9) years; 53.1% of patients were men, the most common medical history was hypertension (69.1%), and 19.7% of patients were obese.

For patients treated with a non-carfilzomib-containing regimen in LOT 2, 1858 patients (70.1%) were white, 445 patients (16.8%) were black, 283 patients (10.7%) were Hispanic, 64 patients (2.4%) were Asian (Table 15-2.7). Overall, the mean (SD) age of patients treated with a non-carfilzomib-containing regimen in LOT 2 was 70.0 (11.0) years; 53.7% of patients were men, the most common medical history was hypertension (66.3%), and 18.5% of patients were obese.

For patients treated with a non-carfilzomib-containing regimen in LOT 3, 918 (71.2%) of patients were white, 218 patients (16.9%) were black, 126 patients (9.8%) were Hispanic, and 28 patients were Asian (2.2%) (Table 15-2.7). Overall, the mean (SD) age of patients treated with a non-carfilzomib-containing regimen in LOT 3 was 69.7 (10.9) years; 55.0% of patients were men, the most common medical history was hypertension (65.3%), and 17.4% of patients were obese.

10.2.3 Humana

For the Humana database, 26 patients (70.3%) were white, 10 patients (27.0%) were black, and < 10 patients were of another race/ethnicity who were treated with a carfilzomib-containing regimen in LOT 1 (Table 15-2.12). Overall, the mean (SD) age of patients treated with a carfilzomib-containing regimen in LOT 1 was 68.2 (6.9) years; 51.4% of patients were men, the most common medical history was hypertension (70.3%), and < 10 patients were obese.

For patients treated with a carfilzomib-containing regimen in LOT 2, 142 (70.6%) of patients were white, 54 patients (26.9%) were black, and < 10 patients were of another race/ethnicity (Table 15-2.12). Overall, the mean (SD) age of patients treated with a carfilzomib-containing regimen in LOT 2 was 72.6 (6.9) years; 66.7% of patients were

men, the most common medical history was hypertension (80.6%), and 27.9% of patients were obese.

For patients treated with a carfilzomib-containing regimen in LOT 3, 81 (77.1%) of patients were white, 21 patients (20.0%) were black, and < 10 patients were of another race/ethnicity (Table 15-2.12). Overall, the mean (SD) age of patients treated with a carfilzomib-containing regimen in LOT 3 was 74.1 (6.9) years; 61.0% of patients were men, the most common medical history was hypertension (75.2%), and 19.0% of patients were obese.

For patients treated with a non-carfilzomib-containing regimen in LOT 1, 2575 patients (68.7%) were white, 1039 patients (27.7%) were black, and 135 patients (3.6%) were of another race/ethnicity (Table 15-2.12). Overall, the mean (SD) age of patients treated with a non-carfilzomib-containing regimen in LOT 1 was 74.0 (7.4) years; 54.9% of patients were men, the most common medical history was hypertension (80.1%), and 29.0% of patients were obese.

For patients treated with a non-carfilzomib-containing regimen in LOT 2, 893 patients (69.1%) were white, 355 patients (27.5%) were black, and 45 patients (3.5%) were of another race/ethnicity (Table 15-2.12). Overall, the mean (SD) age of patients treated with a non-carfilzomib-containing regimen in LOT 2 was 74.1 (7.4) years; 53.4% of patients were men, the most common medical history was hypertension (76.9%), and 29.2% of patients were obese.

For patients treated with a non-carfilzomib-containing regimen in LOT 3, 398 patients (68.7%) were white, 159 patients (27.5%) were black, and 22 patients (3.8%) were of another race/ethnicity (Table 15-2.12). Overall, the mean (SD) age of patients treated with a non-carfilzomib-containing regimen in LOT 3 was 74.4 (7.3) years; 54.2% of patients were men, the most common medical history was hypertension (78.2%), and 27.8% of patients were obese.

10.3 Main Results

10.3.1 Primary Objective

10.3.1.1 Medicare

For white patients, the incidence rate (95% CI) of cardiac failure was 14.47 (12.20, 17.04) per 100 patient-years for patients treated with carfilzomib-containing regimens and 10.73 (10.25, 11.22) per 100 patient-years for

patients treated with non-carfilzomib-containing regimens (Table 10-1). For black patients, the incidence rate (95% CI) of cardiac failure was 15.79 (10.12, 23.50) per 100 patient-years for patients treated with carfilzomib-containing regimens and 12.13 (10.94, 13.42) per 100 patient-years for patients treated with non-carfilzomib-containing regimens. Reporting the incidence rate in Asian, Hispanic, and North American native patients treated with carfilzomib-containing regimens was not done because of event counts of < 11 being suppressed as required by Centers for Medicare & Medicaid Services.

Table 10-1. Incidence Rate of Cardiac Failure of Patients with Multiple Myeloma by Race/Ethnicity Status in Medicare FFS (2013 to 2017) (All LOT)

	Carfilzomib-containing regimen				Non-carfilzomib-containing regimen			
Race	N	PY	Events	IR (95% CI)	N	PY	Events	IR (95% CI)
White	1800	995.02	144	14.47 (12.2, 17.04)	26328	17441.80	1871	10.73 (10.25, 11.22)
Black	281	151.95	24	15.79 (10.12, 23.5)	4771	3131.96	380	12.13 (10.94, 13.42)
Asian	26	15.33	*	* (*, *)	406	299.52	18	6.01 (3.56, 9.50)
Hispanic	31	14.74	*	* (*, *)	521	300.21	29	9.66 (6.47, 13.87)
North American native	*	*	*	* (*, *)	130	86.37	13	15.05 (8.01, 25.74)

FFS = fee-for-service; IR = incidence rate; LOT = line of therapy; PY = patient-years; * = values for cells with < 11 counts were suppressed
Source: Table 15-4.1 and table 15-4.2

10.3.1.2 Optum

For white patients, the incidence rate (95% CI) of cardiac failure was 7.28 (4.17, 11.89) per 100 patient-years for patients treated with carfilzomib-containing regimens and 8.43 (7.54, 9.38) per 100 patient-years for patients treated with non-carfilzomib-containing regimens (Table 10-2). For black patients, the incidence rate (95% CI) of cardiac failure was 8.9 (2.46, 23.76) per 100 patient-years for patients treated with carfilzomib-containing regimens and 11.52 (9.47, 13.88) per 100 patient-years for patients treated with non-carfilzomib-containing regimens.

Table 10-2. Incidence Rate of Cardiac Failure of Patients with Multiple Myeloma by Race/Ethnicity Status in Optum Clinformatics Data Mart (2014 to 2018) (All LOT)

	Carfilzomib-containing regimen				Non-carfilzomib-containing regimen			
Race	N	PY	Events	IR (95% CI)	N	PY	Events	IR (95% CI)
White	429	192.26	14	7.28 (4.17, 11.89)	7918	3833.44	323	8.43 (7.54, 9.38)
Black	78	33.69	3	8.9 (2.46, 23.76)	1848	911.76	105	11.52 (9.47, 13.88)
Other	71	29.85	3	10.05 (2.78, 26.82)	1386	670.24	45	6.71 (4.96, 8.9)

IR = incidence rate; LOT = line of therapy; PY = patient-years
Source: Table 15-4.3 and Table 15-4.4

10.3.1.3 Humana

For white patients, the incidence rate (95% CI) of cardiac failure was 8.74 (4.99, 14.19) per 100 patient-years for patients treated with carfilzomib-containing regimens and 8.10 (7.07, 9.23) per 100 patient-years for patients treated with non-carfilzomib-containing regimens (Table 10-3). For black patients, the incidence rate (95% CI) of cardiac failure was 9.90 (3.97, 20.40) per 100 patient-years for patients treated with carfilzomib-containing regimens and 11.20 (9.34, 13.33) per 100 patient-years for patients treated with non-carfilzomib-containing regimens.

Table 10-3. Incidence Rate of Cardiac Failure of Patients with Multiple Myeloma by Race/Ethnicity Status in the Humana Integrated Databases (2013 to 2019) (All LOT)

	Carfilzomib-containing regimen				Non-carfilzomib-containing regimen			
Race	N	PY	Events	IR (95% CI)	N	PY	Events	IR (95% CI)
White	268	183.06	16	8.74 (4.99, 14.19)	2587	2765.32	224	8.10 (7.07, 9.23)
Black	85	70.70	7	9.90 (3.97, 20.40)	1042	1133.87	127	11.20 (9.34, 13.33)
Other	10	8.88	1	11.27 (0.15, 62.68)	136	146.34	13	8.88 (4.73, 15.19)

IR = incidence rate; LOT = line of therapy; PY = patient-years
Source: Table 15-4.5 and Table 15-4.6

10.3.2 Secondary Objective

10.3.2.1 Medicare

10.3.2.1.1 Baseline Demographics

White patients treated with a carfilzomib-containing regimen in LOT 1 had a mean (SD) age of 72.0 (6.4) years and 58.6% were men (Table 15-2.2). White patients treated with a carfilzomib-containing regimen in LOT 2 had a mean (SD) age of 74.4 (6.7) years and 57.3% were men. White patients treated with a carfilzomib-containing regimen in LOT 3 had a mean (SD) age of 75.5 (6.6) years and 55.5% were men. Black patients treated with a carfilzomib-containing regimen in LOT 1 had a mean (SD) age of 65.0 (6.5) years (Table 15-2.3); the sex of black patients in LOT 1 was not available because of event counts of < 11 being suppressed. Black patients treated with a carfilzomib-containing regimen in LOT 2 had a mean (SD) age of 71.1 (8.4) years and 57.6% were women. Black patients treated with a carfilzomib-containing regimen in LOT 3 had a mean (SD) age of 70.5 (9.5) years and 55.6% were women.

White patients treated with a non-carfilzomib-containing regimen in LOT 1 had a mean (SD) age of 76.2 (7.9) years and 51.5% were men (Table 15-2.2). White patients treated with a non-carfilzomib-containing regimen in LOT 2 had a mean (SD) age of 76.1 (7.7) years and 50.2% were men. White patients treated with a non-carfilzomib-containing regimen in LOT 3 had a mean (SD) age of 75.8 (7.6) years and 50.1% were men. Black patients treated with a non-carfilzomib-containing regimen in LOT 1 had a mean (SD) age of 73.2 (9.2) years and 58.4% were women (Table 15-2.3). Black patients treated with a non-carfilzomib-containing regimen in LOT 2 had a mean (SD) age of 73.4 (8.9) years and 59.9% were women. Black patients treated with a non-carfilzomib-containing regimen in LOT 3 had a mean (SD) age of 72.6 (8.8) years and 61.8% were women.

10.3.2.1.2 Cardiovascular Medical History

The most common (≥ 25% of patients) cardiovascular history in white patients treated with a carfilzomib-containing regimen in LOT 1 included hypertension (68.8%) and hypercholesterolemia (53.9%) (Table 15-2.2). The most common (≥ 25% of patients) cardiovascular history in white patients treated with a carfilzomib-containing regimen in LOT 2 included hypertension (72.8%), hypercholesterolemia (57.7%), dysrhythmias (29.0%), and diabetes (25.9%). The most common (≥ 25% of patients) cardiovascular history in white patients treated with a carfilzomib-containing regimen in LOT 3 included

hypertension (74.5%), hypercholesterolemia (55.8%), and dysrhythmias (32.2%), diabetes (27.7%), and ischemic heart disease (25.3%). The most common (≥ 25% of patients) cardiovascular history in black patients treated with a carfilzomib-containing regimen in LOT 1 included hypertension (86.7%) (Table 15-2.3). The most common (≥ 25% of patients) cardiovascular history in black patients treated with a carfilzomib-containing regimen in LOT 2 included hypertension (86.4%), hypercholesterolemia (53.0%), and diabetes (40.2%). The most common (≥ 25% of patients) cardiovascular history in black patients treated with a carfilzomib-containing regimen in LOT 3 included hypertension (86.4%), hypercholesterolemia (53.1%), diabetes (44.4%), dysrhythmias (33.3%), and ischemic heart disease (29.6%).

The most common (≥ 25% of patients) cardiovascular history in white patients treated with a non-carfilzomib-containing regimen in LOT 1 included hypertension (76.7%), hypercholesterolemia (62.2%), ischemic heart disease (29.2%), dysrhythmias (29.1%), and diabetes (28.0%) (Table 15-2.2). The most common (≥ 25% of patients) cardiovascular history in white patients treated with a non-carfilzomib-containing regimen in LOT 2 included hypertension (77.2%), hypercholesterolemia (59.9%), dysrhythmias (33.8%), ischemic heart disease (29.0%), and diabetes (28.1%). The most common (≥ 25% of patients) cardiovascular history in white patients treated with a non-carfilzomib-containing regimen in LOT 3 included hypertension (74.5%), hypercholesterolemia (56.5%), dysrhythmias (34.6%), and ischemic heart disease (29.5%), and diabetes (26.1%). The most common (≥ 25% of patients) cardiovascular history in black patients treated with a non-carfilzomib-containing regimen in LOT 1 included hypertension (90.2%), hypercholesterolemia (61.5%), diabetes (45.5%), and ischemic heart disease (26.1%) (Table 15-2.3). The most common (≥ 25% of patients) cardiovascular history in black patients treated with a non-carfilzomib-containing regimen in LOT 2 included hypertension (90.1%), hypercholesterolemia (58.0%), diabetes (45.4%), dysrhythmias (28.3%), and ischemic heart disease (27.6%). The most common (≥ 25% of patients) cardiovascular history in black patients treated with a non-carfilzomib-containing regimen in LOT 3 included hypertension (88.1%), hypercholesterolemia (53.0%), diabetes (43.2%), dysrhythmias (25.8%), ischemic heart disease (26.7%), and peripheral vascular disease (25.1%).

10.3.2.1.3 Lifestyle Risk Factors

White patients treated with a carfilzomib-containing regimen in LOT 1 had lifestyle risk factors that included obesity (18.8%) and smoking (8.6%) (Table 15-2.2). White patients treated with a carfilzomib-containing regimen in LOT 2 had lifestyle risk factors that included obesity (18.0%), smoking (11.0%), and alcohol consumption (3.4%). White patients treated with a carfilzomib-containing regimen in LOT 3 had lifestyle risk factors that included obesity (17.9%) and smoking (9.1%). Lifestyle risk factor data for black patients treated with a carfilzomib-containing regimen in LOT 1 was suppressed as there were < 10 patients per category (Table 15-2.3). Black patients treated with a carfilzomib-containing regimen in LOT 2 had lifestyle risk factors that included obesity (27.3%) and smoking (21.2%). Black patients treated with a carfilzomib-containing regimen in LOT 3 had lifestyle risk factors that included obesity (22.2%) and smoking (21.0%).

White patients treated with a non-carfilzomib-containing regimen in LOT 1 had lifestyle risk factors that included obesity (17.6%), smoking (9.6%), and alcohol consumption (2.3%) (Table 15-2.2). White patients treated with a non-carfilzomib-containing regimen in LOT 2 had lifestyle risk factors that included obesity (18.0%), smoking (9.6%), and alcohol consumption (2.1%). White patients treated with a non-carfilzomib-containing regimen in LOT 3 had lifestyle risk factors that included obesity (17.7%), smoking (8.3%), and alcohol consumption (1.9%). Black patients treated with a non-carfilzomib-containing regimen in LOT 1 had lifestyle risk factors that included obesity (27.8%), smoking (15.1%), and alcohol consumption (3.7%) (Table 15-2.3). Black patients treated with a non-carfilzomib-containing regimen in LOT 2 had lifestyle risk factors that included obesity (26.7%), smoking (14.0%), and alcohol consumption (2.9%). Black patients treated with a non-carfilzomib-containing regimen in LOT 3 had lifestyle risk factors that included obesity (30.0%), smoking (15.0%), and alcohol consumption (3.6%).

10.3.2.2 Optum

Baseline demographics, cardiovascular medical history, and lifestyle risk factors for white and black patients in the Optum database are provided in Table 15-2.8 and Table 15-2.10, respectively.

10.3.2.3 Humana

Baseline demographics, cardiovascular medical history, and lifestyle risk factors for white and black patients in the Humana database are provided in Table 15-2.13 and Table 15-2.14, respectively.

10.3.3 Exploratory Objectives

10.3.3.1 Medicare

After propensity score matching (Table 15-11.1 and Table 15-11.2), the hazard ratio (HR) (95% CI) of increased cardiac failure for white patients was 1.77 (1.31, 2.39) in the LOT 2 group and 1.50 (1.12, 2.01) in the combined LOT 3 and 4 group (Table 15-11.4). After propensity score matching (ref), the HR (95% CI) for black patients was 1.78 (0.87, 3.66) in the LOT 2 group and 1.45 (0.73, 2.89) in the combined LOT 3 and 4 group (Table 15-11.3).

10.3.3.2 Optum

Results for the exploratory objectives are provided in Table 15-11.5 and Table 15-11.6. As the standardized differences of the baseline characteristics between the carfilzomib and non-carfilzomib groups in Optum CDM database were not adequately balanced after propensity score matching and small sample size/many covariates would introduce statistical instability for a multivariate adjusted model, the comparative analysis was not performed.

10.3.3.3 Humana

Because of small sample sizes, all LOTs were combined for Humana. After propensity score matching (Table 15-11.7 and Table 15-11.8), the HR (95% CI) of increased cardiac failure for white patients was 1.44 (0.81, 2.56) and 1.23 (0.43, 3.51) for black patients (Table 15-11.9).

10.4 Other Analyses

10.4.1 Quantitative Bias Analysis

10.4.1.1 Medicare

A statistically significant association between carfilzomib treatment and the risk of hospitalization for cardiac failure during second-line therapy among white patients was observed (HR = 1.77 [95% CI: 1.31, 2.39]) (Table 15-11.4).

In the Medicare data, 7141 white patients with multiple myeloma started second-line therapy; of these, 738 patients (~10%) were exposed to carfilzomib-containing regimens. Thus, a prevalence of exposure (P_E) of 0.1 was applied in the sensitivity analysis.

Based on the observed prevalence of myeloma-related factors, other clinical comorbidities, and lifestyle risk factors in this study, a prevalence of unknown confounder (P_C) of 0.05, 0.1, 0.3, and 0.5 was assumed separately in the sensitivity analysis.

The analysis found all combinations of the association between the unknown confounder and the exposure (OR_{EC}) and the association between the confounder and the disease outcome (RR_{CD}) necessary for the observed estimate of the HR to become equal to 1. In other words, the relationship between OR_{EC} and RR_{CD} was plotted for a given apparent relative risk (ARR), the P_C, and the P_E. In Figure 15-11.1, all parameter combinations of OR_{EC} and RR_{CD} above and to the right of the curve with ARR = 1.77 (blue curve) would move the point estimate of the association to 1. That would require that strong risk factors that are fairly imbalanced between the carfilzomib and carfilzomib-free groups must be unmeasured and uncontrolled. Next, the sensitivity analysis was repeated using the lower end of the 95% CI (ARR = 1.31, green curve) to determine the combinations of OR_{EC} and RR_{CD} in which the 95% CI would cross the null. The different curves use different values of prevalence of the unknown confounder (P_C = 0.05, 0.1, 0.3, and 0.5).

For the observed HR point estimate of 1.77 to be fully explained by an unmeasured confounder, such confounder would need to have a strong association with carfilzomib treatment (OR_{EC}) or a strong association with the risk of hospitalization for cardiac failure (RR_{CD}). Similar results were observed for LOT 3 and 4 in the Medicare database (Figure 15-11.2).

10.4.1.2 Humana

A similar rule-out approach to sensitivity analysis was carried out for results in the Humana database. We observed ARR = 1.44 for white patients and ARR = 1.23 for black patients (Table 15-11.9). The areas to the right and above the curves (blue for white patients, green for black patients) give values of OR_{EC} and RR_{CD} that would make the association go away; ie, would move the ARR point estimate to 1 (the null) (Figure 15-11.3). We set the P_E to 0.25. For the P_C we considered 0.50, 0.25, and 0.10.

As found with Medicare data, for an unknown, unmeasured confounder to explain the observed association between carfilzomib treatment (exposure) and the risk of hospitalization for cardiac failure (outcome), we would need an extremely strong

association between such confounder and the exposure or between the confounder and the outcome.

10.5 Adverse Events/Adverse Reactions

This retrospective cohort study involved electronic healthcare records for patients with multiple myeloma treated with carfilzomib-containing or non-carfilzomib-containing regimen hospitalized because of cardiac failure in patients; therefore it was not feasible to make a causality assessment regarding carfilzomib at the individual case level.

11. DISCUSSION

11.1 Key Results

Results from this study showed that cardiac failure events in patients treated with a carfilzomib-containing regimen were generally slightly higher than in patients treated with a non-carfilzomib-containing regimen (Table 10-1, Table 10-2, and Table 10-3); consistent with existing knowledge. A higher rate of cardiac failure was observed in the Medicare database compared with Optum and Humana, reflective of the older-only population (≥ 65 years) in the Medicare database. In both the Medicare and Humana databases, similar rates of cardiac failure were reported in the white and black populations (Table 10-1 and Table 10-3). In the Optum database, similar rates of cardiac failure were observed in patients treated with a carfilzomib-containing and a non-carfilzomib-containing regimen within race/ethnicity and the confidence intervals between races overlap for patients treated with a carfilzomib-containing regimen (Table 10-2). Because of event counts of < 11 being suppressed, no data related to cardiac failure events was available for Asian, Hispanic, or North American native patients treated with a carfilzomib-containing regimen. After propensity score matching, the increased risk of cardiac failure in patients treated with a carfilzomib-containing regimen compared with patients treated with a non-carfilzomib-containing regimen was not different in white and black patients. Overall, the results of this study do not suggest a significant differential race/ethnicity effect for cardiac failure between white and black patients with multiple myeloma treated with a carfilzomib-containing regimen.

11.2 Limitations

The small sample sizes for detecting infrequent cardiac failure events was challenging. The original intent in this study was to use cardiac failure as the primary diagnosis position, but events were too few. Reporting the top 3 positions for cardiac failure hospitalizations increased the sensitivity and number of events. With small sample sizes, it is expected that each additional year of study may increase the sample size by 20%, but databases would still unlikely contain adequate results for Asian, Hispanic, or North American native patients. This study was descriptively designed and was not powered for race comparisons (eg, white vs black). Furthermore, residual confounding in comparative analysis may still exist with regards to disease severity as claims data do not contain all clinical data needed to fully characterize the severity of disease (eg, ventricular ejection fraction as baseline).

11.3 Interpretation

Overall, results from this observational study, which characterized the incidence rates of cardiac failure in patients with multiple myeloma treated with a carfilzomib-containing or non-carfilzomib-containing regimen, do not suggest a significant differential race/ethnicity effect for between white and black patients. Because of the small sample size of Asian, Hispanic, and North American native patients with multiple myeloma treated with a carfilzomib-containing regimen, no specific conclusions regarding the incidence of cardiac failure among Asian, Hispanic, and North American native patients compared with other race/ethnicities could be drawn.

11.4 Generalizability

Because the 3 databases used in this study contain over 120 000 US patient-lines with a multiple myeloma diagnosis during the prespecified dates and the use of limited exclusion criteria, this study result can be considered representative of cardiac failure events in patients treated with a carfilzomib-containing regimen. With the exception of age in the Medicare database and a higher incidence of hypertension in the black population, no significant differences were observed between demographics, clinical characteristics, and lifestyle risk factors in this study.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSION

Results from this observational study suggest that the incidence rates of cardiac failure do not differ between white and black patients with multiple myeloma treated with a carfilzomib-containing regimen; though comparisons with the Asian, Hispanic, and North American native populations were not available because of limited data. The overall incidence of cardiac failure events was slightly higher in patients treated with carfilzomib-containing regimens, consistent with existing knowledge. The benefit:risk profile of carfilzomib remains favourable in the currently approved indications. No new safety signal was identified from this study.

14. REFERENCES

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15. SUMMARY TABLES, FIGURES, AND LISTINGS

Table 15-1.1. Cohort attrition table - Medicare FFS (2013-2017)

Criterion	Include/exclude	Total population	Patient Count excluded	Remaining n
1	Include	MM diagnosis with index date between 01 January 2013 and 30 June 2017	--	84144
2	Include	Race/ethnicity data available (White, Black, Asian, Hispanic, North American Native)	2570	81574
3	Include	Age ≥ 18 years at index MM diagnosis	0	81574
4	Include	Continuously enrolled in Medicare Parts A, B, and D coverage without enrollment in a Medicare Advantage program any time during the 12 months prior to the disease index date (including the index date)	50036	31538
5	Exclude	Received chemotherapy or radiotherapy in 12 months prior to disease index	4510	27189
6	Exclude	Evidence of BMT/SCT or received drug treatment specific to MM in the 12 months prior to MM index date (not including dexamethasone and prednisone because they are not MM-specific)	333	26861
7	Exclude	Missing census region	80	26785
8	Exclude	Patients with evidence of having received multiple PIs (bortezomib, carfilzomib, and ixazomib) on the same day	32	26753
9	Include	Continuously enrolled in Medicare Parts A, B, and D coverage without enrollment in a Medicare Advantage program any time from MM index date to the first LOT index during the study period.	6400	20353
10	Include	First LOT index between 01 January 2013 and 30 September 2017	157	20196
11	Exclude	Evidence of renal transplant, history of renal transplant, or dialysis before the first LOT index (first LOT study cohort)	756	19440
12	Include	Initiated second LOT with index date on or before 30 September 2017 and continuously enrolled in Medicare Parts A, B and D without enrollment in a Medicare Advantage program any time before second LOT index	10548	8892
13	Exclude	Evidence of renal transplant, history of renal transplant, or dialysis before the second LOT index (second LOT study cohort)	230	8662
14	Include	Initiated third LOT with index date on or before 30 September 2017 and continuously enrolled in Medicare Parts A, B and D without enrollment in a Medicare Advantage program any time before third LOT index	4836	3826
15	Exclude	Evidence of renal transplant, history of renal transplant, or dialysis before the third LOT index (third LOT study cohort)	36	3790
16	Include	Initiated fourth LOT with index date on or before 30 September 2017 and continuously enrolled in Medicare Parts A, B and D without enrollment in a Medicare Advantage program any time before fourth LOT index	2238	1552
17	Exclude	Evidence of renal transplant, history of renal transplant, or dialysis before the fourth LOT index (fourth LOT study cohort)	19	1533
18	Include	Initiated fifth LOT with index date on or before 30 September 2017 and continuously enrolled in Medicare Parts A, B and D without enrollment in a Medicare Advantage program and without evidence of evidence of renal transplant, history of renal transplant, or dialysis any time before fifth LOT index (fifth LOT study cohort)	929	604

Footnotes: FFS = Fee for service, n = patient count, LOT = Line of therapy, MM = Multiple myeloma, BMT/SCT = Bone marrow transplant/stem cell transplant, PI = proteasome inhibitor

Table 15-1.1. Cohort attrition table - Medicare FFS (2013-2017)

Criterion	Include/exclude	Total population	Patient Count excluded	Remaining n
19	Include	Initiated sixth LOT with index date on or before 30 September 2017 and continuously enrolled in Medicare Parts A, B and D without enrollment in a Medicare Advantage program and without evidence of evidence of renal transplant, history of renal transplant, or dialysis any time before sixth LOT index (sixth LOT study cohort)	399	205
20	Include	Initiated seventh LOT with index date on or before 30 September 2017 and continuously enrolled in Medicare Parts A, B and D without enrollment in a Medicare Advantage program and without evidence of evidence of renal transplant, history of renal transplant, or dialysis any time before seventh LOT index (seventh LOT study cohort)	142	63

Footnotes: FFS = Fee for service, n = patient count, LOT = Line of therapy, MM = Multiple myeloma, BMT/SCT = Bone marrow transplant/stem cell transplant, PI = proteasome inhibitor Page 2 of 2

Table 15-1.2. Cohort Attrition Table-Optum Clinformatics Ddata Mart (2013-2019)

Criterion	Include/exclude	Total population	Patient Count excluded	Remaining n
1	INCLUDE	MM diagnosis with index date between 01 January 2013 and 3 months prior to the latest data cut	.	22686
2	INCLUDE	Race/ethnicity data available (White, Black, Asian, Hispanic)	3361	19325
3	INCLUDE	Age GE 18 years at index MM diagnosis	23	19302
4	INCLUDE	Continuously enrolled in medical and pharmacy insurance coverage for 12 months prior to disease index (45-day gap permitted)	6697	12605
5	EXCLUDE	Received chemotherapy or radiotherapy in 12 months prior to disease index	2835	9770
6	EXCLUDE	Evidence of BMT/SCT or received drug treatment specific to MM in the 12 months prior to MM index date (not including dexamethasone and prednisone because they are not MM-specific)	45	9725
7	EXCLUDE	Missing census region	53	9672
8	EXCLUDE	Patients with evidence of having received multiple PIs (bortezomib, carfilzomib, and ixazomib) on the same day	207	9465
9	INCLUDE	Continuously enrolled in medical and pharmacy insurance coverage from MM index date to the first LOT index during the study period.	3580	5885
10	INCLUDE	First LOT index between 01 Janauary 2013 and 31 March 2019	.	5885
11	EXCLUDE	Evidence of renal transplant, history of renal transplant, or dialysis before the first observed LOT index.	65	5820
12	INCLUDE	Initiated second LOT with index date at least 3 months prior to the latest data cut and continuously enrolled any time before second LOT index (45-day gap pre-disease index permitted)	2979	2841
13	EXCLUDE	Evidence of renal transplant, history of renal transplant, or dialysis before the second LOT index.	40	2801
14	INCLUDE	Initiated third LOT with index date at least 3 months prior to the latest data cut and continuously enrolled any time before third LOT index (45-day gap pre-disease index permitted)	1385	1416
15	EXCLUDE	Evidence of renal transplant, history of renal transplant, or dialysis before the third LOT index	12	1404
16	INCLUDE	Initiated fourth LOT with index date at least 3 months prior to the latest data cut and continuously enrolled any time before fourth LOT index (45-day gap pre-disease index permitted).	671	733
17	EXCLUDE	Evidence of renal transplant, history of renal transplant, or dialysis before the fourth LOT index	3	730

Footnotes: n = patient count, LOT = Line of therapy, MM = Multiple myeloma, BMT/SCT = Bone marrow transplant/stem cell transplant, PI = proteasome inhibitor

Table 15-1.3. Cohort attrition table - Humana Integrated Databases (2013-2019)

Criterion	Include/exclude	Total population	Patient Count excluded	Remaining n
1	Include	MM diagnosis with index date between 01 January 2013 and 31 March 2019	--	14,578
2	Include	Race/ethnicity data available (White, Black, Asian, Hispanic)	1,449	13,129
3	Include	Age ≥ 18 and <90 years at index MM diagnosis	255	12,874
4	Include	Continuously enrolled in medical and pharmacy MAPD insurance coverage for 12 months prior to disease index (45-day gap permitted)	5,265	7,609
5	Exclude	Received chemotherapy or radiotherapy in 12 months prior to disease index	1,468	6,141
6	Exclude	Evidence of BMT/SCT or received drug treatment specific to MM in the 12 months prior to MM index date (not including dexamethasone and prednisone because they are not MM-specific)	595	5,546
7	Exclude	Missing census region	0	5,546
8	Exclude	Patients with evidence of having received multiple PIs (bortezomib, carfilzomib, and ixazomib) on the same day	3	5,543
9	Include	First LOT index between 01 Janauary 2013 and 31 March 2019	1,595	3,948
10	Include	Continuously enrolled in medical and pharmacy MAPD insurance coverage from MM index date to the first LOT index during the study period.	18	3,930
11	Exclude	Evidence of renal transplant, history of renal transplant, or dialysis before the first observed LOT index	139	3,791
18	Exclude	Age ≤ 18 or >90 years at index MM treatment	5	3,786

Footnotes: n = patient count, LOT = Line of therapy, MM = Multiple myeloma, BMT/SCT = Bone marrow transplant/stem cell transplant, PI = proteasome inhibitor

Table 15-2.1. Baseline characteristics of treated MM patients in Medicare FFS all races combined (2013-2017)

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib containing 146(100.00)	Carfilzomib free 19294(100.00)	Carfilzomib containing 902(100.00)	Carfilzomib free 7760(100.00)	Carfilzomib containing 638(100.00)	Carfilzomib free 3152(100.00)	Carfilzomib containing 309(100.00)	Carfilzomib free 1224(100.00)
Race/ethnicity - n(%)								
White	128(87.67)	15621(80.96)	738(81.82)	6403(82.51)	541(84.80)	2645(83.91)	264(85.44)	1030(84.15)
Black	15(10.27)	3013(15.62)	132(14.63)	1110(14.30)	81(12.70)	419(13.29)	38(12.30)	152(12.42)
Asian	*	253(1.31)	>10	103(1.33)	*	31(0.98)	*	>10
Hispanic	*	326(1.69)	17(1.88)	116(1.49)	*	46(1.46)	*	24(1.96)
North American native	0	81(0.42)	*	28(0.36)	*	11(0.35)	0	*
Age at treatment index (year)								
Mean (Stdev)	71.12(6.77)	75.70(8.27)	73.82(7.16)	75.66(8.01)	74.77(7.23)	75.33(7.90)	74.75(7.67)	75.25(7.62)
Median (IQR25, 75)	70.39 (67.32,74.74)	75.54 (70.37,81.45)	73.51 (69.73,78.22)	75.37 (70.54,81.19)	74.61 (70.50,78.95)	74.83 (70.45,80.66)	74.41 (70.45,78.85)	74.96 (70.70,79.76)
Age at treatment index - n(%)								
18-65 years	19(13.01)	1333(6.91)	70(7.76)	502(6.47)	49(7.68)	227(7.20)	26(8.41)	83(6.78)
66-69 years	51(34.93)	3156(16.36)	174(19.29)	1220(15.72)	96(15.05)	469(14.88)	39(12.62)	170(13.89)
70-74 years	40(27.40)	4657(24.14)	287(31.82)	2042(26.31)	190(29.78)	900(28.55)	97(31.39)	361(29.49)
75-79 years	23(15.75)	4299(22.28)	213(23.61)	1725(22.23)	164(25.71)	691(21.92)	79(25.57)	311(25.41)
80+ years	13(8.90)	5849(30.32)	158(17.52)	2271(29.27)	139(21.79)	865(27.44)	68(22.01)	299(24.43)
Sex- n(%)								
Female	63(43.15)	9657(50.05)	404(44.79)	3979(51.28)	292(45.77)	1632(51.78)	161(52.10)	631(51.55)
Male	83(56.85)	9637(49.95)	498(55.21)	3781(48.72)	346(54.23)	1520(48.22)	148(47.90)	593(48.45)
Months from index MM diagnosis to treatment index								
Mean (Stdev)	3.09(5.13)	2.25(4.98)	11.98(8.82)	13.62(9.18)	19.96(10.07)	21.60(10.46)	25.65(10.30)	27.99(10.35)
Median (IQR25, 75)	1.05(0.60,3.00)	0.77(0.37,1.70)	9.30(5.70,15.33)	10.77(7.03,17.37)	17.78(11.97,25.60)	19.40(13.40,27.93)	23.20(17.60,32.53)	26.83(19.82,35.75)
Calendar year of treatment index - n(%)								
2013	*	3527(18.28)	12(1.33)	358(4.61)	*	17(0.54)	0	0

Footnotes: FFS = Fee for service, n = patient count, LOT = Line of therapy, MM = Multiple myeloma; Stdev = standard deviation; IQR = interquartile range

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Table 15-2.1. Baseline characteristics of treated MM patients in Medicare FFS all races combined (2013-2017)

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	146(100.00)	19294(100.00)	902(100.00)	7760(100.00)	638(100.00)	3152(100.00)	309(100.00)	1224(100.00)
2014	>10	4535(23.50)	115(12.75)	1414(18.22)	>10	301(9.55)	20(6.47)	44(3.59)
2015	27(18.49)	4871(25.25)	255(28.27)	1908(24.59)	199(31.19)	683(21.67)	89(28.80)	180(14.71)
2016	77(52.74)	5301(27.47)	329(36.47)	2331(30.04)	220(34.48)	1094(34.71)	107(34.63)	499(40.77)
2017	22(15.07)	1060(5.49)	191(21.18)	1749(22.54)	145(22.73)	1057(33.53)	93(30.10)	501(40.93)
Census region - n(%)								
Northeast	38(26.03)	3826(19.83)	152(16.85)	1547(19.94)	122(19.12)	629(19.96)	53(17.15)	260(21.24)
Midwest	36(24.66)	4695(24.33)	229(25.39)	1828(23.56)	128(20.06)	745(23.64)	78(25.24)	270(22.06)
South	48(32.88)	7681(39.81)	349(38.69)	3141(40.48)	268(42.01)	1260(39.97)	122(39.48)	494(40.36)
West	24(16.44)	3092(16.03)	172(19.07)	1244(16.03)	120(18.81)	518(16.43)	56(18.12)	200(16.34)
Myeloma-related factors - n(%)								
Renal disease	35(23.97)	6552(33.96)	357(39.58)	3007(38.75)	265(41.54)	1163(36.90)	109(35.28)	494(40.36)
Hypercalcemia	22(15.07)	2572(13.33)	159(17.63)	992(12.78)	84(13.17)	295(9.36)	32(10.36)	91(7.43)
Anemia	82(56.16)	11778(61.04)	695(77.05)	5539(71.38)	473(74.14)	2231(70.78)	231(74.76)	859(70.18)
Stem cell transplant (from MM index to LOT index)	*	*	55(6.10)	887(11.43)	90(14.11)	745(23.64)	88(28.48)	334(27.29)
Other clinical comorbidities - n(%)								
Cardiovascular history								
Hypertension	103(70.55)	15232(78.95)	677(75.06)	6141(79.14)	485(76.02)	2408(76.40)	214(69.26)	938(76.63)
Heart failure	15(10.27)	3305(17.13)	144(15.96)	1546(19.92)	105(16.46)	646(20.49)	55(17.80)	255(20.83)
Cardiomyopathy	*	988(5.12)	43(4.77)	475(6.12)	31(4.86)	198(6.28)	15(4.85)	92(7.52)
Dysrhythmias	26(17.81)	5412(28.05)	247(27.38)	2537(32.69)	203(31.82)	1047(33.22)	97(31.39)	458(37.42)
Ischemic heart disease	29(19.86)	5527(28.65)	215(23.84)	2235(28.80)	164(25.71)	911(28.90)	81(26.21)	355(29.00)
Peripheral vascular disease	23(15.75)	3315(17.18)	183(20.29)	1663(21.43)	135(21.16)	698(22.14)	78(25.24)	283(23.12)
Hypercholesterolemia	80(54.79)	11992(62.15)	517(57.32)	4631(59.68)	351(55.02)	1766(56.03)	162(52.43)	660(53.92)
Chronic obstructive pulmonary disease	24(16.44)	3617(18.75)	185(20.51)	1640(21.13)	101(15.83)	679(21.54)	65(21.04)	293(23.94)

Footnotes: FFS = Fee for service, n = patient count, LOT = Line of therapy, MM = Multiple myeloma; Stdev = standard deviation; IQR = interquartile range

Table 15-2.1. Baseline characteristics of treated MM patients in Medicare FFS all races combined (2013-2017)

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	146(100.00)	19294(100.00)	902(100.00)	7760(100.00)	638(100.00)	3152(100.00)	309(100.00)	1224(100.00)
Diabetes	34(23.29)	6057(31.39)	254(28.16)	2423(31.22)	193(30.25)	918(29.12)	90(29.13)	365(29.82)
Liver disease	*	859(4.45)	43(4.77)	368(4.74)	31(4.86)	120(3.81)	*	40(3.27)
Gastrointestinal bleeding	*	1933(10.02)	93(10.31)	754(9.72)	56(8.78)	249(7.90)	27(8.74)	88(7.19)
Inflammatory diseases	13(8.90)	1283(6.65)	67(7.43)	563(7.26)	44(6.90)	234(7.42)	25(8.09)	84(6.86)
Lifestyle risk factors - n(%)								
Smoking	14(9.59)	2008(10.41)	112(12.42)	788(10.15)	67(10.50)	285(9.04)	23(7.44)	104(8.50)
Obesity	29(19.86)	3702(19.19)	172(19.07)	1490(19.20)	117(18.34)	609(19.32)	53(17.15)	235(19.20)
Alcohol consumption	*	501(2.60)	32(3.55)	173(2.23)	12(1.88)	65(2.06)	*	20(1.63)
Treatments and concomitant medications - n(%)								
Antihypertensive	100(68.49)	15640(81.06)	713(79.05)	6379(82.20)	510(79.94)	2534(80.39)	233(75.40)	977(79.82)
Cholesterol lowering medications	70(47.95)	10691(55.41)	453(50.22)	4031(51.95)	305(47.81)	1560(49.49)	145(46.93)	559(45.67)
Antidiabetics	28(19.18)	4451(23.07)	186(20.62)	1761(22.69)	150(23.51)	673(21.35)	71(22.98)	279(22.79)

Footnotes: FFS = Fee for service, n = patient count, LOT = Line of therapy, MM = Multiple myeloma; Stdev = standard deviation; IQR = interquartile range

Table 15-2.2. Baseline characteristics of treated MM patients in Medicare FFS (2013-2017), white

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	128(100.00)	15621(100.00)	738(100.00)	6403(100.00)	541(100.00)	2645(100.00)	264(100.00)	1030(100.00)
Age at treatment index (year)								
Mean (Stdev)	71.98(6.43)	76.21(7.91)	74.38(6.72)	76.09(7.69)	75.51(6.57)	75.77(7.56)	75.04(7.51)	75.70(7.17)
Median (IQR25, 75)	71.75 (67.73,75.32)	75.97 (70.84,81.75)	73.76 (70.13,78.70)	75.70 (70.92,81.40)	75.08 (71.68,79.34)	75.17 (70.81,80.87)	74.36 (70.84,78.89)	75.10 (71.12,80.07)
Age at treatment index - n(%)								
18-65 years	*	766(4.90)	36(4.88)	294(4.59)	23(4.25)	134(5.07)	16(6.06)	48(4.66)
66-69 years	44(34.38)	2512(16.08)	140(18.97)	996(15.56)	81(14.97)	394(14.90)	34(12.88)	145(14.08)
70-74 years	39(30.47)	3822(24.47)	246(33.33)	1720(26.86)	165(30.50)	772(29.19)	89(33.71)	313(30.39)
75-79 years	22(17.19)	3574(22.88)	179(24.25)	1459(22.79)	148(27.36)	597(22.57)	66(25.00)	263(25.53)
80+ years	>10	4947(31.67)	137(18.56)	1934(30.20)	124(22.92)	748(28.28)	59(22.35)	261(25.34)
Sex - n(%)								
Female	53(41.41)	7574(48.49)	315(42.68)	3189(49.80)	241(44.55)	1321(49.94)	138(52.27)	511(49.61)
Male	75(58.59)	8047(51.51)	423(57.32)	3214(50.20)	300(55.45)	1324(50.06)	126(47.73)	519(50.39)
Months from index MM diagnosis to treatment index								
Mean (Stdev)	3.25(5.40)	2.24(5.01)	11.84(8.58)	13.56(9.18)	20.18(10.03)	21.48(10.48)	25.67(10.25)	27.82(10.27)
Median (IQR25, 75)	1.02 (0.53,3.78)	0.73 (0.33,1.67)	9.22 (5.60,15.47)	10.63 (6.97,17.30)	18.13 (12.30,25.87)	19.20 (13.30,27.73)	23.17 (17.83,32.57)	26.70 (19.73,35.47)
Calendar year of treatment index - n(%)								
2013	*	2813(18.01)	*	285(4.45)	*	17(0.64)	0	0
2014	>10	3637(23.28)	>10	1166(18.21)	>10	258(9.75)	17(6.44)	41(3.98)
2015	25(19.53)	3967(25.40)	212(28.73)	1575(24.60)	162(29.94)	575(21.74)	74(28.03)	156(15.15)
2016	68(53.13)	4345(27.82)	267(36.18)	1916(29.92)	197(36.41)	898(33.95)	93(35.23)	408(39.61)
2017	18(14.06)	859(5.50)	155(21.00)	1461(22.82)	120(22.18)	897(33.91)	80(30.30)	425(41.26)
Census region - n(%)								
Northeast	32(25.00)	3223(20.63)	130(17.62)	1310(20.46)	106(19.59)	538(20.34)	49(18.56)	222(21.55)

Footnotes: FFS = Fee for service, n = patient count, LOT = Line of therapy, MM = Multiple myeloma; Stdev = standard deviation; IQR = interquartile range

Table 15-2.2. Baseline characteristics of treated MM patients in Medicare FFS (2013-2017), white

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	128(100.00)	15621(100.00)	738(100.00)	6403(100.00)	541(100.00)	2645(100.00)	264(100.00)	1030(100.00)
Midwest	32(25.00)	4097(26.23)	201(27.24)	1621(25.32)	113(20.89)	671(25.37)	69(26.14)	245(23.79)
South	42(32.81)	5664(36.26)	259(35.09)	2385(37.25)	219(40.48)	973(36.79)	96(36.36)	391(37.96)
West	22(17.19)	2637(16.88)	148(20.05)	1087(16.98)	103(19.04)	463(17.50)	50(18.94)	172(16.70)
Myeloma-related factors - n(%)								
Renal disease	30(23.44)	4949(31.68)	283(38.35)	2396(37.42)	222(41.04)	943(35.65)	89(33.71)	412(40.00)
Hypercalcemia	18(14.06)	1985(12.71)	125(16.94)	805(12.57)	76(14.05)	244(9.22)	27(10.23)	71(6.89)
Anemia	71(55.47)	9171(58.71)	563(76.29)	4503(70.33)	400(73.94)	1839(69.53)	195(73.86)	714(69.32)
Stem cell transplant (from MM index to LOT index)	*	*	44(5.96)	744(11.62)	81(14.97)	629(23.78)	76(28.79)	288(27.96)
Other clinical comorbidities - n(%)								
Cardiovascular history								
Hypertension	88(68.75)	11982(76.70)	537(72.76)	4943(77.20)	403(74.49)	1970(74.48)	173(65.53)	769(74.66)
Heart failure	*	2527(16.18)	112(15.18)	1237(19.32)	85(15.71)	528(19.96)	43(16.29)	215(20.87)
Cardiomyopathy	*	746(4.78)	34(4.61)	371(5.79)	25(4.62)	164(6.20)	*	79(7.67)
Dysrhythmias	24(18.75)	4546(29.10)	214(29.00)	2163(33.78)	174(32.16)	915(34.59)	82(31.06)	405(39.32)
Ischemic heart disease	23(17.97)	4553(29.15)	177(23.98)	1859(29.03)	137(25.32)	779(29.45)	73(27.65)	308(29.90)
Peripheral vascular disease	18(14.06)	2633(16.86)	150(20.33)	1342(20.96)	115(21.26)	577(21.81)	70(26.52)	241(23.40)
Hypercholesterolemia	69(53.91)	9720(62.22)	426(57.72)	3834(59.88)	302(55.82)	1493(56.45)	137(51.89)	561(54.47)
Chronic obstructive pulmonary disease	20(15.63)	2903(18.58)	148(20.05)	1339(20.91)	81(14.97)	573(21.66)	55(20.83)	244(23.69)
Diabetes	28(21.88)	4374(28.00)	191(25.88)	1798(28.08)	150(27.73)	690(26.09)	68(25.76)	279(27.09)
Liver disease	*	660(4.23)	37(5.01)	286(4.47)	26(4.81)	92(3.48)	*	32(3.11)
Gastrointestinal bleeding	*	1447(9.26)	71(9.62)	596(9.31)	43(7.95)	193(7.30)	24(9.09)	70(6.80)
Inflammatory diseases	12(9.38)	1010(6.47)	54(7.32)	448(7.00)	38(7.02)	190(7.18)	22(8.33)	70(6.80)
Lifestyle risk factors - n(%)								
Smoking	11(8.59)	1501(9.61)	81(10.98)	616(9.62)	49(9.06)	219(8.28)	17(6.44)	87(8.45)

Footnotes: FFS = Fee for service, n = patient count, LOT = Line of therapy, MM = Multiple myeloma; Stdev = standard deviation; IQR = interquartile range

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Table 15-2.2. Baseline characteristics of treated MM patients in Medicare FFS (2013-2017), white

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	128(100.00)	15621(100.00)	738(100.00)	6403(100.00)	541(100.00)	2645(100.00)	264(100.00)	1030(100.00)
Obesity	24(18.75)	2751(17.61)	133(18.02)	1152(17.99)	97(17.93)	469(17.73)	43(16.29)	186(18.06)
Alcohol consumption	*	365(2.34)	25(3.39)	132(2.06)	*	49(1.85)	*	13(1.26)
Treatments and concomitant medications - n(%)								
Antihypertensive (Combined)	86(67.19)	12460(79.76)	573(77.64)	5200(81.21)	427(78.93)	2099(79.36)	191(72.35)	814(79.03)
Anti chf/hypertension	61(47.66)	8279(53.00)	418(56.64)	3683(57.52)	294(54.34)	1453(54.93)	132(50.00)	552(53.59)
Anti IND/hypertension	54(42.19)	9304(59.56)	401(54.34)	3901(60.92)	320(59.15)	1557(58.87)	135(51.14)	614(59.61)
Antihypertensives	44(34.38)	5676(36.34)	222(30.08)	2192(34.23)	144(26.62)	789(29.83)	58(21.97)	272(26.41)
Cholesterol lowering medications	58(45.31)	8715(55.79)	385(52.17)	3387(52.90)	262(48.43)	1324(50.06)	125(47.35)	484(46.99)
Antidiabetics	22(17.19)	3219(20.61)	139(18.83)	1305(20.38)	122(22.55)	495(18.71)	53(20.08)	211(20.49)
Antihypertensive	100(68.49)	15640(81.06)	713(79.05)	6379(82.20)	510(79.94)	2534(80.39)	233(75.40)	977(79.82)
Cholesterol lowering medications	70(47.95)	10691(55.41)	453(50.22)	4031(51.95)	305(47.81)	1560(49.49)	145(46.93)	559(45.67)
Antidiabetics	28(19.18)	4451(23.07)	186(20.62)	1761(22.69)	150(23.51)	673(21.35)	71(22.98)	279(22.79)

Footnotes: FFS = Fee for service, n = patient count, LOT = Line of therapy, MM = Multiple myeloma; Stdev = standard deviation; IQR = interquartile range

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Table 15-2.3. Baseline characteristics of treated MM patients in Medicare FFS (2013-2017), black

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	15(100.00)	3013(100.00)	132(100.00)	1110(100.00)	81(100.00)	419(100.00)	38(100.00)	152(100.00)
Age at treatment index (year)								
Mean (Stdev)	65.01(6.49)	73.22(9.20)	71.11(8.41)	73.42(8.93)	70.51(9.50)	72.62(8.81)	72.86(8.22)	72.61(9.26)
Median (IQR25, 75)	66.43 (60.11,68.99)	73.47 (67.92,79.26)	71.81 (66.92,76.41)	73.57 (68.38,79.65)	71.35 (65.17,76.66)	73.09 (67.93,78.37)	74.26 (67.49,78.09)	73.61 (68.52,78.13)
Age at treatment index - n(%)								
18-65 years	*	486(16.13)	28(21.21)	175(15.77)	23(28.40)	79(18.85)	*	27(17.76)
66-69 years	*	550(18.25)	27(20.45)	184(16.58)	*	65(15.51)	*	21(13.82)
70-74 years	*	698(23.17)	32(24.24)	276(24.86)	22(27.16)	112(26.73)	*	41(26.97)
75-79 years	*	582(19.32)	30(22.73)	213(19.19)	13(16.05)	74(17.66)	12(31.58)	37(24.34)
80+ years	0	697(23.13)	15(11.36)	262(23.60)	>10	89(21.24)	*	26(17.11)
Sex - n(%)								
Female	*	1758(58.35)	76(57.58)	665(59.91)	45(55.56)	259(61.81)	20(52.63)	96(63.16)
Male	*	1255(41.65)	56(42.42)	445(40.09)	36(44.44)	160(38.19)	18(47.37)	56(36.84)
Months from index MM diagnosis to treatment index								
Mean (Stdev)	2.25(2.44)	2.28(4.65)	12.67(9.71)	13.83(9.28)	18.58(9.69)	22.27(10.47)	25.37(11.04)	28.27(10.67)
Median (IQR25, 75)	1.23 (0.83,1.73)	0.87 (0.43,1.97)	9.62 (6.30,14.28)	11.03 (7.20,17.47)	16.70 (11.23,23.67)	20.50 (14.10,29.17)	23.10 (16.97,32.43)	26.78 (20.28,36.13)
Calendar year of treatment index - n(%)								
2013	0	585(19.42)	*	64(5.77)	*	0	0	0
2014	*	728(24.16)	>10	201(18.11)	*	35(8.35)	*	*
2015	*	753(24.99)	32(24.24)	274(24.68)	35(43.21)	84(20.05)	14(36.84)	>10
2016	*	783(25.99)	52(39.39)	337(30.36)	15(18.52)	162(38.66)	13(34.21)	66(43.42)
2017	*	164(5.44)	28(21.21)	234(21.08)	20(24.69)	138(32.94)	*	65(42.76)
Census region - n(%)								
Northeast	*	480(15.93)	>10	193(17.39)	>10	70(16.71)	*	28(18.42)

Footnotes: FFS = Fee for service, n = patient count, LOT = Line of therapy, MM = Multiple myeloma; Stdev = standard deviation; IQR = interquartile range

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Table 15-2.3. Baseline characteristics of treated MM patients in Medicare FFS (2013-2017), black

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	15(100.00)	3013(100.00)	132(100.00)	1110(100.00)	81(100.00)	419(100.00)	38(100.00)	152(100.00)
Midwest	*	539(17.89)	24(18.18)	181(16.31)	15(18.52)	65(15.51)	*	>10
South	*	1817(60.31)	83(62.88)	673(60.63)	47(58.02)	256(61.10)	23(60.53)	91(59.87)
West	*	177(5.87)	*	63(5.68)	*	28(6.68)	*	*
Myeloma-related factors - n(%)								
Renal disease	*	1356(45.00)	62(46.97)	520(46.85)	39(48.15)	192(45.82)	19(50.00)	67(44.08)
Hypercalcemia	*	490(16.26)	27(20.45)	158(14.23)	*	44(10.50)	*	16(10.53)
Anemia	*	2138(70.96)	108(81.82)	854(76.94)	61(75.31)	324(77.33)	30(78.95)	113(74.34)
Stem cell transplant (from MM index to LOT index)	*	*	*	119(10.72)	*	103(24.58)	11(28.95)	39(25.66)
Other clinical comorbidities - n(%)								
Cardiovascular history								
Hypertension	13(86.67)	2718(90.21)	114(86.36)	1000(90.09)	70(86.42)	369(88.07)	35(92.11)	136(89.47)
Heart failure	*	652(21.64)	25(18.94)	266(23.96)	18(22.22)	104(24.82)	12(31.58)	31(20.39)
Cardiomyopathy	*	218(7.24)	*	96(8.65)	*	28(6.68)	*	*
Dysrhythmias	*	706(23.43)	29(21.97)	314(28.29)	27(33.33)	108(25.78)	15(39.47)	40(26.32)
Ischemic heart disease	*	785(26.05)	29(21.97)	306(27.57)	24(29.63)	112(26.73)	*	35(23.03)
Peripheral vascular disease	*	575(19.08)	27(20.45)	270(24.32)	18(22.22)	105(25.06)	*	33(21.71)
Hypercholesterolemia	*	1854(61.53)	70(53.03)	644(58.02)	43(53.09)	222(52.98)	21(55.26)	77(50.66)
Chronic obstructive pulmonary disease	*	592(19.65)	28(21.21)	258(23.24)	19(23.46)	88(21.00)	*	40(26.32)
Diabetes	*	1372(45.54)	53(40.15)	504(45.41)	36(44.44)	181(43.20)	18(47.37)	64(42.11)
Liver disease	*	150(4.98)	*	59(5.32)	*	20(4.77)	*	*
Gastrointestinal bleeding	*	394(13.08)	18(13.64)	132(11.89)	11(13.58)	48(11.46)	*	13(8.55)
Inflammatory diseases	*	219(7.27)	11(8.33)	89(8.02)	*	34(8.11)	*	12(7.89)
Lifestyle risk factors - n(%)								

Footnotes: FFS = Fee for service, n = patient count, LOT = Line of therapy, MM = Multiple myeloma; Stdev = standard deviation; IQR = interquartile range

Table 15-2.3. Baseline characteristics of treated MM patients in Medicare FFS (2013-2017), black

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	15(100.00)	3013(100.00)	132(100.00)	1110(100.00)	81(100.00)	419(100.00)	38(100.00)	152(100.00)
Smoking	*	454(15.07)	28(21.21)	155(13.96)	17(20.99)	63(15.04)	*	17(11.18)
Obesity	*	837(27.78)	36(27.27)	296(26.67)	18(22.22)	125(29.83)	*	44(28.95)
Alcohol consumption	*	112(3.72)	*	32(2.88)	*	15(3.58)	*	*
Treatments and concomitant medications - n(%)								
Antihypertensive (Combined)	13(86.67)	2661(88.32)	115(87.12)	989(89.10)	71(87.65)	367(87.59)	36(94.74)	131(86.18)
Anti chf/hypertension	*	1768(58.68)	79(59.85)	682(61.44)	48(59.26)	248(59.19)	21(55.26)	86(56.58)
Anti IND/hypertension	11(73.33)	2126(70.56)	96(72.73)	794(71.53)	60(74.07)	284(67.78)	31(81.58)	107(70.39)
Antihypertensives	*	1626(53.97)	60(45.45)	572(51.53)	32(39.51)	189(45.11)	12(31.58)	56(36.84)
Cholesterol lowering medications	11(73.33)	1600(53.10)	56(42.42)	513(46.22)	36(44.44)	194(46.30)	17(44.74)	60(39.47)
Antidiabetics	*	1000(33.19)	38(28.79)	362(32.61)	21(25.93)	140(33.41)	15(39.47)	50(32.89)
Antihypertensive	100(68.49)	15640(81.06)	713(79.05)	6379(82.20)	510(79.94)	2534(80.39)	233(75.40)	977(79.82)
Cholesterol lowering medications	70(47.95)	10691(55.41)	453(50.22)	4031(51.95)	305(47.81)	1560(49.49)	145(46.93)	559(45.67)
Antidiabetics	28(19.18)	4451(23.07)	186(20.62)	1761(22.69)	150(23.51)	673(21.35)	71(22.98)	279(22.79)

Footnotes: FFS = Fee for service, n = patient count, LOT = Line of therapy, MM = Multiple myeloma, BMT/SCT = Bone marrow transplant/stem cell transplant, PI = proteasome inhibitor

Table 15-2.4. Baseline characteristics of treated MM patients in Medicare FFS (2013-2017), Asian

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	*	253(100.00)	>10	103(100.00)	*	31(100.00)	*	>10
Age at treatment index (year)								
Mean (Stdev)	*	76.07(8.46)	72.05(8.06)	76.10(8.74)	*	76.64(10.89)	*	73.90(8.49)
Median (IQR25, 75)	*	75.78 (70.56,81.52)	73.87 (67.56,78.02)	76.48 (69.74,82.40)	*	77.07 (70.70,84.89)	*	73.08 (67.78,81.23)
Age at treatment index - n(%)								
18-65 years	0	17(6.72)	*	*	*	*	0	*
66-69 years	*	39(15.42)	*	19(18.45)	*	*	*	0
70-74 years	0	59(23.32)	*	18(17.48)	*	*	0	*
75-79 years	0	61(24.11)	*	24(23.30)	*	*	0	*
80+ years	0	77(30.43)	*	33(32.04)	*	12(38.71)	*	*
Sex - n(%)								
Female	0	129(50.99)	*	56(54.37)	*	18(58.06)	*	*
Male	*	124(49.01)	*	47(45.63)	*	13(41.94)	*	*
Months from index MM diagnosis to treatment index								
Mean (Stdev)	*	1.75(3.38)	11.83(9.44)	14.95(9.98)	*	22.33(10.93)	*	30.62(13.05)
Median (IQR25, 75)	*	0.80 (0.37,1.63)	6.67 (4.53,13.67)	12.67 (6.47,18.40)	*	21.50 (12.67,28.37)	*	29.87 (22.92,40.50)
Calendar year of treatment index - n(%)								
2013	0	57(22.53)	0	*	0	0	0	0
2014	0	63(24.90)	*	21(20.39)	*	*	*	0
2015	0	59(23.32)	*	23(22.33)	0	*	*	*
2016	*	60(23.72)	*	29(28.16)	*	*	*	*
2017	0	14(5.53)	*	27(26.21)	*	*	*	*
Census region - n(%)								
Northeast	0	47(18.58)	*	19(18.45)	*	*	0	*
Midwest	0	23(9.09)	*	11(10.68)	0	*	0	*

Footnotes: FFS = Fee for service, n = patient count, LOT = Line of therapy, MM = Multiple myeloma, Stdev = standard deviation, IQR = interquartile range

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Table 15-2.4. Baseline characteristics of treated MM patients in Medicare FFS (2013-2017), Asian

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	*	253(100.00)	>10	103(100.00)	*	31(100.00)	*	>10
South	0	51(20.16)	*	22(21.36)	*	*	*	*
West	*	132(52.17)	*	51(49.51)	*	13(41.94)	*	*
Myeloma-related factors - n(%)								
Renal disease	*	104(41.11)	*	40(38.83)	*	*	*	*
Hypercalcemia	*	33(13.04)	*	11(10.68)	*	*	*	*
Anemia	*	182(71.94)	*	76(73.79)	*	26(83.87)	*	>10
Stem cell transplant (from MM index to LOT index)	*	*	*	*	*	*	*	*
Other clinical comorbidities - n(%)								
Cardiovascular history								
Hypertension	*	205(81.03)	*	83(80.58)	*	23(74.19)	*	*
Heart failure	*	47(18.58)	*	20(19.42)	*	*	*	*
Cardiomyopathy	*	*	*	*	*	*	*	*
Dysrhythmias	*	60(23.72)	*	24(23.30)	*	12(38.71)	*	*
Ischemic heart disease	*	73(28.85)	*	29(28.16)	*	*	*	*
Peripheral vascular disease	*	38(15.02)	*	17(16.50)	*	*	*	*
Hypercholesterolemia	*	172(67.98)	*	70(67.96)	*	18(58.06)	*	*
Chronic obstructive pulmonary disease	*	35(13.83)	*	16(15.53)	*	*	*	*
Diabetes	*	118(46.64)	*	49(47.57)	*	14(45.16)	*	*
Liver disease	*	18(7.11)	*	11(10.68)	*	*	*	*
Gastrointestinal bleeding	*	41(16.21)	*	14(13.59)	*	*	*	*
Inflammatory diseases	*	23(9.09)	*	*	*	*	*	*
Lifestyle risk factors - n(%)								
Smoking	*	*	*	*	*	*	*	*
Obesity	*	16(6.32)	*	*	*	*	*	*

Footnotes: FFS = Fee for service, n = patient count, LOT = Line of therapy, MM = Multiple myeloma, Stdev = standard deviation, IQR = interquartile range

Table 15-2.4. Baseline characteristics of treated MM patients in Medicare FFS (2013-2017), Asian

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	*	253(100.00)	>10	103(100.00)	*	31(100.00)	*	>10
Alcohol consumption	*	*	*	*	*	*	*	*
Treatments and concomitant medications - n(%)								
Antihypertensive (Combined)	*	194(76.68)	*	78(75.73)	*	22(70.97)	*	*
Anti chf/hypertension	*	142(56.13)	*	55(53.40)	*	*	*	*
Anti IND/hypertension	*	159(62.85)	*	57(55.34)	*	18(58.06)	*	*
Antihypertensives	*	71(28.06)	*	23(22.33)	*	*	*	*
Cholesterol lowering medications	*	158(62.45)	*	67(65.05)	*	17(54.84)	*	*
Antidiabetics	*	83(32.81)	*	37(35.92)	*	*	*	*
Antihypertensive	100(68.49)	15640(81.06)	713(79.05)	6379(82.20)	510(79.94)	2534(80.39)	233(75.40)	977(79.82)
Cholesterol lowering medications	70(47.95)	10691(55.41)	453(50.22)	4031(51.95)	305(47.81)	1560(49.49)	145(46.93)	559(45.67)
Antidiabetics	28(19.18)	4451(23.07)	186(20.62)	1761(22.69)	150(23.51)	673(21.35)	71(22.98)	279(22.79)

Footnotes: FFS = Fee for service, n = patient count, LOT = Line of therapy, MM = Multiple myeloma, Stdev = standard deviation, IQR = interquartile range

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Table 15-2.5. Baseline characteristics of treated MM patients in Medicare FFS (2013-2017), Hispanic

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	*	326(100.00)	17(100.00)	116(100.00)	*	46(100.00)	*	24(100.00)
Age at treatment index (year)								
Mean (Stdev)	*	74.45(11.01)	71.09(8.68)	73.34(11.60)	*	73.26(11.16)	*	72.89(11.20)
Median (IQR25, 75)	*	75.37 (68.60,82.97)	71.04 (66.88,74.97)	74.27 (67.63,82.18)	*	73.65 (66.91,80.79)	*	74.69 (66.45,81.28)
Age at treatment index - n(%)								
18-65 years	*	53(16.26)	*	23(19.83)	*	*	*	*
66-69 years	0	44(13.50)	*	18(15.52)	*	*	0	*
70-74 years	0	62(19.02)	*	19(16.38)	*	*	0	*
75-79 years	0	57(17.48)	*	20(17.24)	*	*	*	*
80+ years	0	110(33.74)	*	36(31.03)	0	14(30.43)	0	*
Sex - n(%)								
Female	0	158(48.47)	*	56(48.28)	*	27(58.70)	*	>10
Male	*	168(51.53)	>10	60(51.72)	*	19(41.30)	*	*
Months from index MM diagnosis to treatment index								
Mean (Stdev)	*	3.09(7.14)	9.60(4.85)	13.71(7.56)	*	20.66(9.19)	*	29.88(9.99)
Median (IQR25, 75)	*	0.97 (0.47,2.17)	8.70 (6.83,10.50)	12.13 (8.48,17.20)	*	17.70 (13.77,26.17)	*	29.32 (21.17,39.27)
Calendar year of treatment index - n(%)								
2013	0	54(16.56)	0	*	0	0	0	0
2014	*	94(28.83)	*	21(18.10)	0	*	0	0
2015	0	67(20.55)	*	31(26.72)	*	12(26.09)	0	*
2016	0	92(28.22)	*	34(29.31)	*	20(43.48)	0	15(62.50)
2017	*	19(5.83)	*	25(21.55)	*	11(23.91)	*	*
Census region - n(%)								
Northeast	0	72(22.09)	*	22(18.97)	*	11(23.91)	0	*

Footnotes: FFS = Fee for service, n = patient count, LOT = Line of therapy, MM = Multiple myeloma, Stdev = standard deviation, IQR = interquartile range

Table 15-2.5. Baseline characteristics of treated MM patients in Medicare FFS (2013-2017), Hispanic

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	*	326(100.00)	17(100.00)	116(100.00)	*	46(100.00)	*	24(100.00)
Midwest	*	26(7.98)	*	12(10.34)	0	*	*	*
South	*	119(36.50)	*	51(43.97)	*	21(45.65)	*	*
West	0	109(33.44)	*	31(26.72)	*	*	0	*
Myeloma-related factors - n(%)								
Renal disease	*	117(35.89)	*	42(36.21)	*	15(32.61)	*	*
Hypercalcemia	*	48(14.72)	*	13(11.21)	*	*	*	*
Anemia	*	227(69.63)	15(88.24)	85(73.28)	*	35(76.09)	*	17(70.83)
Stem cell transplant (from MM index to LOT index)	*	*	*	16(13.79)	*	*	*	*
Other clinical comorbidities - n(%)								
Cardiovascular history								
Hypertension	*	257(78.83)	14(82.35)	91(78.45)	*	36(78.26)	*	19(79.17)
Heart failure	*	59(18.10)	*	14(12.07)	*	*	*	*
Cardiomyopathy	*	11(3.37)	*	*	*	*	*	*
Dysrhythmias	*	79(24.23)	*	25(21.55)	*	*	*	*
Ischemic heart disease	*	91(27.91)	*	30(25.86)	*	11(23.91)	*	*
Peripheral vascular disease	*	58(17.79)	*	27(23.28)	*	*	*	*
Hypercholesterolemia	*	206(63.19)	*	69(59.48)	*	30(65.22)	*	12(50.00)
Chronic obstructive pulmonary disease	*	72(22.09)	*	20(17.24)	*	12(26.09)	*	*
Diabetes	*	152(46.63)	*	59(50.86)	*	25(54.35)	*	13(54.17)
Liver disease	*	25(7.67)	*	*	*	*	*	*
Gastrointestinal bleeding	*	42(12.88)	*	*	*	*	*	*
Inflammatory diseases	*	27(8.28)	*	14(12.07)	*	*	*	*
Lifestyle risk factors - n(%)								
Smoking	*	29(8.90)	*	*	*	*	*	*

Footnotes: FFS = Fee for service, n = patient count, LOT = Line of therapy, MM = Multiple myeloma, Stdev = standard deviation, IQR = interquartile range

Table 15-2.5. Baseline characteristics of treated MM patients in Medicare FFS (2013-2017), Hispanic

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	*	326(100.00)	17(100.00)	116(100.00)	*	46(100.00)	*	24(100.00)
Obesity	*	74(22.70)	*	25(21.55)	*	*	*	*
Alcohol consumption	*	16(4.91)	*	*	*	*	*	*
Treatments and concomitant medications - n(%)								
Antihypertensive (Combined)	*	262(80.37)	14(82.35)	88(75.86)	*	37(80.43)	*	21(87.50)
Anti chf/hypertension	*	194(59.51)	*	64(55.17)	*	31(67.39)	*	17(70.83)
Anti IND/hypertension	*	190(58.28)	*	60(51.72)	*	23(50.00)	*	13(54.17)
Antihypertensives	*	115(35.28)	*	33(28.45)	*	11(23.91)	*	*
Cholesterol lowering medications	*	177(54.29)	*	52(44.83)	*	21(45.65)	*	*
Antidiabetics	*	119(36.50)	*	46(39.66)	*	21(45.65)	*	11(45.83)
Antihypertensive								
Cholesterol lowering medications								
Antidiabetics								

Footnotes: FFS = Fee for service, n = patient count, LOT = Line of therapy, MM = Multiple myeloma, Stdev = standard deviation, IQR = interquartile range

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Table 15-2.6. Baseline characteristics of treated MM patients in Medicare FFS (2013-2017), North American Native

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	0	81(100.00)	*	28(100.00)	*	11 (100.00)	0	*
Age at treatment index (year)								
Mean (Stdev)		74.56(9.04)	*	75.41(6.70)	*	76.46(4.05)		*
Median (IQR25, 75)		75.33 (69.79,79.40)	*	75.94 (72.11,78.85)	*	77.16 (74.37,77.60)		*
Age at treatment index - n(%)								
18-65 years		11(13.58)	*	*	*	*		*
66-69 years		11(13.58)	*	*	*	*		*
70-74 years		16(19.75)	*	*	*	*		*
75-79 years		25(30.86)	*	*	*	*		*
80+ years		18(22.22)	*	*	*	*		*
Sex - n(%)								
Female		43(53.09)	*	15(53.57)	*	*		*
Male		38(46.91)	*	13(46.43)	*	*		*
Months from index MM diagnosis to treatment index								
Mean (Stdev)		2.27(4.50)	*	13.55(7.52)	*	25.69(7.44)		*
Median (IQR25, 75)		1.00 (0.50,1.90)	*	12.67 (7.90,16.32)	*	28.20 (20.03,29.57)		*
Calendar year of treatment index - n(%)								
2013		18(22.22)	*	*	*	*		*
2014		13(16.05)	*	*	*	*		*
2015		25(30.86)	*	*	*	*		*
2016		21(25.93)	*	15(53.57)	*	*		*
2017		*	*	*	*	*		*
Census region - n(%)								
Northeast		*	*	*	*	*		*
Midwest		*	*	*	*	*		*

Footnotes: FFS = Fee for service, n = patient count, LOT = Line of therapy, MM = Multiple myeloma, Stdev = standard deviation, IQR = interquartile range

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Table 15-2.6. Baseline characteristics of treated MM patients in Medicare FFS (2013-2017), North American Native

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	0	81(100.00)	*	28(100.00)	*	11 (100.00)	0	*
South		30(37.04)	*	*	*	*		*
West		37(45.68)	*	12(42.86)	*	*		*
Myeloma-related factors - n(%)								
Renal disease		26(32.10)	*	*	*	*		*
Hypercalcemia		16(19.75)	*	*	*	*		*
Anemia		60(74.07)	*	21(75.00)	*	*		*
Stem cell transplant (from MM index to LOT index)		*	*	*	*	*		*
Other clinical comorbidities - n(%)								
Cardiovascular history								
Hypertension		70(86.42)	*	24(85.71)	*	*		*
Heart failure		20(24.69)	*	*	*	*		*
Cardiomyopathy		*	*	*	*	*		*
Dysrhythmias		21(25.93)	*	11(39.29)	*	*		*
Ischemic heart disease		25(30.86)	*	11(39.29)	*	*		*
Peripheral vascular disease		11(13.58)	*	*	*	*		*
Hypercholesterolemia		40(49.38)	*	14(50.00)	*	*		*
Chronic obstructive pulmonary disease		15(18.52)	*	*	*	*		*
Diabetes		41(50.62)	*	13(46.43)	*	*		*
Liver disease		*	*	*	*	*		*
Gastrointestinal bleeding		*	*	*	*	*		*
Inflammatory diseases		*	*	*	*	*		*
Lifestyle risk factors - n(%)								
Smoking		15(18.52)	*	*	*	*		*
Obesity		24(29.63)	*	*	*	*		*

Footnotes: FFS = Fee for service, n = patient count, LOT = Line of therapy, MM = Multiple myeloma, Stdev = standard deviation, IQR = interquartile range

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Table 15-2.6. Baseline characteristics of treated MM patients in Medicare FFS (2013-2017), North American Native

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	0	81(100.00)	*	28(100.00)	*	11 (100.00)	0	*
Alcohol consumption		*	*	*	*	*		*
Treatments and concomitant medications - n(%)								
Antihypertensive (Combined)		63(77.78)	*	24(85.71)	*	*		*
Anti chf/hypertension		55(67.90)	*	19(67.86)	*	*		*
Anti IND/hypertension		39(48.15)	*	16(57.14)	*	*		*
Antihypertensives		33(40.74)	*	*	*	*		*
Cholesterol lowering medications		41(50.62)	*	12(42.86)	*	*		*
Antidiabetics		30(37.04)	*	11(39.29)	*	*		*
Antihypertensive								
Cholesterol lowering medications								
Antidiabetics								

Footnotes: FFS = Fee for service, n = patient count, LOT = Line of therapy, MM = Multiple myeloma, Stdev = standard deviation, IQR = interquartile range

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Table 15-2.7. Baseline characteristics of treated MM patients in Optum Clinformatics Data Mart (2013-2019) of all races

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing
	5726 (98.38)	94 (1.62)	2650 (94.61)	151 (5.39)	1290 (91.88)	114 (8.12)	661 (90.55)	69 (9.45)
Race/ethnicity - n (%)								
Asian	144 (2.51)	4 (4.26)	64 (2.42)	6 (3.97)	28 (2.17)	2 (1.75)	12 (1.82)	1 (1.45)
Black	959 (16.75)	11 (11.7)	445 (16.79)	23 (15.23)	218 (16.9)	14 (12.28)	107 (16.19)	11 (15.94)
Hispanic	570 (9.95)	9 (9.57)	283 (10.68)	15 (9.93)	126 (9.77)	10 (8.77)	68 (10.29)	3 (4.35)
White	4053 (70.78)	70 (74.47)	1858 (70.11)	107 (70.86)	918 (71.16)	88 (77.19)	474 (71.71)	54 (78.26)
Age at treatment index (year)								
AGE AT TREATMENT Median (IQR25, 75)	72 (64,79)	67 (58,71)	71 (63,78)	69 (58,77)	71 (62,78)	72 (61,77)	71 (62,78)	69 (59,76)
AGE AT TREATMENT MEAN (STD)	70.57 (10.87)	65.14 (9.92)	70.04 (11.02)	67.99 (10.98)	69.71 (10.93)	69.1 (10.82)	69.73 (11.06)	67.58 (10.88)
Age at treatment index - n (%)								
18-65 years	1552 (27.1)	44 (46.81)	793 (29.92)	58 (38.41)	402 (31.16)	40 (35.09)	213 (32.22)	30 (43.48)
66-69 years	773 (13.5)	13 (13.83)	316 (11.92)	18 (11.92)	148 (11.47)	8 (7.02)	63 (9.53)	7 (10.14)
70-74 years	1134 (19.8)	23 (24.47)	542 (20.45)	25 (16.56)	272 (21.09)	28 (24.56)	142 (21.48)	8 (11.59)
75-79 years	1028 (17.95)	6 (6.38)	456 (17.21)	28 (18.54)	230 (17.83)	15 (13.16)	114 (17.25)	16 (23.19)
80+ years	1239 (21.64)	8 (8.51)	543 (20.49)	22 (14.57)	238 (18.45)	23 (20.18)	129 (19.52)	8 (11.59)
Sex - n (%)								
Female	2686 (46.91)	40 (42.55)	1226 (46.26)	65 (43.05)	581 (45.04)	51 (44.74)	301 (45.54)	35 (50.72)
Male	3038 (53.06)	54 (57.45)	1424 (53.74)	86 (56.95)	709 (54.96)	63 (55.26)	360 (54.46)	34 (49.28)
Unknown	2 (0.03)							
Months from index MM diagnosis to treatment								
DIAGNOSIS TO TREATMENT Median (IQR25, 75)	0.72 (0.33,1.84)	0.66 (0.36,1.44)	7.38 (4.62,11.84)	7.18 (5.21,11.34)	12.92 (8.69,20.56)	14.43 (9.9,20.26)	18.98 (12.26,28.07)	18.98 (15.61,28.03)
DIAGNOSIS TO TREATMENT MEAN (STD)	2.03 (4.39)	1.3 (2.49)	9.78 (8.47)	9.3 (6.86)	15.98 (10.29)	16.72 (9.3)	21.43 (11.93)	22.13 (9.82)
Calendar year of treatment index - n (%)								
2013	679 (11.86)	1 (1.06)	160 (6.04)	4 (2.65)	30 (2.33)		10 (1.51)	
2014	715 (12.49)	4 (4.26)	324 (12.23)	10 (6.62)	130 (10.08)	14 (12.28)	39 (5.9)	5 (7.25)
2015	840 (14.67)	15 (15.96)	350 (13.21)	29 (19.21)	157 (12.17)	23 (20.18)	75 (11.35)	11 (15.94)
2016	938 (16.38)	17 (18.09)	505 (19.06)	44 (29.14)	253 (19.61)	21 (18.42)	130 (19.67)	13 (18.84)
2017	1179 (20.59)	22 (23.4)	603 (22.75)	33 (21.85)	294 (22.79)	23 (20.18)	161 (24.36)	17 (24.64)

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy Page 1 of 3

Table 15-2.7. Baseline characteristics of treated MM patients in Optum Clinformatics Data Mart (2013-2019) of all races

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing
	5726 (98.38)	94 (1.62)	2650 (94.61)	151 (5.39)	1290 (91.88)	114 (8.12)	661 (90.55)	69 (9.45)
2018	1374 (24)	35 (37.23)	708 (26.72)	31 (20.53)	426 (33.02)	33 (28.95)	246 (37.22)	23 (33.33)
2019	1 (0.02)							
Census region - n (%)								
Midwest	1481 (25.86)	21 (22.34)	652 (24.6)	41 (27.15)	331 (25.66)	22 (19.3)	143 (21.63)	21 (30.43)
Northeast	768 (13.41)	14 (14.89)	308 (11.62)	16 (10.6)	153 (11.86)	15 (13.16)	78 (11.8)	10 (14.49)
South	2459 (42.94)	40 (42.55)	1172 (44.23)	61 (40.4)	560 (43.41)	47 (41.23)	293 (44.33)	24 (34.78)
West	1018 (17.78)	19 (20.21)	518 (19.55)	33 (21.85)	246 (19.07)	30 (26.32)	147 (22.24)	14 (20.29)
Myeloma-related factors - n (%)								
Renal_disease	1833 (32.01)	19 (20.21)	785 (29.62)	37 (24.5)	356 (27.6)	23 (20.18)	165 (24.96)	19 (27.54)
Hypercalcemia	599 (10.46)	13 (13.83)	267 (10.08)	25 (16.56)	123 (9.53)	16 (14.04)	65 (9.83)	7 (10.14)
Anemia	2772 (48.41)	43 (45.74)	1223 (46.15)	66 (43.71)	587 (45.5)	51 (44.74)	286 (43.27)	33 (47.83)
Other clinical comorbidities - n (%)								
Cardiovascular history								
Hypertension	3957 (69.11)	45 (47.87)	1758 (66.34)	96 (63.58)	842 (65.27)	72 (63.16)	425 (64.3)	39 (56.52)
Cardiac_failure	752 (13.13)	5 (5.32)	269 (10.15)	11 (7.28)	114 (8.84)	6 (5.26)	50 (7.56)	6 (8.7)
Cardiomyopathy	261 (4.56)		101 (3.81)	2 (1.32)	37 (2.87)	3 (2.63)	22 (3.33)	1 (1.45)
Cardiacarrhythmias	1233 (21.53)	12 (12.77)	498 (18.79)	21 (13.91)	226 (17.52)	19 (16.67)	111 (16.79)	13 (18.84)
Ischemic_heart_disease	1159 (20.24)	14 (14.89)	463 (17.47)	22 (14.57)	212 (16.43)	15 (13.16)	102 (15.43)	7 (10.14)
Peripheral_vascular_disease	868 (15.16)	9 (9.57)	346 (13.06)	17 (11.26)	150 (11.63)	17 (14.91)	77 (11.65)	6 (8.7)
Hypercholesterolemia	3127 (54.61)	50 (53.19)	1373 (51.81)	81 (53.64)	676 (52.4)	53 (46.49)	339 (51.29)	29 (42.03)
Chronic obstructive pulmonary disease	1046 (18.27)	10 (10.64)	455 (17.17)	26 (17.22)	207 (16.05)	15 (13.16)	103 (15.58)	12 (17.39)
Diabetes	1606 (28.05)	21 (22.34)	670 (25.28)	49 (32.45)	303 (23.49)	30 (26.32)	146 (22.09)	18 (26.09)
Liver_disease	293 (5.12)	5 (5.32)	124 (4.68)	10 (6.62)	44 (3.41)	8 (7.02)	21 (3.18)	8 (11.59)
GI_bleeding_disorders	225 (3.93)	4 (4.26)	96 (3.62)	10 (6.62)	42 (3.26)	6 (5.26)	21 (3.18)	4 (5.8)
Inflammatory_disease	393 (6.86)	9 (9.57)	181 (6.83)	10 (6.62)	95 (7.36)	3 (2.63)	44 (6.66)	2 (2.9)
Lifestyle risk factors - n (%)								
Obesity	1128 (19.7)	19 (20.21)	490 (18.49)	37 (24.5)	224 (17.36)	24 (21.05)	120 (18.15)	17 (24.64)

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy Page 2 of 3

Table 15-2.7. Baseline characteristics of treated MM patients in Optum Clinformatics Data Mart (2013-2019) of all races

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing
	5726 (98.38)	94 (1.62)	2650 (94.61)	151 (5.39)	1290 (91.88)	114 (8.12)	661 (90.55)	69 (9.45)
Smoking	554 (9.68)	9 (9.57)	255 (9.62)	14 (9.27)	114 (8.84)	15 (13.16)	56 (8.47)	10 (14.49)
Alcohol	140 (2.44)	3 (3.19)	61 (2.3)	4 (2.65)	25 (1.94)	3 (2.63)	12 (1.82)	3 (4.35)
Treatments and concomitant medications - n (%)								
Antihypertensives	3806 (66.47)	58 (61.7)	1918 (72.38)	97 (64.24)	954 (73.95)	80 (70.18)	497 (75.19)	51 (73.91)
Cholesterolmeds	2753 (48.08)	49 (52.13)	1362 (51.4)	77 (50.99)	705 (54.65)	54 (47.37)	361 (54.61)	31 (44.93)
Antidiabetics	1218 (21.27)	23 (24.47)	579 (21.85)	39 (25.83)	286 (22.17)	27 (23.68)	143 (21.63)	21 (30.43)

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy

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Table 15-2.8. Baseline characteristics of treated MM patients in Optum Clinformatics Data Mart (2013-2019), White

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing
	4053 (98.3)	70 (1.7)	1858 (94.55)	107 (5.45)	918 (91.25)	88 (8.75)	474 (89.77)	54 (10.23)
Age at treatment index (year)								
AGE AT TREATMENT Median (IQR25, 75)	72 (65,79)	66.5 (59,72)	71 (63,78)	70 (59,77)	71 (62,78)	72 (61,78.5)	71 (62,78)	71 (62,77)
AGE AT TREATMENT MEAN (STD)	70.89 (10.79)	65.89 (9.33)	70.33 (10.79)	68.32 (11.02)	69.87 (10.67)	69.38 (10.91)	69.96 (10.74)	69.07 (10.44)
Age at treatment index - n (%)								
18-65 years	1080 (26.65)	34 (48.57)	549 (29.55)	41 (38.32)	287 (31.26)	31 (35.23)	151 (31.86)	20 (37.04)
66-69 years	525 (12.95)	7 (10)	214 (11.52)	12 (11.21)	101 (11)	7 (7.95)	47 (9.92)	6 (11.11)
70-74 years	803 (19.81)	17 (24.29)	388 (20.88)	17 (15.89)	198 (21.57)	20 (22.73)	103 (21.73)	6 (11.11)
75-79 years	718 (17.72)	5 (7.14)	323 (17.38)	20 (18.69)	163 (17.76)	11 (12.5)	76 (16.03)	15 (27.78)
80+ years	927 (22.87)	7 (10)	384 (20.67)	17 (15.89)	169 (18.41)	19 (21.59)	97 (20.46)	7 (12.96)
Sex - n (%)								
Female	1797 (44.34)	26 (37.14)	803 (43.22)	42 (39.25)	373 (40.63)	38 (43.18)	200 (42.19)	26 (48.15)
Male	2254 (55.61)	44 (62.86)	1055 (56.78)	65 (60.75)	545 (59.37)	50 (56.82)	274 (57.81)	28 (51.85)
Unknown	2 (0.05)							
Months from index MM diagnosis to treatm								
DIAGNOSIS TO TREATMENT Median (IQR25, 75)	0.72 (0.3,1.8)	0.57 (0.3,1.34)	7.38 (4.59,12.07)	7.31 (5.34,13.21)	12.92 (8.75,21.41)	14.72 (10.36,20.15)	19.13 (11.93,28.07)	19.87 (16.1,28.03)
DIAGNOSIS TO TREATMENT MEAN (STD)	2.06 (4.51)	1.25 (2.8)	9.92 (8.72)	9.96 (7.5)	16.23 (10.33)	16.78 (9.12)	21.43 (11.98)	22.4 (9.71)
Calendar year of treatment index - n (%)								
2013	511 (12.61)	1 (1.43)	121 (6.51)	4 (3.74)	19 (2.07)		8 (1.69)	
2014	531 (13.1)	4 (5.71)	246 (13.24)	6 (5.61)	95 (10.35)	10 (11.36)	27 (5.7)	4 (7.41)
2015	622 (15.35)	12 (17.14)	260 (13.99)	21 (19.63)	114 (12.42)	18 (20.45)	58 (12.24)	8 (14.81)
2016	665 (16.41)	14 (20)	350 (18.84)	33 (30.84)	179 (19.5)	18 (20.45)	88 (18.57)	13 (24.07)
2017	779 (19.22)	15 (21.43)	405 (21.8)	23 (21.5)	215 (23.42)	17 (19.32)	112 (23.63)	14 (25.93)
2018	945 (23.32)	24 (34.29)	476 (25.62)	20 (18.69)	296 (32.24)	25 (28.41)	181 (38.19)	15 (27.78)
2019								
Census region - n (%)								
Midwest	1237 (30.52)	18 (25.71)	548 (29.49)	31 (28.97)	279 (30.39)	20 (22.73)	123 (25.95)	17 (31.48)
Northeast	549 (13.55)	9 (12.86)	206 (11.09)	14 (13.08)	103 (11.22)	15 (17.05)	53 (11.18)	10 (18.52)

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy Page 1 of 3

Table 15-2.8. Baseline characteristics of treated MM patients in Optum Clinformatics Data Mart (2013-2019), White

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing
	4053 (98.3)	70 (1.7)	1858 (94.55)	107 (5.45)	918 (91.25)	88 (8.75)	474 (89.77)	54 (10.23)
South	1481 (36.54)	31 (44.29)	709 (38.16)	38 (35.51)	355 (38.67)	26 (29.55)	184 (38.82)	14 (25.93)
West	786 (19.39)	12 (17.14)	395 (21.26)	24 (22.43)	181 (19.72)	27 (30.68)	114 (24.05)	13 (24.07)
Myeloma-related factors - n (%)								
Renal_disease	1228 (30.3)	14 (20)	524 (28.2)	23 (21.5)	245 (26.69)	19 (21.59)	115 (24.26)	18 (33.33)
Hypercalcemia	422 (10.41)	9 (12.86)	193 (10.39)	16 (14.95)	90 (9.8)	11 (12.5)	48 (10.13)	5 (9.26)
Anemia	1847 (45.57)	29 (41.43)	791 (42.57)	45 (42.06)	379 (41.29)	37 (42.05)	183 (38.61)	27 (50)
Other clinical comorbidities - n (%)								
Cardiovascular history								
Hypertension	2712 (66.91)	33 (47.14)	1190 (64.05)	65 (60.75)	584 (63.62)	54 (61.36)	297 (62.66)	32 (59.26)
Cardiac_failure	493 (12.16)	4 (5.71)	172 (9.26)	6 (5.61)	69 (7.52)	5 (5.68)	30 (6.33)	6 (11.11)
Cardiomyopathy	163 (4.02)		63 (3.39)	2 (1.87)	21 (2.29)	3 (3.41)	14 (2.95)	1 (1.85)
Cardiacarrhythmias	900 (22.21)	8 (11.43)	364 (19.59)	17 (15.89)	161 (17.54)	17 (19.32)	80 (16.88)	9 (16.67)
Ischemic_heart_disease	829 (20.45)	12 (17.14)	318 (17.12)	16 (14.95)	147 (16.01)	11 (12.5)	67 (14.14)	7 (12.96)
Peripheral_vascular_disease	603 (14.88)	6 (8.57)	233 (12.54)	7 (6.54)	96 (10.46)	13 (14.77)	56 (11.81)	5 (9.26)
Hypercholesterolemia	2199 (54.26)	39 (55.71)	962 (51.78)	61 (57.01)	486 (52.94)	41 (46.59)	238 (50.21)	24 (44.44)
Chronic obstructive pulmonary disease	750 (18.5)	5 (7.14)	328 (17.65)	12 (11.21)	148 (16.12)	12 (13.64)	73 (15.4)	9 (16.67)
Diabetes	986 (24.33)	14 (20)	401 (21.58)	29 (27.1)	180 (19.61)	21 (23.86)	85 (17.93)	16 (29.63)
Liver_disease	190 (4.69)	2 (2.86)	77 (4.14)	6 (5.61)	27 (2.94)	5 (5.68)	12 (2.53)	5 (9.26)
GI_bleeding_disorders	139 (3.43)	2 (2.86)	61 (3.28)	7 (6.54)	28 (3.05)	5 (5.68)	14 (2.95)	4 (7.41)
Inflammatory_disease	277 (6.83)	7 (10)	120 (6.46)	8 (7.48)	68 (7.41)	1 (1.14)	32 (6.75)	2 (3.7)
Lifestyle risk factors - n (%)								
Obesity	748 (18.46)	11 (15.71)	318 (17.12)	26 (24.3)	150 (16.34)	17 (19.32)	78 (16.46)	14 (25.93)
Smoking	394 (9.72)	5 (7.14)	185 (9.96)	7 (6.54)	82 (8.93)	10 (11.36)	37 (7.81)	6 (11.11)
Alcohol	96 (2.37)	1 (1.43)	40 (2.15)	2 (1.87)	17 (1.85)	2 (2.27)	7 (1.48)	2 (3.7)

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy Page 2 of 3

Table 15-2.8. Baseline characteristics of treated MM patients in Optum Clinformatics Data Mart (2013-2019), White

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing
	4053 (98.3)	70 (1.7)	1858 (94.55)	107 (5.45)	918 (91.25)	88 (8.75)	474 (89.77)	54 (10.23)
Treatments and concomitant medications - n (%)								
Antihypertensives	2597 (64.08)	41 (58.57)	1305 (70.24)	65 (60.75)	672 (73.2)	58 (65.91)	354 (74.68)	39 (72.22)
Cholesterolmeds	1862 (45.94)	36 (51.43)	916 (49.3)	56 (52.34)	495 (53.92)	40 (45.45)	252 (53.16)	25 (46.3)
Antidiabetics	732 (18.06)	15 (21.43)	341 (18.35)	26 (24.3)	179 (19.5)	19 (21.59)	93 (19.62)	17 (31.48)

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy Page 3 of 3

Table 15-2.9. Baseline characteristics of treated MM patients in Optum Clinformatics Data Mart (2013-2019), Asian

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing
	144 (97.3)	4 (2.7)	64 (91.43)	6 (8.57)	28 (93.33)	2 (6.67)	12 (92.31)	1 (7.69)
Age at treatment index (year)								
AGE AT TREATMENT Median (IQR25, 75)	72 (66,78)	53 (36.5,70)	72 (61.5,78)	70.5 (67,75)	72 (62,78.5)	71.5 (71,72)	72.5 (66.5,81.5)	60 (60,60)
AGE AT TREATMENT MEAN (STD)	70.97 (10.88)	53.25 (19.36)	69.64 (12.38)	69.83 (8.73)	70.21 (12.13)	71.5 (0.71)	73.33 (9.57)	60 (.)
Age at treatment index - n (%)								
18-65 years	34 (23.61)	2 (50)	20 (31.25)	1 (16.67)	9 (32.14)		3 (25)	1 (100)
66-69 years	17 (11.81)	1 (25)	5 (7.81)	1 (16.67)	1 (3.57)			
70-74 years	32 (22.22)	1 (25)	15 (23.44)	2 (33.33)	8 (28.57)	2 (100)	4 (33.33)	
75-79 years	29 (20.14)		10 (15.63)	1 (16.67)	4 (14.29)			
80+ years	32 (22.22)		14 (21.88)	1 (16.67)	6 (21.43)		5 (41.67)	
Sex - n (%)								
Female	62 (43.06)	1 (25)	28 (43.75)	3 (50)	13 (46.43)		4 (33.33)	1 (100)
Male	82 (56.94)	3 (75)	36 (56.25)	3 (50)	15 (53.57)	2 (100)	8 (66.67)	
Unknown								
Months from index MM diagnosis to treatm								
DIAGNOSIS TO TREATMENT Median (IQR25, 75)	0.79 (0.23,2.72)	1.93 (0.93,3.66)	6.97 (4.51,11.82)	8.89 (4.59,14.39)	13.02 (9.23,16.3)	22.54 (11.93,33.15)	13.08 (9.02,26.92)	17.87 (17.87,17.87)
DIAGNOSIS TO TREATMENT MEAN (STD)	2.6 (5.49)	2.3 (1.77)	10.12 (9.57)	9.55 (5.67)	16.09 (12.5)	22.54 (15)	18.69 (12.8)	17.87 (.)
Calendar year of treatment index - n (%)								
2013	18 (12.5)		7 (10.94)	1 (16.67)	3 (10.71)			
2014	19 (13.19)		6 (9.38)		5 (17.86)		2 (16.67)	1 (100)
2015	27 (18.75)	2 (50)	16 (25)	2 (33.33)	7 (25)		4 (33.33)	
2016	28 (19.44)		17 (26.56)	2 (33.33)	4 (14.29)	1 (50)	3 (25)	
2017	35 (24.31)	2 (50)	16 (25)	1 (16.67)	8 (28.57)	1 (50)	2 (16.67)	
2018	1 (0.69)							
2019								
Census region - n (%)								
Midwest	15 (10.42)		7 (10.94)	1 (16.67)	3 (10.71)	1 (50)		
Northeast	45 (31.25)	1 (25)	21 (32.81)	2 (33.33)	9 (32.14)		4 (33.33)	

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy Page 1 of 3

Table 15-2.9. Baseline characteristics of treated MM patients in Optum Clinformatics Data Mart (2013-2019), Asian

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing
	144 (97.3)	4 (2.7)	64 (91.43)	6 (8.57)	28 (93.33)	2 (6.67)	12 (92.31)	1 (7.69)
South	38 (26.39)	1 (25)	19 (29.69)		8 (28.57)		4 (33.33)	1 (100)
West	46 (31.94)	2 (50)	17 (26.56)	3 (50)	8 (28.57)	1 (50)	4 (33.33)	
Myeloma-related factors - n (%)								
Renal_disease	46 (31.94)	1 (25)	18 (28.13)	2 (33.33)	9 (32.14)		6 (50)	
Hypercalcemia	16 (11.11)	1 (25)	4 (6.25)	1 (16.67)	2 (7.14)		2 (16.67)	
Anemia	69 (47.92)	2 (50)	37 (57.81)	3 (50)	18 (64.29)		10 (83.33)	
Other clinical comorbidities - n (%)								
Cardiovascular history								
Hypertension	102 (70.83)	1 (25)	44 (68.75)	2 (33.33)	19 (67.86)	1 (50)	9 (75)	
Cardiac_failure	23 (15.97)		7 (10.94)		3 (10.71)		2 (16.67)	
Cardiomyopathy	10 (6.94)		2 (3.13)					
Cardiacarrhythmias	27 (18.75)	1 (25)	10 (15.63)		4 (14.29)		1 (8.33)	
Ischemic_heart_disease	31 (21.53)		10 (15.63)	1 (16.67)	7 (25)		4 (33.33)	
Peripheral_vascular_disease	21 (14.58)		10 (15.63)	1 (16.67)	7 (25)		3 (25)	
Hypercholesterolemia	87 (60.42)	1 (25)	37 (57.81)	2 (33.33)	17 (60.71)	1 (50)	9 (75)	
Chronic obstructive pulmonary disease	18 (12.5)		5 (7.81)	1 (16.67)	2 (7.14)		1 (8.33)	
Diabetes	38 (26.39)	1 (25)	14 (21.88)	3 (50)	6 (21.43)	1 (50)	2 (16.67)	
Liver_disease	7 (4.86)		2 (3.13)					
GI_bleeding_disorders	9 (6.25)		2 (3.13)	1 (16.67)	1 (3.57)		1 (8.33)	
Inflammatory_disease	13 (9.03)		5 (7.81)		2 (7.14)		2 (16.67)	
Lifestyle risk factors - n (%)								
Obesity	11 (7.64)	1 (25)	7 (10.94)		2 (7.14)		1 (8.33)	
Smoking	5 (3.47)		3 (4.69)					
Alcohol	2 (1.39)		2 (3.13)		2 (7.14)		2 (16.67)	

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy Page 2 of 3

Table 15-2.9. Baseline characteristics of treated MM patients in Optum Clinformatics Data Mart (2013-2019), Asian

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing
	144 (97.3)	4 (2.7)	64 (91.43)	6 (8.57)	28 (93.33)	2 (6.67)	12 (92.31)	1 (7.69)
Treatments and concomitant medications - n (%)								
Antihypertensives	101 (70.14)	2 (50)	51 (79.69)	4 (66.67)	22 (78.57)	1 (50)	9 (75)	1 (100)
Cholesterolmeds	71 (49.31)	1 (25)	36 (56.25)	3 (50)	17 (60.71)	1 (50)	8 (66.67)	
Antidiabetics	27 (18.75)	1 (25)	15 (23.44)	2 (33.33)	6 (21.43)		1 (8.33)	

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy Page 3 of 3

Table 15-2.10. Baseline characteristics of treated MM patients in Optum Clinformatics Data Mart (2013-2019), Black

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing
	959 (98.87)	11 (1.13)	445 (95.09)	23 (4.91)	218 (93.97)	14 (6.03)	107 (90.68)	11 (9.32)
Age at treatment index (year)								
AGE AT TREATMENT Median (IQR25, 75)	71 (64,78)	70 (59,73)	71 (64,78)	69 (57,75)	70.5 (63,78)	65.5 (57,73)	70 (60,78)	59 (53,73)
AGE AT TREATMENT MEAN (STD)	70.12 (10.75)	66.82 (7.39)	69.99 (10.99)	66.43 (11.3)	69.18 (11.47)	64.21 (11.36)	68.67 (12.43)	63.18 (10.74)
Age at treatment index - n (%)								
18-65 years	267 (27.84)	4 (36.36)	124 (27.87)	10 (43.48)	65 (29.82)	7 (50)	36 (33.64)	7 (63.64)
66-69 years	148 (15.43)	1 (9.09)	65 (14.61)	3 (13.04)	31 (14.22)	1 (7.14)	10 (9.35)	1 (9.09)
70-74 years	185 (19.29)	5 (45.45)	91 (20.45)	3 (13.04)	48 (22.02)	3 (21.43)	24 (22.43)	1 (9.09)
75-79 years	173 (18.04)	1 (9.09)	74 (16.63)	5 (21.74)	34 (15.6)	2 (14.29)	19 (17.76)	1 (9.09)
80+ years	186 (19.4)		91 (20.45)	2 (8.7)	40 (18.35)	1 (7.14)	18 (16.82)	1 (9.09)
Sex - n (%)								
Female	557 (58.08)	8 (72.73)	257 (57.75)	15 (65.22)	127 (58.26)	7 (50)	65 (60.75)	6 (54.55)
Male	402 (41.92)	3 (27.27)	188 (42.25)	8 (34.78)	91 (41.74)	7 (50)	42 (39.25)	5 (45.45)
Months from index MM diagnosis to treatment								
DIAGNOSIS TO TREATMENT Median (IQR25, 75)	0.85 (0.39,1.87)	0.85 (0.43,1.74)	7.15 (4.66,11.8)	6.59 (4.49,9.21)	13.23 (8.56,19.25)	12.44 (7.57,20.2)	18.98 (13.08,28.56)	19.54 (11.67,34.52)
DIAGNOSIS TO TREATMENT MEAN (STD)	1.89 (3.95)	1.07 (0.74)	9.54 (7.86)	7.94 (5.38)	15.33 (9.89)	14.21 (9.13)	21.71 (11.5)	22.87 (11.82)
Calendar year of treatment index - n (%)								
2013	96 (10.01)		28 (6.29)		7 (3.21)			
2014	106 (11.05)		31 (6.97)	1 (4.35)	19 (8.72)	1 (7.14)	10 (9.35)	
2015	114 (11.89)	2 (18.18)	50 (11.24)	1 (4.35)	20 (9.17)	3 (21.43)	6 (5.61)	1 (9.09)
2016	166 (17.31)	1 (9.09)	83 (18.65)	8 (34.78)	41 (18.81)	1 (7.14)	26 (24.3)	
2017	232 (24.19)	4 (36.36)	119 (26.74)	6 (26.09)	52 (23.85)	4 (28.57)	27 (25.23)	3 (27.27)
2018	245 (25.55)	4 (36.36)	134 (30.11)	7 (30.43)	79 (36.24)	5 (35.71)	38 (35.51)	7 (63.64)
Census region - n (%)								
Midwest	186 (19.4)	3 (27.27)	80 (17.98)	7 (30.43)	41 (18.81)	1 (7.14)	16 (14.95)	4 (36.36)
Northeast	99 (10.32)	2 (18.18)	48 (10.79)		22 (10.09)		13 (12.15)	
South	641 (66.84)	4 (36.36)	299 (67.19)	15 (65.22)	145 (66.51)	13 (92.86)	72 (67.29)	7 (63.64)

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy Page 1 of 2

Table 15-2.10. Baseline characteristics of treated MM patients in Optum Clinformatics Data Mart (2013-2019), Black

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing
	959 (98.87)	11 (1.13)	445 (95.09)	23 (4.91)	218 (93.97)	14 (6.03)	107 (90.68)	11 (9.32)
West	33 (3.44)	2 (18.18)	18 (4.04)	1 (4.35)	10 (4.59)		6 (5.61)	
Myeloma-related factors - n (%)								
Renal_disease	359 (37.43)	2 (18.18)	154 (34.61)	8 (34.78)	67 (30.73)	3 (21.43)	27 (25.23)	1 (9.09)
Hypercalcemia	108 (11.26)	2 (18.18)	46 (10.34)	7 (30.43)	22 (10.09)	3 (21.43)	10 (9.35)	2 (18.18)
Anemia	569 (59.33)	8 (72.73)	258 (57.98)	13 (56.52)	123 (56.42)	7 (50)	57 (53.27)	4 (36.36)
Other clinical comorbidities - n (%)								
Cardiovascular history								
Hypertension	774 (80.71)	5 (45.45)	344 (77.3)	19 (82.61)	165 (75.69)	8 (57.14)	80 (74.77)	5 (45.45)
Cardiac_failure	172 (17.94)		67 (15.06)	3 (13.04)	35 (16.06)	1 (7.14)	16 (14.95)	
Cardiomyopathy	65 (6.78)		29 (6.52)		14 (6.42)		8 (7.48)	
Cardiacarrhythmias	203 (21.17)	2 (18.18)	85 (19.1)	2 (8.7)	41 (18.81)	2 (14.29)	17 (15.89)	4 (36.36)
Ischemic_heart_disease	196 (20.44)		83 (18.65)	3 (13.04)	38 (17.43)	1 (7.14)	19 (17.76)	
Peripheral_vascular_disease	157 (16.37)	2 (18.18)	59 (13.26)	5 (21.74)	24 (11.01)	1 (7.14)	10 (9.35)	1 (9.09)
Hypercholesterolemia	537 (56)	5 (45.45)	232 (52.13)	9 (39.13)	113 (51.83)	6 (42.86)	62 (57.94)	4 (36.36)
Chronic obstructive pulmonary disease	196 (20.44)	4 (36.36)	84 (18.88)	10 (43.48)	43 (19.72)	2 (14.29)	21 (19.63)	2 (18.18)
Diabetes	375 (39.1)	1 (9.09)	163 (36.63)	7 (30.43)	80 (36.7)	3 (21.43)	37 (34.58)	1 (9.09)
Liver_disease	45 (4.69)	1 (9.09)	28 (6.29)	1 (4.35)	12 (5.5)		6 (5.61)	1 (9.09)
GI_bleeding_disorders	50 (5.21)		19 (4.27)	1 (4.35)	7 (3.21)		5 (4.67)	
Inflammatory_disease	71 (7.4)	2 (18.18)	38 (8.54)	1 (4.35)	15 (6.88)	1 (7.14)	6 (5.61)	
Lifestyle risk factors - n (%)								
Obesity	241 (25.13)	4 (36.36)	108 (24.27)	7 (30.43)	56 (25.69)	3 (21.43)	30 (28.04)	3 (27.27)
Smoking	113 (11.78)	3 (27.27)	45 (10.11)	7 (30.43)	27 (12.39)	3 (21.43)	14 (13.08)	4 (36.36)
Alcohol	25 (2.61)	1 (9.09)	12 (2.7)	1 (4.35)	4 (1.83)	1 (7.14)	1 (0.93)	1 (9.09)
Treatments and concomitant medications - n (%)								
Antihypertensives	723 (75.39)	9 (81.82)	345 (77.53)	19 (82.61)	167 (76.61)	11 (78.57)	84 (78.5)	9 (81.82)
Cholesterolmeds	514 (53.6)	6 (54.55)	241 (54.16)	11 (47.83)	121 (55.5)	6 (42.86)	63 (58.88)	4 (36.36)
Antidiabetics	281 (29.3)	2 (18.18)	128 (28.76)	4 (17.39)	63 (28.9)	3 (21.43)	28 (26.17)	2 (18.18)

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy Page 2 of 2

Table 15-2.11. Baseline characteristics of treated MM patients in Optum Clinformatics Data Mart (2013-2019), Hispanic

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing
	570 (98.45)	9 (1.55)	283 (94.97)	15 (5.03)	126 (92.65)	10 (7.35)	68 (95.77)	3 (4.23)
Age at treatment index (year)								
AGE AT TREATMENT Median (IQR25, 75)	71 (62,77)	66 (54,67)	71 (58,77)	69 (62,78)	71 (59,78)	74.5 (71,80)	72 (57.5,77)	62 (42,74)
AGE AT TREATMENT MEAN (STD)	68.96 (11.45)	62.56 (9.86)	68.28 (12.09)	67.27 (11.73)	69.28 (11.63)	73 (8.77)	69.15 (11.25)	59.33 (16.17)
Age at treatment index - n (%)								
18-65 years	171 (30)	4 (44.44)	100 (35.34)	6 (40)	41 (32.54)	2 (20)	23 (33.82)	2 (66.67)
66-69 years	83 (14.56)	4 (44.44)	32 (11.31)	2 (13.33)	15 (11.9)		6 (8.82)	
70-74 years	114 (20)		48 (16.96)	3 (20)	18 (14.29)	3 (30)	11 (16.18)	1 (33.33)
75-79 years	108 (18.95)		49 (17.31)	2 (13.33)	29 (23.02)	2 (20)	19 (27.94)	
80+ years	94 (16.49)	1 (11.11)	54 (19.08)	2 (13.33)	23 (18.25)	3 (30)	9 (13.24)	
Sex - n (%)								
Female	270 (47.37)	5 (55.56)	138 (48.76)	5 (33.33)	68 (53.97)	6 (60)	32 (47.06)	2 (66.67)
Male	300 (52.63)	4 (44.44)	145 (51.24)	10 (66.67)	58 (46.03)	4 (40)	36 (52.94)	1 (33.33)
Months from index MM diagnosis to treatment								
DIAGNOSIS TO TREATMENT Median (IQR25, 75)	0.72 (0.3,1.8)	1.08 (0.66,1.8)	7.8 (4.62,10.98)	6.59 (4.79,8.79)	12.84 (8.69,18.26)	14.61 (11.18,23.57)	17.3 (12.21,28.3)	16.07 (12.69,18.85)
DIAGNOSIS TO TREATMENT MEAN (STD)	1.89 (3.82)	1.47 (1.26)	9.12 (7.36)	6.57 (2.68)	15.28 (10.21)	18.58 (10.72)	21.45 (12.28)	15.87 (3.09)
Calendar year of treatment index - n (%)								
2013	56 (9.82)		9 (3.18)		3 (2.38)		1 (1.47)	
2014	60 (10.53)		40 (14.13)	2 (13.33)	13 (10.32)	3 (30)	2 (2.94)	1 (33.33)
2015	85 (14.91)	1 (11.11)	34 (12.01)	7 (46.67)	18 (14.29)	2 (20)	9 (13.24)	1 (33.33)
2016	80 (14.04)		56 (19.79)	1 (6.67)	26 (20.63)	2 (20)	12 (17.65)	
2017	140 (24.56)	3 (33.33)	62 (21.91)	2 (13.33)	23 (18.25)	1 (10)	19 (27.94)	
2018	149 (26.14)	5 (55.56)	82 (28.98)	3 (20)	43 (34.13)	2 (20)	25 (36.76)	1 (33.33)
Census region - n (%)								
Midwest	43 (7.54)		17 (6.01)	2 (13.33)	8 (6.35)		4 (5.88)	
Northeast	75 (13.16)	2 (22.22)	33 (11.66)		19 (15.08)		8 (11.76)	
South	299 (52.46)	4 (44.44)	145 (51.24)	8 (53.33)	52 (41.27)	8 (80)	33 (48.53)	2 (66.67)
West	153 (26.84)	3 (33.33)	88 (31.1)	5 (33.33)	47 (37.3)	2 (20)	23 (33.82)	1 (33.33)

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy Page 1 of 2

Table 15-2.11. Baseline characteristics of treated MM patients in Optum Clinformatics Data Mart (2013-2019), Hispanic

	LOT 1		LOT 2		LOT 3		LOT 4	
	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing
	570 (98.45)	9 (1.55)	283 (94.97)	15 (5.03)	126 (92.65)	10 (7.35)	68 (95.77)	3 (4.23)
Myeloma-related factors - n (%)								
Renal_disease	200 (35.09)	2 (22.22)	89 (31.45)	4 (26.67)	35 (27.78)	1 (10)	17 (25)	
Hypercalcemia	53 (9.3)	1 (11.11)	24 (8.48)	1 (6.67)	9 (7.14)	2 (20)	5 (7.35)	
Anemia	287 (50.35)	4 (44.44)	137 (48.41)	5 (33.33)	67 (53.17)	7 (70)	36 (52.94)	2 (66.67)
Other clinical comorbidities - n (%)								
Cardiovascular history								
Hypertension	369 (64.74)	6 (66.67)	180 (63.6)	10 (66.67)	74 (58.73)	9 (90)	39 (57.35)	2 (66.67)
Cardiac_failure	64 (11.23)	1 (11.11)	23 (8.13)	2 (13.33)	7 (5.56)		2 (2.94)	
Cardiomyopathy	23 (4.04)		7 (2.47)		2 (1.59)			
Cardiacarrhythmias	103 (18.07)	1 (11.11)	39 (13.78)	2 (13.33)	20 (15.87)		13 (19.12)	
Ischemic_heart_disease	103 (18.07)	2 (22.22)	52 (18.37)	2 (13.33)	20 (15.87)	3 (30)	12 (17.65)	
Peripheral_vascular_disease	87 (15.26)	1 (11.11)	44 (15.55)	4 (26.67)	23 (18.25)	3 (30)	8 (11.76)	
Hypercholesterolemia	304 (53.33)	5 (55.56)	142 (50.18)	9 (60)	60 (47.62)	5 (50)	30 (44.12)	1 (33.33)
Chronic obstructive pulmonary disease	82 (14.39)	1 (11.11)	38 (13.43)	3 (20)	14 (11.11)	1 (10)	8 (11.76)	1 (33.33)
Diabetes	207 (36.32)	5 (55.56)	92 (32.51)	10 (66.67)	37 (29.37)	5 (50)	22 (32.35)	1 (33.33)
Liver_disease	51 (8.95)	2 (22.22)	17 (6.01)	3 (20)	5 (3.97)	3 (30)	3 (4.41)	2 (66.67)
GI_bleeding_disorders	27 (4.74)	2 (22.22)	14 (4.95)	1 (6.67)	6 (4.76)	1 (10)	1 (1.47)	
Inflammatory_disease	32 (5.61)		18 (6.36)	1 (6.67)	10 (7.94)	1 (10)	4 (5.88)	
Lifestyle risk factors - n (%)								
Obesity	128 (22.46)	3 (33.33)	57 (20.14)	4 (26.67)	16 (12.7)	4 (40)	11 (16.18)	
Smoking	42 (7.37)	1 (11.11)	22 (7.77)		5 (3.97)	2 (20)	5 (7.35)	
Alcohol	17 (2.98)	1 (11.11)	7 (2.47)	1 (6.67)	2 (1.59)		2 (2.94)	
Treatments and concomitant medications - n (%)								
Antihypertensives	385 (67.54)	6 (66.67)	217 (76.68)	9 (60)	93 (73.81)	10 (100)	50 (73.53)	2 (66.67)
Cholesterolmeds	306 (53.68)	6 (66.67)	169 (59.72)	7 (46.67)	72 (57.14)	7 (70)	38 (55.88)	2 (66.67)
Antidiabetics	178 (31.23)	5 (55.56)	95 (33.57)	7 (46.67)	38 (30.16)	5 (50)	21 (30.88)	2 (66.67)

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy Page 2 of 2

Table 15-2.12. Baseline characteristics of treated MM patients in the Humana Integrated Database (2013-2019), all races

	LOT 1		LOT 2		LOT 3		LOT 4*	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	37 (100%)	3,749 (100%)	201 (100%)	1,293 (100%)	105 (100%)	579 (100%)	72 (100%)	385 (100%)
Race/ethnicity - n (%)								
White	26 (70.3%)	2,575 (68.7%)	142 (70.6%)	893 (69.1%)	81 (77.1%)	398 (68.7%)	58 (80.6%)	283 (73.5%)
Black	10 (27.0%)	1,039 (27.7%)	54 (26.9%)	355 (27.5%)	21 (20.0%)	159 (27.5%)	13 (18.1%)	83 (21.6%)
Other	<10	135 (3.6%)	<10	45 (3.5%)	<10	22 (3.8%)	<10	19 (4.9%)
Age at treatment index (year)								
Mean (Stdev)	68.2 (6.9)	74.0 (7.4)	72.6 (6.9)	74.1 (7.4)	74.1 (6.9)	74.4 (7.3)	72.5 (7.5)	74.3 (7.4)
Median (IQR25, 75)	69.0 (65.0 , 73.0)	74.0 (70.0 , 79.0)	72.0 (69.0 , 77.0)	74.0 (70.0 , 79.0)	74.0 (71.0 , 79.0)	74.0 (70.0 , 80.0)	72.5 (69.5 , 77.0)	75.0 (70.0 , 79.0)
Age at treatment index - n (%)								
18-65 years	10 (27.0%)	313 (8.3%)	19 (9.5%)	129 (10.0%)	<10	54 (9.3%)	<10	52 (13.5%)
66-69 years	<10	621 (16.6%)	43 (21.4%)	167 (12.9%)	13 (12.4%)	79 (13.6%)	10 (13.9%)	29 (7.5%)
70-74 years	11 (29.7%)	1,045 (27.9%)	69 (34.3%)	373 (28.8%)	36 (34.3%)	165 (28.5%)	23 (31.9%)	109 (28.3%)
75-79 years	<10	899 (24.0%)	31 (15.4%)	316 (24.4%)	25 (23.8%)	135 (23.3%)	22 (30.6%)	99 (25.7%)
80+ years	0 (0.0%)	871 (23.2%)	39 (19.4%)	308 (23.8%)	23 (21.9%)	146 (25.2%)	<10	96 (24.9%)
Sex - n (%)								
Female	18 (48.6%)	1,689 (45.1%)	67 (33.3%)	602 (46.6%)	41 (39.0%)	265 (45.8%)	29 (40.3%)	175 (45.5%)
Male	19 (51.4%)	2,060 (54.9%)	134 (66.7%)	691 (53.4%)	64 (61.0%)	314 (54.2%)	43 (59.7%)	210 (54.5%)
Months from index MM diagnosis to treatment index								
Mean (Stdev)	4.0 (6.2)	2.9 (7.1)	13.6 (11.2)	16.6 (12.4)	23.7 (13.2)	25.5 (14.1)	34.0 (15.6)	38.0 (14.7)
Median (IQR25, 75)	1.2 (0.5 , 4.6)	0.7 (0.3 , 1.8)	9.6 (6.1 , 17.2)	12.7 (7.9 , 22.1)	20.8 (12.9 , 29.3)	22.4 (14.4 , 33.5)	30.2 (22.0 , 43.1)	37.0 (26.1 , 48.7)
Calendar year of treatment index - n (%)								
2013	<10	499 (13.3%)	24 (11.9%)	226 (17.5%)	31 (29.5%)	122 (21.1%)	21 (29.2%)	113 (29.4%)
2014	<10	542 (14.5%)	38 (18.9%)	223 (17.2%)	16 (15.2%)	113 (19.5%)	17 (23.6%)	95 (24.7%)
2015	<10	599 (16.0%)	43 (21.4%)	229 (17.7%)	23 (21.9%)	129 (22.3%)	17 (23.6%)	100 (26.0%)
2016	<10	608 (16.2%)	43 (21.4%)	231 (17.9%)	18 (17.1%)	95 (16.4%)	12 (16.7%)	52 (13.5%)
2017	<10	673 (18.0%)	27 (13.4%)	234 (18.1%)	11 (10.5%)	87 (15.0%)	<10	22 (5.7%)
2018	10 (27.0%)	650 (17.3%)	23 (11.4%)	138 (10.7%)	<10	33 (5.7%)	<10	<10
2019	<10	178 (4.7%)	<10	12 (0.9%)	0	0	0	0

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy

Table 15-2.12. Baseline characteristics of treated MM patients in the Humana Integrated Database (2013-2019), all races

	LOT 1		LOT 2		LOT 3		LOT 4*	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	37 (100%)	3,749 (100%)	201 (100%)	1,293 (100%)	105 (100%)	579 (100%)	72 (100%)	385 (100%)
Census region - n (%)								
Northeast	0 (0.0%)	92 (2.5%)	<10	29 (2.2%)	<10	<10	0 (0.0%)	<10
Midwest	<10	845 (22.5%)	52 (25.9%)	263 (20.3%)	23 (21.9%)	123 (21.2%)	14 (19.4%)	105 (27.3%)
South	27 (73.0%)	2,500 (66.7%)	137 (68.2%)	905 (70.0%)	73 (69.5%)	415 (71.7%)	55 (76.4%)	255 (66.2%)
West	<10	312 (8.3%)	11 (5.5%)	96 (7.4%)	<10	35 (6.0%)	<10	20 (5.2%)
Myeloma-related factors - n (%)								
Renal disease	<10	1,448 (38.6%)	86 (42.8%)	571 (44.2%)	46 (43.8%)	275 (47.5%)	34 (47.2%)	173 (44.9%)
Hypercalcemia	<10	425 (11.3%)	30 (14.9%)	140 (10.8%)	13 (12.4%)	48 (8.3%)	11 (15.3%)	28 (7.3%)
Anemia	17 (45.9%)	2,087 (55.7%)	154 (76.6%)	870 (67.3%)	84 (80.0%)	394 (68.0%)	53 (73.6%)	258 (67.0%)
Other clinical comorbidities - n (%)								
Cardiovascular history								
Hypertension	26 (70.3%)	3,002 (80.1%)	162 (80.6%)	1,029 (79.6%)	79 (75.2%)	453 (78.2%)	54 (75.0%)	275 (71.4%)
Heart failure	<10	613 (16.4%)	26 (12.9%)	240 (18.6%)	16 (15.2%)	123 (21.2%)	12 (16.7%)	71 (18.4%)
Cariomyopathy	<10	197 (5.3%)	<10	76 (5.9%)	<10	40 (6.9%)	<10	23 (6.0%)
Dysrhythmias	<10	866 (23.1%)	47 (23.4%)	350 (27.1%)	28 (26.7%)	166 (28.7%)	<10	99 (25.7%)
Ischemic heart disease	<10	918 (24.5%)	43 (21.4%)	288 (22.3%)	21 (20.0%)	136 (23.5%)	<10	70 (18.2%)
Perhipheral vascular disease	<10	714 (19.0%)	48 (23.9%)	308 (23.8%)	25 (23.8%)	142 (24.5%)	21 (29.2%)	84 (21.8%)
Hypercholesterolemia	18 (48.6%)	2,240 (59.7%)	114 (56.7%)	757 (58.5%)	62 (59.0%)	337 (58.2%)	37 (51.4%)	188 (48.8%)
Chronic obstructive pulmonary disease	<10	746 (19.9%)	37 (18.4%)	261 (20.2%)	16 (15.2%)	135 (23.3%)	22 (30.6%)	101 (26.2%)
Diabetes	<10	1,295 (34.5%)	64 (31.8%)	459 (35.5%)	33 (31.4%)	187 (32.3%)	27 (37.5%)	128 (33.2%)
Liver disease	<10	118 (3.1%)	13 (6.5%)	43 (3.3%)	<10	19 (3.3%)	<10	13 (3.4%)
Gastrointestinal bleeding	<10	347 (9.3%)	20 (10.0%)	129 (10.0%)	<10	39 (6.7%)	<10	31 (8.1%)
Inflammatory diseases	<10	211 (5.6%)	13 (6.5%)	63 (4.9%)	<10	27 (4.7%)	<10	<10
Lifestyle risk factors - n (%)								
Smoking	<10	445 (11.9%)	22 (10.9%)	154 (11.9%)	<10	56 (9.7%)	<10	30 (7.8%)
Obesity	<10	1,087 (29.0%)	56 (27.9%)	377 (29.2%)	20 (19.0%)	161 (27.8%)	14 (19.4%)	104 (27.0%)
Alcohol consumption	<10	100 (2.7%)	<10	25 (1.9%)	<10	14 (2.4%)	0 (0.0%)	<10

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy

Table 15-2.12. Baseline characteristics of treated MM patients in the Humana Integrated Database (2013-2019), all races

	LOT 1		LOT 2		LOT 3		LOT 4*	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	37 (100%)	3,749 (100%)	201 (100%)	1,293 (100%)	105 (100%)	579 (100%)	72 (100%)	385 (100%)
Treatments and concomitant medications - n (%)								
Antihypertensives	25 (67.6%)	2,908 (77.6%)	154 (76.6%)	1,012 (78.3%)	79 (75.2%)	457 (78.9%)	57 (79.2%)	289 (75.1%)
Cholesterol lowering medications	<10	1,983 (52.9%)	101 (50.2%)	659 (51.0%)	49 (46.7%)	286 (49.4%)	25 (34.7%)	181 (47.0%)
Antidiabetics	<10	937 (25.0%)	46 (22.9%)	311 (24.1%)	22 (21.0%)	123 (21.2%)	25 (34.7%)	89 (23.1%)

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy Page 3 of 3

Table 15-2.13. Baseline characteristics of treated MM patients in the Humana Integrated Database (2013-2019), white

	LOT 1		LOT 2		LOT 3		LOT 4*	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	26 (100%)	2,575 (100%)	142 (100%)	893 (100%)	81 (100%)	398 (100%)	58 (100%)	283 (100%)
Age at treatment index (year)								
Mean (Stdev)	67.6 (7.9)	74.4 (7.2)	73.1 (6.7)	74.4 (7.3)	74.0 (7.0)	74.5 (7.1)	72.8 (7.6)	74.7 (7.4)
Median (IQR25, 75)	69.0 (63.0 , 74.0)	74.0 (70.0 , 79.0)	72.0 (69.0 , 78.0)	75.0 (70.0 , 79.0)	74.0 (71.0 , 78.0)	75.0 (70.0 , 80.0)	72.0 (69.0 , 77.0)	75.0 (71.0 , 80.0)
Age at treatment index - n (%)								
18-65 years	<10	194 (7.5%)	11 (7.7%)	79 (8.8%)	<10	37 (9.3%)	<10	38 (13.4%)
66-69 years	<10	384 (14.9%)	29 (20.4%)	100 (11.2%)	10 (12.3%)	56 (14.1%)	10 (17.2%)	16 (5.7%)
70-74 years	<10	740 (28.7%)	48 (33.8%)	266 (29.8%)	29 (35.8%)	105 (26.4%)	18 (31.0%)	69 (24.4%)
75-79 years	<10	624 (24.2%)	24 (16.9%)	227 (25.4%)	20 (24.7%)	99 (24.9%)	17 (29.3%)	88 (31.1%)
80+ years	0 (0.0%)	633 (24.6%)	30 (21.1%)	221 (24.7%)	17 (21.0%)	101 (25.4%)	<10	72 (25.4%)
Sex - n (%)								
Female	12 (46.2%)	1,081 (42.0%)	40 (28.2%)	385 (43.1%)	31 (38.3%)	161 (40.5%)	18 (31.0%)	116 (41.0%)
Male	14 (53.8%)	1,494 (58.0%)	102 (71.8%)	508 (56.9%)	50 (61.7%)	237 (59.5%)	40 (69.0%)	167 (59.0%)
Months from index MM diagnosis to treatment index								
Mean (Stdev)	4.6 (7.1)	3.0 (7.2)	13.1 (11.2)	16.8 (12.1)	23.1 (12.1)	25.3 (13.9)	34.8 (15.1)	38.8 (14.6)
Median (IQR25, 75)	1.1 (0.5 , 5.8)	0.7 (0.3 , 1.7)	9.6 (6.1 , 15.3)	12.9 (8.2 , 22.5)	20.8 (13.5 , 27.4)	22.4 (14.2 , 33.3)	30.2 (22.8 , 43.4)	37.9 (27.4 , 49.2)
Calendar year of treatment index - n (%)								
2013	<10	361 (14.0%)	17 (12.0%)	164 (18.4%)	23 (28.4%)	85 (21.4%)	17 (29.3%)	86 (30.4%)
2014	<10	377 (14.6%)	24 (16.9%)	165 (18.5%)	11 (13.6%)	81 (20.4%)	15 (25.9%)	75 (26.5%)
2015	<10	401 (15.6%)	31 (21.8%)	150 (16.8%)	21 (25.9%)	80 (20.1%)	14 (24.1%)	66 (23.3%)
2016	<10	432 (16.8%)	34 (23.9%)	160 (17.9%)	15 (18.5%)	70 (17.6%)	10	40 (14.1%)
2017	<10	459 (17.8%)	19 (13.4%)	161 (18.0%)	<10	59 (14.8%)	<10	13 (4.6%)
2018	<10	419 (16.3%)	15 (10.6%)	85 (9.5%)	<10	23 (5.8%)	<10	<10
2019	<10	126 (4.9%)	<10	<10				
Census region - n (%)								
Northeast	0 (0.0%)	68 (2.6%)	<10	18 (2.0%)	<10	<10	0 (0.0%)	<10
Midwest	<10	654 (25.4%)	38 (26.8%)	212 (23.7%)	21 (25.9%)	99 (24.9%)	12 (20.7%)	84 (29.7%)

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy

Table 15-2.13. Baseline characteristics of treated MM patients in the Humana Integrated Database (2013-2019), white

	LOT 1		LOT 2		LOT 3		LOT 4*	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	26 (100%)	2,575 (100%)	142 (100%)	893 (100%)	81 (100%)	398 (100%)	58 (100%)	283 (100%)
South	18 (69.2%)	1,593 (61.9%)	93 (65.5%)	582 (65.2%)	53 (65.4%)	267 (67.1%)	44 (75.9%)	178 (62.9%)
West	<10	260 (10.1%)	10 (7.0%)	81 (9.1%)	<10	28 (7.0%)	<10	17 (6.0%)
Myeloma-related factors - n (%)								
Renal disease	<10	896 (34.8%)	57 (40.1%)	356 (39.9%)	30 (37.0%)	171 (43.0%)	25 (43.1%)	119 (42.0%)
Hypercalcemia	<10	274 (10.6%)	25 (17.6%)	88 (9.9%)	10 (12.3%)	31 (7.8%)	<10	23 (8.1%)
Anemia	12 (46.2%)	1,311 (50.9%)	103 (72.5%)	569 (63.7%)	61 (75.3%)	242 (60.8%)	40 (69.0%)	181 (64.0%)
Other clinical comorbidities - n (%)								
Cardiovascular history								
Hypertension	19 (73.1%)	1,964 (76.3%)	110 (77.5%)	672 (75.3%)	57 (70.4%)	292 (73.4%)	41 (70.7%)	191 (67.5%)
Heart failure	<10	398 (15.5%)	19 (13.4%)	164 (18.4%)	11 (13.6%)	82 (20.6%)	12 (20.7%)	49 (17.3%)
Cariomyopathy	0 (0.0%)	120 (4.7%)	<10	44 (4.9%)	<10	26 (6.5%)	<10	13 (4.6%)
Dysrhythmias	<10	628 (24.4%)	37 (26.1%)	252 (28.2%)	21 (25.9%)	113 (28.4%)	<10	75 (26.5%)
Ischemic heart disease	<10	661 (25.7%)	31 (21.8%)	207 (23.2%)	15 (18.5%)	97 (24.4%)	<10	54 (19.1%)
Perhipheral vascular disease	<10	436 (16.9%)	33 (23.2%)	199 (22.3%)	21 (25.9%)	89 (22.4%)	14 (24.1%)	57 (20.1%)
Hypercholesterolemia	14 (53.8%)	1,509 (58.6%)	82 (57.7%)	505 (56.6%)	44 (54.3%)	227 (57.0%)	29 (50.0%)	136 (48.1%)
Chronic obstructive pulmonary disease	<10	515 (20.0%)	25 (17.6%)	183 (20.5%)	13 (16.0%)	86 (21.6%)	16 (27.6%)	71 (25.1%)
Diabetes	<10	776 (30.1%)	47 (33.1%)	285 (31.9%)	22 (27.2%)	112 (28.1%)	22 (37.9%)	96 (33.9%)
Liver disease	<10	82 (3.2%)	10 (7.0%)	32 (3.6%)	<10	15 (3.8%)	<10	<10
Gastrointestinal bleeding	0 (0.0%)	216 (8.4%)	13 (9.2%)	84 (9.4%)	<10	22 (5.5%)	<10	19 (6.7%)
Inflammatory diseases	<10	149 (5.8%)	<10	44 (4.9%)	<10	18 (4.5%)	<10	<10
Lifestyle risk factors - n (%)								
Smoking	<10	315 (12.2%)	17 (12.0%)	104 (11.6%)	<10	41 (10.3%)	<10	20 (7.1%)
Obesity	<10	667 (25.9%)	38 (26.8%)	224 (25.1%)	13 (16.0%)	99 (24.9%)	<10	67 (23.7%)
Alcohol consumption	0 (0.0%)	66 (2.6%)	<10	14 (1.6%)	0 (0.0%)	<10	0 (0.0%)	<10

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy Page 2 of 3

Table 15-2.13. Baseline characteristics of treated MM patients in the Humana Integrated Database (2013-2019), white

	LOT 1		LOT 2		LOT 3		LOT 4*	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	26 (100%)	2,575 (100%)	142 (100%)	893 (100%)	81 (100%)	398 (100%)	58 (100%)	283 (100%)
Treatments and concomitant medications - n (%)								
Antihypertensives	19 (73.1%)	1,912 (74.3%)	106 (74.6%)	663 (74.2%)	59 (72.8%)	300 (75.4%)	46 (79.3%)	211 (74.6%)
Cholesterol lowering medications	<10	1,335 (51.8%)	75 (52.8%)	433 (48.5%)	34 (42.0%)	199 (50.0%)	20 (34.5%)	139 (49.1%)
Antidiabetics	<10	560 (21.7%)	36 (25.4%)	189 (21.2%)	16 (19.8%)	75 (18.8%)	20 (34.5%)	70 (24.7%)

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy Page 3 of 3

Table 15-2.14. Baseline characteristics of treated MM patients in the Humana Integrated Database (2013-2019), black

	LOT 1		LOT 2		LOT 3		LOT 4*	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	10 (100%)	1,039 (100%)	54 (100%)	355 (100%)	21 (100%)	159 (100%)	13 (100%)	83 (100%)
Age at treatment index (year)								
Mean (Stdev)	68.8 (2.7)	73.2 (7.5)	71.6 (6.6)	73.2 (7.6)	74.3 (6.5)	74.1 (7.4)	72.2 (6.8)	72.5 (7.1)
Median (IQR25, 75)	69.0 (66.0 , 70.0)	73.0 (69.0 , 78.0)	70.5 (68.0 , 75.0)	73.0 (69.0 , 79.0)	73.0 (70.0 , 79.0)	74.0 (70.0 , 79.0)	73.0 (72.0 , 75.0)	72.0 (69.0 , 75.0)
Age at treatment index - n (%)								
18-65 years	<10	109 (10.5%)	<10	46 (13.0%)	<10	15 (9.4%)	<10	12 (14.5%)
66-69 years	<10	210 (20.2%)	13 (24.1%)	55 (15.5%)	<10	17 (10.7%)	0 (0.0%)	<10
70-74 years	<10	273 (26.3%)	19 (35.2%)	101 (28.5%)	<10	56 (35.2%)	<10	37 (44.6%)
75-79 years	0 (0.0%)	241 (23.2%)	<10	80 (22.5%)	<10	33 (20.8%)	<10	11 (13.3%)
80+ years	0 (0.0%)	206 (19.8%)	<10	73 (20.6%)	<10	38 (23.9%)	<10	14 (16.9%)
Sex - n (%)								
Female	<10	549 (52.8%)	26 (48.1%)	194 (54.6%)	10 (47.6%)	93 (58.5%)	11 (84.6%)	49 (59.0%)
Male	<10	490 (47.2%)	28 (51.9%)	161 (45.4%)	11 (52.4%)	66 (41.5%)	<10	34 (41.0%)
Months from index MM diagnosis to treatment index								
Mean (Stdev)	2.3 (3.0)	2.9 (7.0)	14.8 (11.2)	16.4 (13.1)	24.8 (16.3)	26.2 (14.8)	30.7 (17.4)	36.6 (15.2)
Median (IQR25, 75)	1.1 (0.7 , 2.1)	0.9 (0.4 , 2.0)	10.6 (6.0 , 20.6)	12.6 (7.1 , 21.3)	20.6 (11.2 , 31.3)	22.9 (14.4 , 34.4)	28.2 (17.4 , 35.1)	35.0 (24.5 , 45.3)
Calendar year of treatment index - n (%)								
2013	0 (0.0%)	124 (11.9%)	<10	56 (15.8%)	<10	34 (21.4%)	<10	24 (28.9%)
2014	<10	144 (13.9%)	13 (24.1%)	49 (13.8%)	<10	28 (17.6%)	<10	17 (20.5%)
2015	0 (0.0%)	174 (16.7%)	12 (22.2%)	69 (19.4%)	<10	40 (25.2%)	<10	23 (27.7%)
2016	0 (0.0%)	153 (14.7%)	<10	65 (18.3%)	<10	23 (14.5%)	<10	11 (13.3%)
2017	<10	184 (17.7%)	<10	62 (17.5%)	<10	24 (15.1%)	<10	<10
2018	<10	213 (20.5%)	<10	51 (14.4%)	<10	10 (6.3%)	0	0
2019	<10	47 (4.5%)	<10	<10	0	0	0	0
Census region - n (%)								
Northeast	0 (0.0%)	19 (1.8%)	0 (0.0%)	<10	0 (0.0%)	<10	0 (0.0%)	<10
Midwest	<10	175 (16.8%)	13 (24.1%)	48 (13.5%)	<10	22 (13.8%)	<10	19 (22.9%)

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy

Table 15-2.14. Baseline characteristics of treated MM patients in the Humana Integrated Database (2013-2019), black

	LOT 1		LOT 2		LOT 3		LOT 4*	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	10 (100%)	1,039 (100%)	54 (100%)	355 (100%)	21 (100%)	159 (100%)	13 (100%)	83 (100%)
South	<10	820 (78.9%)	40 (74.1%)	289 (81.4%)	17 (81.0%)	133 (83.6%)	11 (84.6%)	62 (74.7%)
West	0 (0.0%)	25 (2.4%)	<10	<10	<10	<10	0 (0.0%)	<10
Myeloma-related factors - n (%)								
Renal disease	<10	485 (46.7%)	26 (48.1%)	192 (54.1%)	14 (66.7%)	93 (58.5%)	<10	42 (50.6%)
Hypercalcemia	0 (0.0%)	133 (12.8%)	<10	44 (12.4%)	<10	15 (9.4%)	<10	<10
Anemia	<10	685 (65.9%)	46 (85.2%)	269 (75.8%)	20 (95.2%)	134 (84.3%)	13 (100.0%)	64 (77.1%)
Other clinical comorbidities - n (%)								
Cardiovascular history								
Hypertension	<10	929 (89.4%)	48 (88.9%)	320 (90.1%)	19 (90.5%)	144 (90.6%)	12 (92.3%)	70 (84.3%)
Heart failure	<10	198 (19.1%)	<10	68 (19.2%)	<10	38 (23.9%)	0 (0.0%)	19 (22.9%)
Cariomyopathy	<10	70 (6.7%)	<10	31 (8.7%)	<10	13 (8.2%)	0 (0.0%)	10 (12.0%)
Dysrhythmias	<10	210 (20.2%)	10 (18.5%)	88 (24.8%)	<10	48 (30.2%)	<10	18 (21.7%)
Ischemic heart disease	0 (0.0%)	227 (21.8%)	<10	76 (21.4%)	<10	37 (23.3%)	<10	15 (18.1%)
Perhipheral vascular disease	<10	246 (23.7%)	11 (20.4%)	98 (27.6%)	<10	46 (28.9%)	<10	19 (22.9%)
Hypercholesterolemia	<10	653 (62.8%)	29 (53.7%)	223 (62.8%)	15 (71.4%)	96 (60.4%)	<10	42 (50.6%)
Chronic obstructive pulmonary disease	<10	206 (19.8%)	12 (22.2%)	68 (19.2%)	<10	44 (27.7%)	<10	27 (32.5%)
Diabetes	<10	471 (45.3%)	15 (27.8%)	160 (45.1%)	10 (47.6%)	66 (41.5%)	<10	25 (30.1%)
Liver disease	0 (0.0%)	27 (2.6%)	<10	<10	<10	<10	0 (0.0%)	<10
Gastrointestinal bleeding	<10	117 (11.3%)	<10	41 (11.5%)	<10	15 (9.4%)	<10	12 (14.5%)
Inflammatory diseases	0 (0.0%)	53 (5.1%)	<10	16 (4.5%)	<10	<10	<10	<10
Lifestyle risk factors - n (%)								
Smoking	<10	122 (11.7%)	<10	46 (13.0%)	<10	15 (9.4%)	0 (0.0%)	<10
Obesity	<10	383 (36.9%)	17 (31.5%)	141 (39.7%)	<10	58 (36.5%)	<10	35 (42.2%)
Alcohol consumption	<10	28 (2.7%)	<10	<10	<10	<10	0 (0.0%)	<10

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy

Table 15-2.14. Baseline characteristics of treated MM patients in the Humana Integrated Database (2013-2019), black

	LOT 1		LOT 2		LOT 3		LOT 4*	
	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free	Carfilzomib containing	Carfilzomib free
	10 (100%)	1,039 (100%)	54 (100%)	355 (100%)	21 (100%)	159 (100%)	13 (100%)	83 (100%)
Treatments and concomitant medications - n (%)								
Antihypertensives	<10	891 (85.8%)	45 (83.3%)	314 (88.5%)	17 (81.0%)	139 (87.4%)	11 (84.6%)	69 (83.1%)
Cholesterol lowering medications	<10	582 (56.0%)	23 (42.6%)	206 (58.0%)	13 (61.9%)	78 (49.1%)	<10	35 (42.2%)
Antidiabetics	<10	337 (32.4%)	<10	110 (31.0%)	<10	41 (25.8%)	<10	13 (15.7%)

Footnotes: n = Patient-lines, Stdev = standard deviation, IQR = Interquartile range, MM = Multiple myeloma, LOT = Line of therapy Page 3 of 3

Table 15-4.1. Incidence rate of heart failure of multiple myeloma patients treated with carfilzomib-containing regimens by race/ethnicity status in Medicare FFS (2013-2017)

Line of Therapy	Race	N	PY	Events	IR (95% CI)
All	White	1800	995.02	144	14.47 (12.2, 17.04)
	Black	281	151.95	24	15.79 (10.12, 23.5)
	Asian	26	15.33	*	* (*, *)
	Hispanic	31	14.74	*	* (*, *)
	North American native	*	*	*	* (*, *)
1	White	128	68.70	11	16.01 (7.98, 28.65)
	Black	15	9.23	*	* (*, *)
	Asian	*	*	*	* (*, *)
	Hispanic	*	*	*	* (*, *)
	North American native	0	0.00	0	(,)
2	White	738	421.07	62	14.72 (11.29, 18.88)
	Black	132	74.29	*	* (*, *)
	Asian	>10	6.66	*	* (*, *)
	Hispanic	17	7.44	*	* (*, *)
	North American native	*	*	*	* (*, *)
3	White	541	296.40	47	15.86 (11.65, 21.09)
	Black	81	36.94	*	* (*, *)
	Asian	*	*	*	* (*, *)
	Hispanic	*	*	*	* (*, *)
	North American native	*	*	*	* (*, *)
4+	White	393	208.86	24	11.49 (7.36, 17.1)
	Black	53	31.49	*	* (*, *)
	Asian	*	*	*	* (*, *)
	Hispanic	*	*	*	* (*, *)
	North American native	0	0.00	0	(,)

Footnotes: N = Patient-lines, PY = Person-Years, IR = Incidence Rate, * = Values for cells with less than 11 counts must be suppressed

Table 15-4.2. Incidence rate of heart failure of multiple myeloma patients treated with non-carfilzomib-containing regimens by race/ethnicity status in Medicare FFS (2013-2017)

Line of Therapy	Race	N	PY	Events	IR (95% CI)
All	White	26328	17441.80	1871	10.73 (10.25, 11.22)
	Black	4771	3131.96	380	12.13 (10.94, 13.42)
	Asian	406	299.52	18	6.01 (3.56, 9.5)
	Hispanic	521	300.21	29	9.66 (6.47, 13.87)
	North American native	130	86.37	13	15.05 (8.01, 25.74)
1	White	15621	10942.78	1312	11.99 (11.35, 12.66)
	Black	3013	2104.68	287	13.64 (12.1, 15.31)
	Asian	253	209.00	13	6.22 (3.31, 10.64)
	Hispanic	326	188.05	19	10.1 (6.08, 15.78)
	North American native	81	58.55	*	* (*, *)
2	White	6403	4108.98	345	8.4 (7.53, 9.33)
	Black	1110	692.38	59	8.52 (6.49, 10.99)
	Asian	103	67.10	*	* (*, *)
	Hispanic	116	66.12	*	* (*, *)
	North American native	28	17.47	*	* (*, *)
3	White	2645	1566.39	129	8.24 (6.88, 9.79)
	Black	419	230.76	24	10.4 (6.66, 15.48)
	Asian	31	16.54	*	* (*, *)
	Hispanic	46	30.11	*	* (*, *)
	North American native	11	6.65	*	* (*, *)
4+	White	1659	823.65	85	10.32 (8.24, 12.76)
	Black	229	104.15	*	* (*, *)
	Asian	19	6.87	*	* (*, *)
	Hispanic	33	15.93	*	* (*, *)
	North American native	*	*	*	* (*, *)

Footnotes: N = Patient-lines, PY = Person-Years, IR = Incidence Rate, * = Values for cells with less than 11 counts must be suppressed

Table 15-4.3. Incidence rate of heart failure of multiple myeloma (MM) patients treated with carfilzomib-containing regimens by race/ethnicity status and line of therapy in Optum Clinformatics Data Mart (2014-2018)

Line of Therapy	Race	N	PY	Events	IR (95% CI)
All	White	429	192.26	14	7.28 (4.17, 11.89)
	Black	78	33.69	3	8.9 (2.46, 23.76)
	Other	71	29.85	3	10.05 (2.78, 26.82)
1	White	70	42.17	2	4.74 (0.95, 15.2)
	Black	11	4.79	1	20.87 (1.89, 97.31)
	Other	13	5.91	1	16.93 (1.53, 78.91)
2	White	107	53.22	5	9.39 (3.56, 20.59)
	Black	23	10.20	1	9.8 (0.89, 45.7)
	Other	21	11.56	1	8.65 (0.78, 40.31)
3	White	88	49.63	4	8.06 (2.69, 19.16)
	Black	14	6.95	1	14.39 (1.31, 67.09)
	Other	12	3.67	.	(,)
4+	White	164	47.24	3	6.35 (1.76, 16.94)
	Black	30	11.75	.	(,)
	Other	25	8.71	1	11.49 (1.04, 53.55)

Footnotes: N = Patient-lines, PY = Person-Years, IR = Incidence Rate

Table 15-4.4. Incidence rate of heart failure of multiple myeloma (MM) patients treated with non-carfilzomib-containing regimens by race/ethnicity status and line of therapy in Optum Clinformatics Data Mart (2014-2018)

Line of Therapy	Race	N	PY	Events	IR (95% CI)
All	White	7918	3833.44	323	8.43 (7.54, 9.38)
	Black	1848	911.76	105	11.52 (9.47, 13.88)
	Other	1386	670.24	45	6.71 (4.96, 8.9)
1	White	4053	2007.56	194	9.66 (8.37, 11.1)
	Black	959	478.32	67	14.01 (10.95, 17.67)
	Other	714	345.97	33	9.54 (6.68, 13.23)
2	White	1858	935.62	61	6.52 (5.03, 8.31)
	Black	445	225.77	18	7.97 (4.89, 12.33)
	Other	347	170.92	7	4.1 (1.83, 8.04)
3	White	918	451.25	33	7.31 (5.13, 10.14)
	Black	218	110.06	6	5.45 (2.27, 11.24)
	Other	154	79.66	3	3.77 (1.04, 10.05)
4+	White	1089	439.00	35	7.97 (5.65, 10.96)
	Black	226	97.61	14	14.34 (8.21, 23.42)
	Other	171	73.68	2	2.71 (0.54, 8.7)

Footnotes: N = Patient-lines, PY = Person-Years, IR = Incidence Rate

Table 15-4.5. Incidence rate of heart failure (HF) of multiple myeloma (MM) patients treated with carfilzomib-containing regimens by race/ethnicity status in The Humana Integrated Databases (2013-2019)

Line of Therapy	Race	N	PY	Events	IR (95% CI)
All	White	268	183.06	16	8.74 (4.99, 14.19)
	Black	85	70.70	7	9.9 (3.97, 20.4)
	Other	10	8.88	1	11.27 (0.15, 62.68)
1	White	26	15.98	1	6.26 (0.08, 34.83)
	Black	10	7.38	0	0 (., 49.7)
	Other	1	2.88	1	34.7 (0.45, 193.04)
2	White	142	78.29	10	12.77 (6.11, 23.49)
	Black	54	45.82	4	8.73 (2.35, 22.35)
	Other	5	4.20	0	0 (., 87.28)
3	White	81	50.65	3	5.92 (1.19, 17.31)
	Black	21	12.16	2	16.45 (1.85, 59.38)
	Other	3	1.27	0	0 (., 289.8)
4+	White	55	38.15	2	5.24 (0.59, 18.93)
	Black	12	5.34	1	18.74 (0.24, 104.25)
	Other	1	0.53	0	0 (., 697.32)

Footnotes: N = Patient-lines, PY = Person-Years, IR = Incidence Rate

Table 15-4.6. Incidence rate of heart failure (HF) of multiple myeloma (MM) patients treated with carfilzomib-free regimens by race/ethnicity status in the Humana Integrated Databases (2013-2019)

Line of Therapy	Race	N	PY	Events	IR (95% CI)
All	White	2587	2765.32	224	8.1 (7.07, 9.23)
	Black	1042	1133.87	127	11.2 (9.34, 13.33)
	Other	136	146.34	13	8.88 (4.73, 15.19)
1	White	2575	1786.04	155	8.68 (7.37, 10.16)
	Black	1039	738.19	88	11.92 (9.56, 14.69)
	Other	135	91.18	13	14.26 (7.58, 24.38)
2	White	893	557.80	39	6.99 (4.97, 9.56)
	Black	355	250.43	25	9.98 (6.46, 14.74)
	Other	45	29.76	0	0 (., 12.32)
3	White	398	266.71	16	6 (3.43, 9.74)
	Black	159	99.81	9	9.02 (4.11, 17.12)
	Other	22	15.11	0	0 (., 24.28)
4+	White	186	154.78	14	9.05 (4.94, 15.18)
	Black	58	45.44	5	11 (3.55, 25.68)
	Other	12	10.28	0	0 (., 35.67)

Footnotes: N = Patient-lines, PY = Person-Years, IR = Incidence Rate

Table 15-11.1. Baseline characteristics by receipt of carfilzomib-containing therapy status before and after matching by LOT, blacks, in Medicare

	LOT 2						LOT 3 + 4					
	Before match			After match			Before match			After match (matched by LOT)		
	Carfilzomib containing	Carfilzomib free	SMD	Carfilzomib containing	Carfilzomib free	SMD	Carfilzomib containing	Carfilzomib free	SMD	Carfilzomib containing	Carfilzomib free	SMD
	132(100.00)	1110(100.00)		131(100.00)	496(100.00)		119(100.00)	571(100.00)		117(100.00)	336(100.00)	
Age at treatment index (year)												
Mean (Stdev)	71.11(8.41)	73.42(8.93)	-0.2662	71.14(8.44)	71.54(8.60)	-0.0462	71.26(9.14)	72.62(8.92)	-0.1505	71.32(9.16)	72.24(9.39)	-0.0993
Age at treatment index - n(%)												
18-65 years	28(21.21)	175(15.77)	0.1406	28(21.37)	91(18.35)	0.0759	31(26.05)	106(18.56)	0.1806	30(25.64)	72(21.43)	0.0994
66-69 years	27(20.45)	184(16.58)	0.1000	26(19.85)	107(21.57)	-0.0426	14(11.76)	86(15.06)	-0.0968	14(11.97)	41(12.20)	-0.0073
70-74 years	32(24.24)	276(24.86)	-0.0145	32(24.43)	125(25.20)	-0.0179	30(25.21)	153(26.80)	-0.0361	30(25.64)	86(25.60)	0.0010
75-79 years	30(22.73)	213(19.19)	0.0870	30(22.90)	116(23.39)	-0.0115	25(21.01)	111(19.44)	0.0391	24(20.51)	71(21.13)	-0.0152
80+ years	15(11.36)	262(23.60)	-0.3265	15(11.45)	57(11.49)	-0.0013	19(15.97)	115(20.14)	-0.1087	19(16.24)	66(19.64)	-0.0888
Sex - n(%)												
Female	76(57.58)	665(59.91)	-0.0474	76(58.02)	298(60.08)	-0.0420	65(54.62)	355(62.17)	-0.1536	65(55.56)	202(60.12)	-0.0925
Male	56(42.42)	445(40.09)	0.0474	55(41.98)	198(39.92)	0.0420	54(45.38)	216(37.83)	0.1536	52(44.44)	134(39.88)	0.0925
Months from index MM diagnosis to treatment index												
Mean (Stdev)	12.67(9.71)	13.83(9.28)	-0.1215	12.70(9.74)	12.96(9.69)	-0.0272	20.75(10.58)	23.86(10.85)	-0.2909	20.88(10.61)	21.92(10.57)	-0.0985
Calendar year of treatment index - n(%)												
2013	*	64(5.77)	*	*	*	*	13(10.92)	38(6.65)	0.1512	13(11.11)	34(10.12)	0.0322
2014	18(13.64)	201(18.11)	-0.1226	18(13.74)	66(13.31)	0.0127						
2015	32(24.24)	274(24.68)	-0.0103	32(24.43)	131(26.41)	-0.0456	49(41.18)	102(17.86)	0.5287	47(40.17)	96(28.57)	0.2461
2016	>44 (33.33)	337(30.36)	0.1904	>42 (>32.06)	>179 (>36.09)	0.0545	28(23.53)	228(39.93)	-0.3580	28(23.93)	102(30.36)	-0.1449
2017	28(21.21)	234(21.08)	0.0032	28(21.37)	109(21.98)	-0.0146	29(24.37)	203(35.55)	-0.2459	29(24.79)	104(30.95)	-0.1379
Census region - n(%)												
Northeast	17(12.88)	193(17.39)	-0.1261	17(12.98)	60(12.10)	0.0266	17(14.29)	98(17.16)	-0.0791	17(14.53)	56(16.67)	-0.0589
Midwest	24(18.18)	181(16.31)	0.0497	24(18.32)	93(18.75)	-0.0111	23(19.33)	88(15.41)	0.1035	21(17.95)	58(17.26)	0.0180
South	>80 (>60.63)	673(60.63)	0.0463	>80 (>60.63)	310(62.50)	0.0020	>68 (>57.14)	347(60.77)	-0.0397	>68 (>57.11)	199(59.23)	0.0123

Footnotes: n = Patient-lines, Stdev = standard deviation, MM = Multiple myeloma, LOT = Line of therapy, SMD = standardized mean difference

Table 15-11.1. Baseline characteristics by receipt of carfilzomib-containing therapy status before and after matching by LOT, blacks, in Medicare

	LOT 2						LOT 3 + 4					
	Before match			After match			Before match			After match (matched by LOT)		
	Carfilzomib containing	Carfilzomib free	SMD	Carfilzomib containing	Carfilzomib free	SMD	Carfilzomib containing	Carfilzomib free	SMD	Carfilzomib containing	Carfilzomib free	SMD
	132(100.00)	1110(100.00)		131(100.00)	496(100.00)		119(100.00)	571(100.00)		117(100.00)	336(100.00)	
West	*	63(5.68)	*	*	33(6.65)	*	*	38(6.65)	*	*	23(6.85)	*
Myeloma-related factors - n(%)												
Renal disease	62(46.97)	520(46.85)	0.0025	61(46.56)	222(44.76)	0.0363	58(48.74)	259(45.36)	0.0678	56(47.86)	161(47.92)	-0.0011
Hypercalcemia	27(20.45)	158(14.23)	0.1648	26(19.85)	97(19.56)	0.0073	11(9.24)	60(10.51)	-0.0424	11(9.40)	29(8.63)	0.0269
Anemia	108(81.82)	854(76.94)	0.1209	107(81.68)	386(77.82)	0.0961	91(76.47)	437(76.53)	-0.0015	89(76.07)	251(74.70)	0.0317
Stem cell transplant (from MM index to LOT index)	*	119(10.72)	*	*	35(7.06)	*	18(15.13)	142(24.87)	-0.2454	18(15.38)	54(16.07)	-0.0189
Other clinical comorbidities - n(%)												
Cardiovascular history												
Hypertension	114(86.36)	1000(90.09)	-0.1158	113(86.26)	433(87.30)	-0.0307	105(88.24)	505(88.44)	-0.0064	103(88.03)	302(89.88)	-0.0589
Heart failure	25(18.94)	266(23.96)	-0.1226	25(19.08)	101(20.36)	-0.0321	30(25.21)	135(23.64)	0.0365	29(24.79)	86(25.60)	-0.0186
Cardiomyopathy	*	96(8.65)	*	*	29(5.85)	*	*	38(6.65)	*	*	25(7.44)	*
Dysrhythmias	29(21.97)	314(28.29)	-0.1461	29(22.14)	112(22.58)	-0.0106	42(35.29)	148(25.92)	0.2045	41(35.04)	110(32.74)	0.0487
Ischemic heart disease	29(21.97)	306(27.57)	-0.1300	29(22.14)	112(22.58)	-0.0106	31(26.05)	147(25.74)	0.0070	31(26.50)	95(28.27)	-0.0399
Peripheral vascular disease	27(20.45)	270(24.32)	-0.0929	27(20.61)	109(21.98)	-0.0334	25(21.01)	138(24.17)	-0.0756	25(21.37)	72(21.43)	-0.0015
Hypercholesterolemia	70(53.03)	644(58.02)	-0.1005	69(52.67)	270(54.44)	-0.0354	64(53.78)	299(52.36)	0.0284	62(52.99)	173(51.49)	0.0301
Chronic obstructive pulmonary disease	28(21.21)	258(23.24)	-0.0489	28(21.37)	112(22.58)	-0.0291	27(22.69)	128(22.42)	0.0065	26(22.22)	69(20.54)	0.0411
Diabetes	53(40.15)	504(45.41)	-0.1063	52(39.69)	202(40.73)	-0.0210	54(45.38)	245(42.91)	0.0498	52(44.44)	148(44.05)	0.0080
Liver disease	*	59(5.32)	*	*	24(4.84)	*	*	25(4.38)	*	*	16(4.76)	*
Gastrointestinal bleeding	18(13.64)	132(11.89)	0.0523	18(13.74)	60(12.10)	0.0490	14(11.76)	61(10.68)	0.0343	14(11.97)	37(11.01)	0.0299
Inflammatory diseases	11(8.33)	89(8.02)	0.0115	11(8.40)	41(8.27)	0.0047	*	46(8.06)	*	*	26(7.74)	*
Lifestyle risk factors - n(%)												
Smoking	28(21.21)	155(13.96)	0.1912	27(20.61)	94(18.95)	0.0417	23(19.33)	80(14.01)	0.1430	23(19.66)	54(16.07)	0.0937
Obesity	36(27.27)	296(26.67)	0.0137	36(27.48)	144(29.03)	-0.0345	28(23.53)	169(29.60)	-0.1377	28(23.93)	93(27.68)	-0.0857

Footnotes: n = Patient-lines, Stdev = standard deviation, MM = Multiple myeloma, LOT = Line of therapy, SMD = standardized mean difference

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Table 15-11.1. Baseline characteristics by receipt of carfilzomib-containing therapy status before and after matching by LOT, blacks, in Medicare

	LOT 2						LOT 3 + 4					
	Before match			After match			Before match			After match (matched by LOT)		
	Carfilzomib containing	Carfilzomib free	SMD	Carfilzomib containing	Carfilzomib free	SMD	Carfilzomib containing	Carfilzomib free	SMD	Carfilzomib containing	Carfilzomib free	SMD
	132(100.00)	1110(100.00)		131(100.00)	496(100.00)		119(100.00)	571(100.00)		117(100.00)	336(100.00)	
Alcohol consumption	*	32(2.88)	*	*	22(4.44)	*	*	20(3.50)	*	*	*	*
Line of Therapy - n(%)												
3							81(68.07)	419(73.38)	-0.1170	79(67.52)	233(69.35)	-0.0392
4							38(31.93)	152(26.62)	0.1170	38(32.48)	103(30.65)	0.0392

Footnotes: n = Patient-lines, Stdev = standard deviation, MM = Multiple myeloma, LOT = Line of therapy, SMD = standardized mean difference

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Table 15-11.2. Baseline characteristics by receipt of carfilzomib-containing therapy status before and after matching by LOT, whites, in Medicare

	LOT 2						LOT 3 + 4					
	Before match			After match			Before match			After match (matched by LOT)		
	Carfilzomib containing	Carfilzomib free	SMD	Carfilzomib containing	Carfilzomib free	SMD	Carfilzomib containing	Carfilzomib free	SMD	Carfilzomib containing	Carfilzomib free	SMD
	738(100.00)	6403(100.00)		738(100.00)	2849(100.00)		805(100.00)	3675(100.00)		804(100.00)	2753(100.00)	
Age at treatment index (year)												
Mean (Stdev)	74.38(6.72)	76.09(7.69)	-0.2358	74.38(6.72)	74.67(7.08)	-0.0418	75.36(6.89)	75.75(7.45)	-0.0553	75.36(6.90)	75.54(7.21)	-0.0260
Age at treatment index - n(%)												
18-65 years	36(4.88)	294(4.59)	0.0135	36(4.88)	138(4.84)	0.0016	39(4.84)	182(4.95)	-0.0050	39(4.85)	129(4.69)	0.0077
66-69 years	140(18.97)	996(15.56)	0.0905	140(18.97)	545(19.13)	-0.0041	115(14.29)	539(14.67)	-0.0108	115(14.30)	397(14.42)	-0.0033
70-74 years	246(33.33)	1720(26.86)	0.1414	246(33.33)	918(32.22)	0.0237	254(31.55)	1085(29.52)	0.0441	253(31.47)	845(30.69)	0.0167
75-79 years	179(24.25)	1459(22.79)	0.0346	179(24.25)	710(24.92)	-0.0155	214(26.58)	860(23.40)	0.0736	214(26.62)	713(25.90)	0.0163
80+ years	137(18.56)	1934(30.20)	-0.2736	137(18.56)	538(18.88)	-0.0082	183(22.73)	1009(27.46)	-0.1091	183(22.76)	669(24.30)	-0.0363
Sex - n(%)												
Female	315(42.68)	3189(49.80)	-0.1432	315(42.68)	1225(43.00)	-0.0064	379(47.08)	1832(49.85)	-0.0554	379(47.14)	1338(48.60)	-0.0293
Male	423(57.32)	3214(50.20)	0.1432	423(57.32)	1624(57.00)	0.0064	426(52.92)	1843(50.15)	0.0554	425(52.86)	1415(51.40)	0.0293
Months from index MM diagnosis to treatment index	11.84(8.58)	13.56(9.18)	-0.1942	11.84(8.58)	12.59(9.07)	-0.0850	21.98(10.42)	23.26(10.81)	-0.1206	22.00(10.41)	22.42(10.47)	-0.0404
Mean (Stdev)												
Calendar year of treatment index - n(%)												
2013	*	285(4.45)	*	*	49(1.72)	*	79(9.81)	316(8.60)	0.0420	79(9.83)	257(9.34)	0.0167
2014	94 (12.74)	1166(18.21)	-0.1518	94 (12.74)	384(13.48)	-0.0220	236(29.32)	731(19.89)	0.2202	235(29.23)	667(24.23)	0.1132
2015	212(28.73)	1575(24.60)	0.0935	212(28.73)	809(28.40)	0.0073						
2016	>266(>36.0)	1916(29.92)	0.1333	>266(>36.0)	997(34.99)	0.0247	290(36.02)	1306(35.54)	0.0102	290(36.07)	1044(37.92)	-0.0384
2017	155(21.00)	1461(22.82)	-0.0439	155(21.00)	610(21.41)	-0.0100	200(24.84)	1322(35.97)	-0.2437	200(24.88)	785(28.51)	-0.0823
Census region - n(%)												
Northeast	130(17.62)	1310(20.46)	-0.0725	130(17.62)	522(18.32)	-0.0184	155(19.25)	760(20.68)	-0.0357	155(19.28)	564(20.49)	-0.0303
Midwest	201(27.24)	1621(25.32)	0.0436	201(27.24)	775(27.20)	0.0007	182(22.61)	916(24.93)	-0.0544	182(22.64)	632(22.96)	-0.0076
South	259(35.09)	2385(37.25)	-0.0448	259(35.09)	1017(35.70)	-0.0126	315(39.13)	1364(37.12)	0.0415	315(39.18)	1054(38.29)	0.0183

Footnotes: n = Patient-lines, Stdev = standard deviation, MM = Multiple myeloma, LOT = Line of therapy, SMD = standardized mean difference Page 1 of 3

Table 15-11.2. Baseline characteristics by receipt of carfilzomib-containing therapy status before and after matching by LOT, whites, in Medicare

	LOT 2						LOT 3 + 4					
	Before match			After match			Before match			After match (matched by LOT)		
	Carfilzomib containing	Carfilzomib free	SMD	Carfilzomib containing	Carfilzomib free	SMD	Carfilzomib containing	Carfilzomib free	SMD	Carfilzomib containing	Carfilzomib free	SMD
	738(100.00)	6403(100.00)		738(100.00)	2849(100.00)		805(100.00)	3675(100.00)		804(100.00)	2753(100.00)	
West	148(20.05)	1087(16.98)	0.0793	148(20.05)	535(18.78)	0.0323	153(19.01)	635(17.28)	0.0448	152(18.91)	503(18.27)	0.0163
Myeloma-related factors - n(%)												
Renal disease	283(38.35)	2396(37.42)	0.0191	283(38.35)	1078(37.84)	0.0105	311(38.63)	1355(36.87)	0.0364	310(38.56)	1031(37.45)	0.0228
Hypercalcemia	125(16.94)	805(12.57)	0.1233	125(16.94)	444(15.58)	0.0367	103(12.80)	315(8.57)	0.1371	102(12.69)	273(9.92)	0.0876
Anemia	563(76.29)	4503(70.33)	0.1351	563(76.29)	2124(74.55)	0.0403	595(73.91)	2553(69.47)	0.0988	594(73.88)	1982(71.99)	0.0425
Stem cell transplant (from MM index to LOT index)	44(5.96)	744(11.62)	-0.2008	44(5.96)	162(5.69)	0.0118	157(19.50)	917(24.95)	-0.1313	157(19.53)	615(22.34)	-0.0692
Other clinical comorbidities - n(%)												
Cardiovascular history												
Hypertension	537(72.76)	4943(77.20)	-0.1025	537(72.76)	2103(73.82)	-0.0238	576(71.55)	2739(74.53)	-0.0671	575(71.52)	2021(73.41)	-0.0424
Heart failure	112(15.18)	1237(19.32)	-0.1098	112(15.18)	447(15.69)	-0.0142	128(15.90)	743(20.22)	-0.1124	128(15.92)	482(17.51)	-0.0426
Cardiomyopathy	34(4.61)	371(5.79)	-0.0535	34(4.61)	129(4.53)	0.0038	35(4.35)	243(6.61)	-0.0996	35(4.35)	139(5.05)	-0.0329
Dysrhythmias	214(29.00)	2163(33.78)	-0.1032	214(29.00)	840(29.48)	-0.0107	256(31.80)	1320(35.92)	-0.0871	256(31.84)	927(33.67)	-0.0390
Ischemic heart disease	177(23.98)	1859(29.03)	-0.1146	177(23.98)	712(24.99)	-0.0234	210(26.09)	1087(29.58)	-0.0780	210(26.12)	745(27.06)	-0.0213
Peripheral vascular disease	150(20.33)	1342(20.96)	-0.0157	150(20.33)	585(20.53)	-0.0052	185(22.98)	818(22.26)	0.0173	185(23.01)	614(22.30)	0.0169
Hypercholesterolemia	426(57.72)	3834(59.88)	-0.0438	426(57.72)	1643(57.67)	0.0011	439(54.53)	2054(55.89)	-0.0273	439(54.60)	1512(54.92)	-0.0064
Chronic obstructive pulmonary disease	148(20.05)	1339(20.91)	-0.0213	148(20.05)	610(21.41)	-0.0335	136(16.89)	817(22.23)	-0.1348	136(16.92)	520(18.89)	-0.0515
Diabetes	191(25.88)	1798(28.08)	-0.0496	191(25.88)	757(26.57)	-0.0157	218(27.08)	969(26.37)	0.0161	218(27.11)	710(25.79)	0.0300
Liver disease	37(5.01)	286(4.47)	0.0257	37(5.01)	142(4.98)	0.0013	33(4.10)	124(3.37)	0.0382	33(4.10)	97(3.52)	0.0303
Gastrointestinal bleeding	71(9.62)	596(9.31)	0.0107	71(9.62)	292(10.25)	-0.0210	67(8.32)	263(7.16)	0.0437	67(8.33)	196(7.12)	0.0455
Inflammatory diseases	54(7.32)	448(7.00)	0.0124	54(7.32)	194(6.81)	0.0198	60(7.45)	260(7.07)	0.0146	60(7.46)	198(7.19)	0.0104
Lifestyle risk factors - n(%)												
Smoking	81(10.98)	616(9.62)	0.0446	81(10.98)	310(10.88)	0.0030	66(8.20)	306(8.33)	-0.0046	66(8.21)	226(8.21)	0.0000
Obesity	738(100.00)	6403(100.00)		738(100.00)	2849(100.00)		805(100.00)	3675(100.00)		804(100.00)	2753(100.00)	

Footnotes: n = Patient-lines, Stdev = standard deviation, MM = Multiple myeloma, LOT = Line of therapy, SMD = standardized mean difference Page 2 of 3

Table 15-11.2. Baseline characteristics by receipt of carfilzomib-containing therapy status before and after matching by LOT, whites, in Medicare

	LOT 2						LOT 3 + 4					
	Before match			After match			Before match			After match (matched by LOT)		
	Carfilzomib containing	Carfilzomib free	SMD	Carfilzomib containing	Carfilzomib free	SMD	Carfilzomib containing	Carfilzomib free	SMD	Carfilzomib containing	Carfilzomib free	SMD
Alcohol consumption	133(18.02)	1152(17.99)	0.0008	133(18.02)	527(18.50)	-0.0123	140(17.39)	655(17.82)	-0.0113	140(17.41)	470(17.07)	0.0090
Line of Therapy - n(%)	25(3.39)	132(2.06)	0.0815	25(3.39)	96(3.37)	0.0010	13(1.61)	62(1.69)	-0.0057	13(1.62)	45(1.63)	-0.0014
3												
4							541(67.20)	2645(71.97)	-0.1038	540(67.16)	1879(68.25)	-0.0233
4							264(32.80)	1030(28.03)	0.1038	264(32.84)	874(31.75)	0.0233

Footnotes: n = Patient-lines, Stdev = standard deviation, MM = Multiple myeloma, LOT = Line of therapy, SMD = standardized mean difference

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Table 15-11.3. Crude and adjusted risks of hospitalization for cardiac failure between patients with multiple myeloma of African American race treated with carfilzomib-containing regimens and those treated with carfilzomib-free regimens, in Medicare

LOT	Matched/Non-Matched Analysis	Regimen Type	N	Events	HR (95% CI)
2	Non-Matched	Carfilzomib-containing	132	<11	1.43 (0.73, 2.81)
		Carfilzomib-free	1110	59	
	Matched	Carfilzomib-containing	131	<11	1.78 (0.87, 3.66)
		Carfilzomib-free	496	21	
3 and 4	Non-Matched	Carfilzomib-containing	119	12	1.91 (0.98, 3.73)
		Carfilzomib-free	571	30	
	Matched	Carfilzomib-containing	117	11	1.45 (0.73, 2.89)
		Carfilzomib-free	336	20	

Footnotes: LOT = Line of therapy, N = patient-lines, HR = Hazard ratio, CI = confidence interval

Table 15-11.4. Crude and adjusted risks of hospitalization for cardiac failure between patients with multiple myeloma of White race treated with carfilzomib-containing regimens and those treated with carfilzomib-free regimens, in Medicare

LOT	Matched/Non-Matched Analysis	Regimen Type	N	Events	HR (95% CI)
2	Non-Matched	Carfilzomib-containing	738	62	1.62 (1.23, 2.12)
		Carfilzomib-free	6403	345	
	Matched	Carfilzomib-containing	738	62	1.77 (1.31, 2.39)
		Carfilzomib-free	2849	138	
3 and 4	Non-Matched	Carfilzomib-containing	805	63	1.49 (1.12, 1.98)
		Carfilzomib-free	3675	193	
	Matched	Carfilzomib-containing	804	63	1.50 (1.12, 2.01)
		Carfilzomib-free	2737	145	

Footnotes: LOT = Line of therapy, N = patient-lines, HR = Hazard ratio, CI = confidence interval

Table 15-11.5. Baseline characteristics by receipt of carfilzomib-containing therapy status before and after matching by LOT, blacks, in Optum

	Before Match			After Match		
	Carfilzomib free	Carfilzomib containing	SMD	Carfilzomib free	Carfilzomib containing	SMD
	770 (94.13)	48 (5.87)		128 (80)	32 (20)	
Age at treatment index (year)			-0.406			-0.0854
AGE AT TREATMENT Median(IQR25,75)	71 (64,78)	66 (57,74)		69 (59,76)	68 (57,75)	
AGE AT TREATMENT MEAN (STD)	69.58 (11.33)	65.04 (11.05)		67.27 (11.56)	66.28 (11.5)	
Age at treatment index - n (%)			0.4943			0.2473
18-65 years	225 (29.22)	24 (50)		52 (40.63)	15 (46.88)	
66-69 years	106 (13.77)	5 (10.42)		15 (11.72)	3 (9.38)	
70-74 years	163 (21.17)	7 (14.58)		25 (19.53)	4 (12.5)	
75-79 years	127 (16.49)	8 (16.67)		18 (14.06)	6 (18.75)	
80+ years	149 (19.35)	4 (8.33)		18 (14.06)	4 (12.5)	
Sex - n (%)						
Male	321 (41.69)	20 (41.67)	0.0004	48 (37.5)	13 (40.63)	-0.0634
Months from index MM diagnosis to treatment index - n (%)			-0.08			-0.2284
Less than 12 months	451 (58.57)	30 (62.5)		74 (57.81)	22 (68.75)	
> or EQ 12 months	319 (41.43)	18 (37.5)		54 (42.19)	10 (31.25)	
DIAGNOSIS TO TREATMENT Median(IQR25,75)	9.9 (6,16.89)	9.05 (6.34,18.15)		9.41 (4.87,18.75)	8.31 (5.57,17.89)	
DIAGNOSIS TO TREATMENT MEAN (STD)	12.87 (10.03)	13.19 (10.11)		12.91 (10.37)	12.17 (10.08)	
Calendar year of treatment index - n (%)			-0.3			0
> or EQ 2015	675 (87.66)	46 (95.83)		124 (96.88)	31 (96.88)	
Before 2015	95 (12.34)	2 (4.17)		4 (3.13)	1 (3.13)	
Census region - n (%)			0.529			0.0533
Midwest	137 (17.79)	12 (25)		27 (21.09)	7 (21.88)	
Northeast	83 (10.78)					
South	516 (67.01)	35 (72.92)		98 (76.56)	24 (75)	
West	34 (4.42)	1 (2.08)		3 (2.34)	1 (3.13)	
Myeloma-related factors - n (%)						
Anemia	438 (56.88)	24 (50)	-0.138	56 (43.75)	16 (50)	0.1255
Hypercalcemia	78 (10.13)	12 (25)	0.3985	18 (14.06)	6 (18.75)	0.1268
Renal_disease	248 (32.21)	12 (25)	-0.16	29 (22.66)	10 (31.25)	0.1946
Other clinical comorbidities - n (%)						
Cardiovascular history						
Hypertension	589 (76.49)	32 (66.67)	-0.219	88 (68.75)	24 (75)	0.1393
Cardiac_failure	118 (15.32)	4 (8.33)	-0.218	7 (5.47)	3 (9.38)	0.1494
Cardiomyopathy	51 (6.62)		-0.377			
Cardiacarrhythmias	143 (18.57)	8 (16.67)	-0.05	15 (11.72)	4 (12.5)	0.0239
Ischemic_heart_disease	140 (18.18)	4 (8.33)	-0.294	8 (6.25)	3 (9.38)	0.1166
Peripheral_vascular_disease	93 (12.08)	7 (14.58)	0.0738	18 (14.06)	3 (9.38)	-0.1461

Footnotes: SMD = standardized mean difference, Stdev = standard deviation, MM = Multiple myeloma, LOT = Line of therapy

Table 15-11.5. Baseline characteristics by receipt of carfilzomib-containing therapy status before and after matching by LOT, blacks, in Optum

	Before Match			After Match		
	Carfilzomib free	Carfilzomib containing	SMD	Carfilzomib free	Carfilzomib containing	SMD
	770 (94.13)	48 (5.87)		128 (80)	32 (20)	
COPD	148 (19.22)	14 (29.17)	0.2338	30 (23.44)	7 (21.88)	-0.0373
Hypercholesterolemia	407 (52.86)	19 (39.58)	-0.269	54 (42.19)	11 (34.38)	-0.1612
Diabetes	280 (36.36)	11 (22.92)	-0.298	33 (25.78)	7 (21.88)	-0.0918
Liver_disease	46 (5.97)	2 (4.17)	-0.083	3 (2.34)	1 (3.13)	0.0479
GI_bleeding_disorders	31 (4.03)	1 (2.08)	-0.113		1 (3.13)	0.254
Inflammatory_disease	59 (7.66)	2 (4.17)	-0.149	5 (3.91)	2 (6.25)	0.1069
Lifestyle risk factors - n (%)						
Obesity	194 (25.19)	13 (27.08)	0.043	28 (21.88)	7 (21.88)	0
Smoking	86 (11.17)	14 (29.17)	0.4603	22 (17.19)	5 (15.63)	-0.0422

Footnotes: SMD = standardized mean difference, Stdev = standard deviation, MM = Multiple myeloma, LOT = Line of therapy
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Table 15-11.6. Baseline characteristics by receipt of carfilzomib-containing therapy status before and after matching by LOT, whites, in Optum

	Before Matching			After Matching		
	Carfilzomib free	Carfilzomib containing	SMD	Carfilzomib free	Carfilzomib containing	SMD
	3250 (92.88)	249 (7.12)		732 (80)	183 (20)	
Age at treatment index (year)			-0.12			-0.021
AGE AT TREATMENT Median(IQR25,75)	71 (63,78)	71 (60,77)		71 (62,78)	71 (60,77)	
AGE AT TREATMENT MEAN (STD)	70.15 (10.75)	68.86 (10.82)		69.64 (10.84)	69.42 (10.79)	
Age at treatment index - n (%)			0.1643			0.0575
18-65 years	987 (30.37)	92 (36.95)		240 (32.79)	60 (32.79)	
66-69 years	362 (11.14)	25 (10.04)		85 (11.61)	22 (12.02)	
70-74 years	689 (21.2)	43 (17.27)		137 (18.72)	33 (18.03)	
75-79 years	562 (17.29)	46 (18.47)		139 (18.99)	38 (20.77)	
80+ years	650 (20)	43 (17.27)		131 (17.9)	30 (16.39)	
Sex - n (%)						
Male	1874 (57.66)	143 (57.43)	0.0047	433 (59.15)	108 (59.02)	0.0028
Months from index MM diagnosis to treatment index - n (%)			0.2535			0.0082
Less than 12 months	1922 (59.14)	116 (46.59)		391 (53.42)	97 (53.01)	
> or EQ 12 months	1328 (40.86)	133 (53.41)		341 (46.58)	86 (46.99)	
DIAGNOSIS TO TREATMENT Median(IQR25,75)	9.9 (5.84,17.93)	13.02 (7.41,19.74)		11.13 (5.85,21.05)	11.34 (6.92,18.49)	
DIAGNOSIS TO TREATMENT MEAN (STD)	13.38 (10.63)	15.07 (9.87)		14.4 (11.23)	14.24 (10)	
Calendar year of treatment index - n (%)			-0.188			0.0222
> or EQ 2015	2734 (84.12)	225 (90.36)		657 (89.75)	163 (89.07)	
Before 2015	516 (15.88)	24 (9.64)		75 (10.25)	20 (10.93)	
Census region - n (%)			0.1996			0.0575
Midwest	950 (29.23)	68 (27.31)		212 (28.96)	50 (27.32)	
Northeast	362 (11.14)	39 (15.66)		101 (13.8)	24 (13.11)	
South	1248 (38.4)	78 (31.33)		241 (32.92)	65 (35.52)	
West	690 (21.23)	64 (25.7)		178 (24.32)	44 (24.04)	
Myeloma-related factors - n (%)						
Anemia	1353 (41.63)	109 (43.78)	0.0434	308 (42.08)	80 (43.72)	0.0331
Hypercalcemia	331 (10.18)	32 (12.85)	0.0836	82 (11.2)	23 (12.57)	0.0422
Renal_disease	884 (27.2)	60 (24.1)	-0.071	179 (24.45)	44 (24.04)	-0.01
Other clinical comorbidities - n (%)						
Cardiovascular history						
Hypertension	2071 (63.72)	151 (60.64)	-0.064	446 (60.93)	116 (63.39)	0.0507
Cardiac_failure	271 (8.34)	17 (6.83)	-0.057	40 (5.46)	11 (6.01)	0.0235
Cardiomyopathy	98 (3.02)	6 (2.41)	-0.037	20 (2.73)	5 (2.73)	0
Cardiacarrhythmias	605 (18.62)	43 (17.27)	-0.035	135 (18.44)	31 (16.94)	-0.039
Ischemic_heart_disease	532 (16.37)	34 (13.65)	-0.076	110 (15.03)	29 (15.85)	0.0227
Peripheral_vascular_disease	385 (11.85)	25 (10.04)	-0.058	76 (10.38)	15 (8.2)	-0.075

Footnotes: SMD = standardized mean difference, Stdev = standard deviation, MM = Multiple myeloma, LOT = Line of therapy

Table 15-11.6. Baseline characteristics by receipt of carfilzomib-containing therapy status before and after matching by LOT, whites, in Optum

	Before Matching			After Matching		
	Carfilzomib free	Carfilzomib containing	SMD	Carfilzomib free	Carfilzomib containing	SMD
	3250 (92.88)	249 (7.12)		732 (80)	183 (20)	
COPD	549 (16.89)	33 (13.25)	-0.102	85 (11.61)	23 (12.57)	0.0293
Hypercholesterolemia	1686 (51.88)	126 (50.6)	-0.026	383 (52.32)	100 (54.64)	0.0466
Diabetes	666 (20.49)	66 (26.51)	0.1422	163 (22.27)	47 (25.68)	0.0801
Liver_disease	116 (3.57)	16 (6.43)	0.1314	33 (4.51)	6 (3.28)	-0.064
GI_bleeding_disorders	103 (3.17)	16 (6.43)	0.1528	29 (3.96)	7 (3.83)	-0.007
Inflammatory_disease	220 (6.77)	11 (4.42)	-0.103	37 (5.05)	11 (6.01)	0.0418
Lifestyle risk factors - n (%)						
Obesity	546 (16.8)	57 (22.89)	0.1532	152 (20.77)	40 (21.86)	0.0267
Smoking	304 (9.35)	23 (9.24)	-0.004	54 (7.38)	11 (6.01)	-0.055

Footnotes: SMD = standardized mean difference, Stdev = standard deviation, MM = Multiple myeloma, LOT = Line of therapy

Table 15-11.7. Baseline characteristics by receipt of carfilzomib-containing therapy status before and after matching by LOT, whites, in Humana

	Before match			After Match**		
	Carfilzomib containing 281 (100%)	Carfilzomib free 1,574 (100%)	SMD	Carfilzomib containing 262 (100%)	Carfilzomib free 839 (100%)	SMD
Age at treatment index (year)						
Mean (Stdev); Median (IQR)	73.3 (7.0); 73.0 (70.0, 78.0)	74.5 (7.3); 75.0 (70.0, 80.0)	0.165	73.7 (6.5); 73.0 (70.0, 78.0)	74.1 (6.9); 74.0 (70.0, 78.0)	0.028
Male - n (%)	192 (68.3%)	912 (57.9%)	0.217	176 (67.2%)	523 (62.3%)	0.046
Months from index MM diagnosis to treatment index						
Mean (Stdev); Median (IQR)	20.5 (15.0); 16.1 (8.7, 27.3)	22.9 (15.5); 19.0 (10.5, 32.3)	0.158	20.7 (15.2); 16.5 (8.4, 27.5)	21.9 (14.7); 18.2 (10.2, 31.1)	0.038
Census region (South) - n (%)	190 (67.6%)	1,027 (65.2%)	0.051	176 (67.2%)	552 (65.8%)	0.00
Myeloma-related factors - n (%)						
Renal disease	112 (39.9%)	646 (41.0%)	0.022	106 (40.5%)	339 (40.4%)	0.025
Hypercalcemia	43 (15.3%)	142 (9.0%)	0.194	33 (12.6%)	88 (10.5%)	0.067
Anemia	204 (72.6%)	992 (63.0%)	0.207	188 (71.8%)	568 (67.7%)	0.027
Other clinical comorbidities - n (%)						
Cardiovascular history						
Hypertension	208 (74.0%)	1,155 (73.4%)	0.014	192 (73.3%)	622 (74.1%)	0.023
Heart failure	42 (14.9%)	295 (18.7%)	0.102	41 (15.6%)	156 (18.6%)	0.035
Cariomyopathy	<10	83 (5.3%)	0.104	<10	35 (4.2%)	0.016
Dysrhythmias	64 (22.8%)	440 (28.0%)	0.12	62 (23.7%)	221 (26.3%)	0.014
Ischemic heart disease	53 (18.9%)	358 (22.7%)	0.094	52 (19.8%)	194 (23.1%)	0.037
Perhipheral vascular disease	68 (24.2%)	345 (21.9%)	0.055	63 (24.0%)	184 (21.9%)	0.026
Hypercholesterolemia	155 (55.2%)	868 (55.1%)	0.002	146 (55.7%)	477 (56.9%)	0.018
Chronic obstructive pulmonary disease	54 (19.2%)	340 (21.6%)	0.06	48 (18.3%)	165 (19.7%)	0.018
Diabetes	91 (32.4%)	493 (31.3%)	0.024	80 (30.5%)	260 (31.0%)	0.047
Liver disease	19 (6.8%)	56 (3.6%)	0.145	15 (5.7%)	40 (4.8%)	0.017
Gastrointestinal bleeding	21 (7.5%)	125 (7.9%)	0.015	18 (6.9%)	63 (7.5%)	0.042
Inflammatory diseases	16 (5.7%)	67 (4.3%)	0.064	14 (5.3%)	36 (4.3%)	0.023
Lifestyle risk factors - n (%)						
Smoking	30 (10.7%)	165 (10.5%)	0.006	27 (10.3%)	85 (10.1%)	0.026
Obesity	60 (21.4%)	390 (24.8%)	0.081	56 (21.4%)	176 (21.0%)	0.03
Alcohol consumption	<10	29 (1.8%)	0	<10	19 (2.3%)	0.065
Treatments and concomitant medications - n (%)						
Antihypertensives	211 (75.1%)	1,174 (74.6%)	0.012	193 (73.7%)	629 (75.0%)	0.041
Cholesterol lowering medications	129 (45.9%)	771 (49.0%)	0.062	122 (46.6%)	408 (48.6%)	0.008
Antidiabetics	72 (25.6%)	334 (21.2%)	0.104	63 (24.0%)	192 (22.9%)	0.03

Footnotes: Stdev = standard deviation, MM = Multiple myeloma, LOT = Line of therapy, SMD = standardized mean difference, n = patient-lines

Table 15-11.8. Baseline characteristics by receipt of carfilzomib-containing therapy status before and after matching by LOT, black, in Humana

	Before match			After Match**		
	Carfilzomib containing 88 (100%)	Carfilzomib free 597 (100%)	SMD	Carfilzomib containing 72 (100%)	Carfilzomib free 212 (100%)	SMD
Age at treatment index (year)						
Mean (Stdev); Median (IQR)	72.3 (6.7); 72.0 (69.0, 76.0)	73.4 (7.5); 73.0 (69.0, 79.0)	0.148	72.6 (6.8); 72.0 (69.0, 76.5)	73.0 (7.6); 73.0 (69.0, 78.5)	0.009
Male - n (%)	41 (46.6%)	261 (43.7%)	0.058	34 (47.2%)	94 (44.3%)	0.068
Months from index MM diagnosis to treatment index						
Mean (Stdev); Median (IQR)	19.5 (15.0); 16.2 (8.6, 27.0)	21.8 (15.7); 16.7 (9.7, 30.2)	0.149	20.1 (15.1); 16.5 (8.8, 27.0)	19.6 (15.2); 14.4 (8.2, 27.5)	0.019
Census region (South) - n (%)	68 (77.3%)	484 (81.1%)	0.094	57 (79.2%)	168 (79.2%)	0.046
Myeloma-related factors - n (%)						
Renal disease	49 (55.7%)	327 (54.8%)	0.018	38 (52.8%)	112 (52.8%)	0.052
Hypercalcemia	11 (12.5%)	64 (10.7%)	0.056	<10	26 (12.3%)	0.022
Anemia	79 (89.8%)	467 (78.2%)	0.32	64 (88.9%)	180 (84.9%)	0.037
Other clinical comorbidities - n (%)						
Cardiovascular history						
Hypertension	79 (89.8%)	534 (89.4%)	0.013	64 (88.9%)	187 (88.2%)	0.006
Heart failure	11 (12.5%)	125 (20.9%)	0.227	11 (15.3%)	35 (16.5%)	0.014
Cariomyopathy	<10	54 (9.0%)	0.082	<10	19 (9.0%)	0.038
Dysrhythmias	19 (21.6%)	154 (25.8%)	0.099	15 (20.8%)	43 (20.3%)	0.027
Ischemic heart disease	16 (18.2%)	128 (21.4%)	0.08	14 (19.4%)	41 (19.3%)	0.026
Perhipheral vascular disease	22 (25.0%)	163 (27.3%)	0.052	15 (20.8%)	54 (25.5%)	0.046
Hypercholesterolemia	52 (59.1%)	361 (60.5%)	0.029	45 (62.5%)	135 (63.7%)	0.021
Chronic obstructive pulmonary disease	21 (23.9%)	139 (23.3%)	0.014	15 (20.8%)	41 (19.3%)	0.063
Diabetes	30 (34.1%)	251 (42.0%)	0.163	26 (36.1%)	82 (38.7%)	0.012
Liver disease	<10	13 (2.2%)	0.266	<10	<10	0.076
Gastrointestinal bleeding	10 (11.4%)	68 (11.4%)	0	<10	28 (13.2%)	0.102
Inflammatory diseases	<10	26 (4.4%)	0.15	<10	<10	0.036
Lifestyle risk factors - n (%)						
Smoking	<10	69 (11.6%)	0.167	<10	13 (6.1%)	0.049
Obesity	27 (30.7%)	234 (39.2%)	0.179	26 (36.1%)	71 (33.5%)	0.163
Alcohol consumption	<10	15 (2.5%)	0.109	<10	<10	0.053
Treatments and concomitant medications - n (%)						
Antihypertensives	73 (83.0%)	522 (87.4%)	0.124	62 (86.1%)	182 (85.8%)	0.015
Cholesterol lowering medications	41 (46.6%)	319 (53.4%)	0.136	36 (50.0%)	112 (52.8%)	0.03
Antidiabetics	18 (20.5%)	164 (27.5%)	0.164	16 (22.2%)	51 (24.1%)	0.026

Footnotes: Stdev = standard deviation, MM = Multiple myeloma, LOT = Line of therapy, SMD = standardized mean difference, n = patient-lines

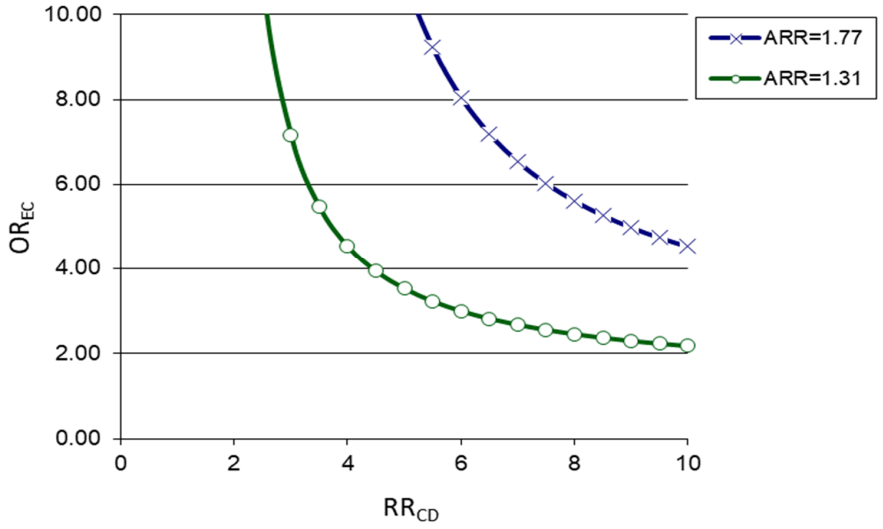
Table 15-11.9. Hazard Ratio of Heart Failure among Patients with Multiple Myeloma Receiving Carfilzomib-Containing Regimens compared to Non-Carfilzomib Regimens, Propensity Score Matched Cohorts, in Humana

Race	Regimen Type	N	Events	HR (95% CI)
White	Carfilzomib-containing	262	15	1.44 (0.81, 2.56)
	Carfilzomib-free	839	35	
Black	Carfilzomib-containing	72	5	1.23 (0.43, 3.51)
	Carfilzomib-free	212	11	

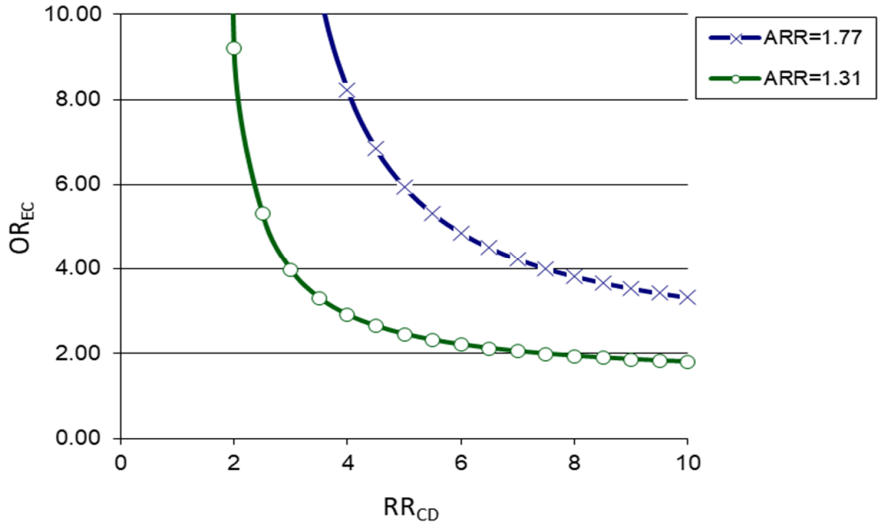
Footnotes: N = patient-lines, HR = Hazard ratio, CI = confidence interval

Figure 15-11.1. Sensitivity analysis of residual confounding on the estimated association between the receipt of carfilzomib-containing regimens and the risk of hospitalization for heart failure at second-line therapy among white patients in Medicare: Rule Out approach

a. Assuming prevalence of confounder of 0.05



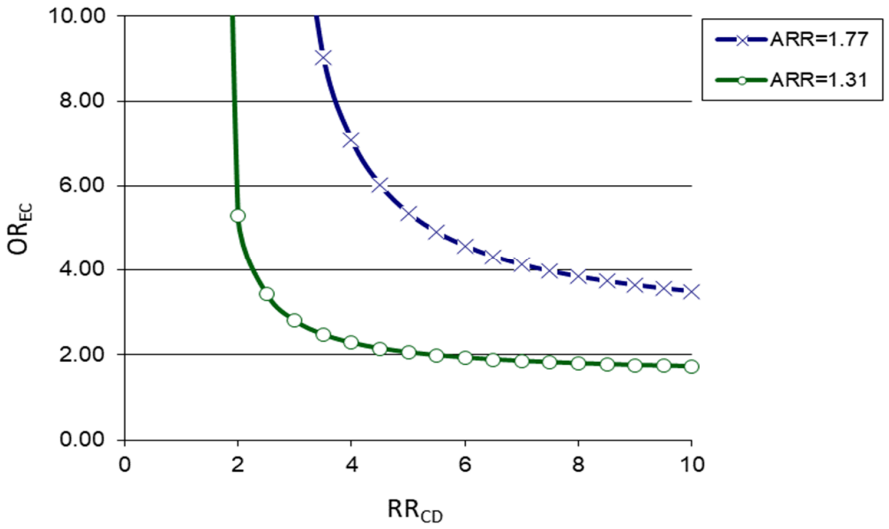
b. Assuming prevalence of confounder of 0.1



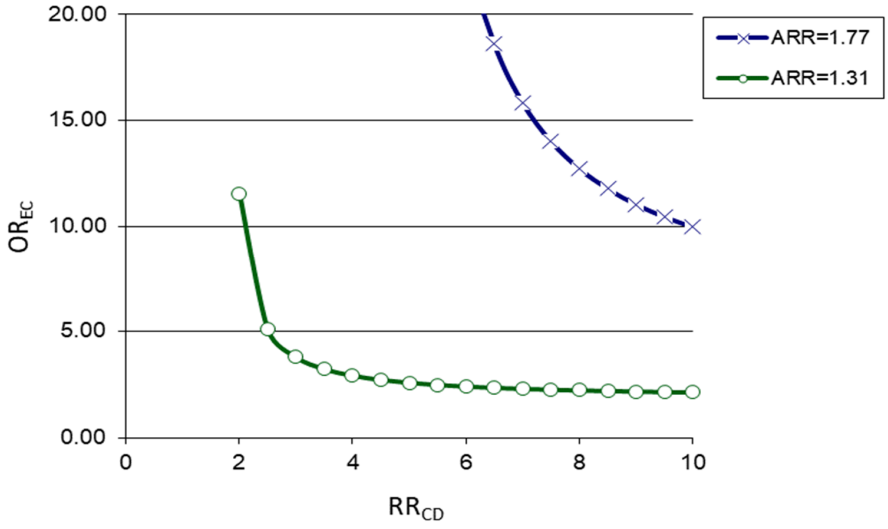
RRCD = Association between confounder and disease outcome (i.e. hospitalization for heart failure)
OREC = Association between exposure (i.e. receipt of carfilzomib-containing regimen) and confounder
ARR = Apparent (or observed) exposure relative risk

Figure 15-11.1. Sensitivity analysis of residual confounding on the estimated association between the receipt of carfilzomib-containing regimens and the risk of hospitalization for heart failure at second-line therapy among white patients in Medicare: Rule Out approach

c. Assuming prevalence of confounder of 0.3



d. Assuming prevalence of confounder of 0.5



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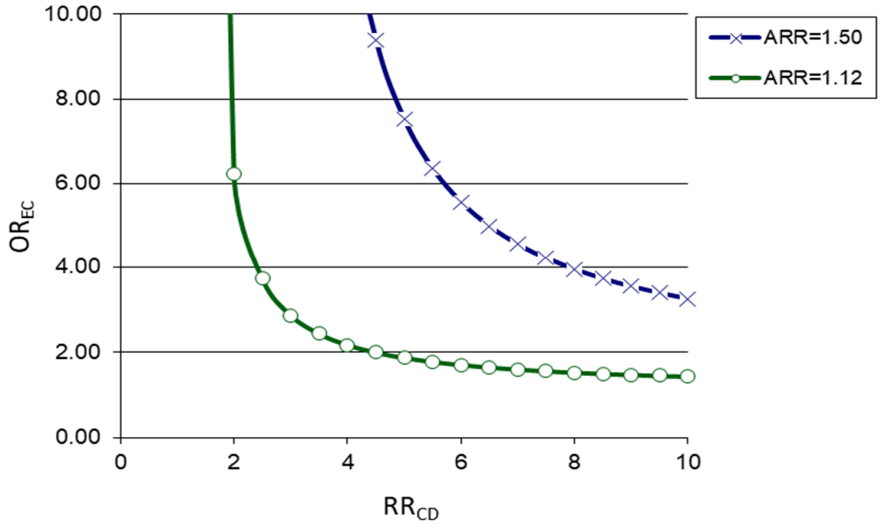
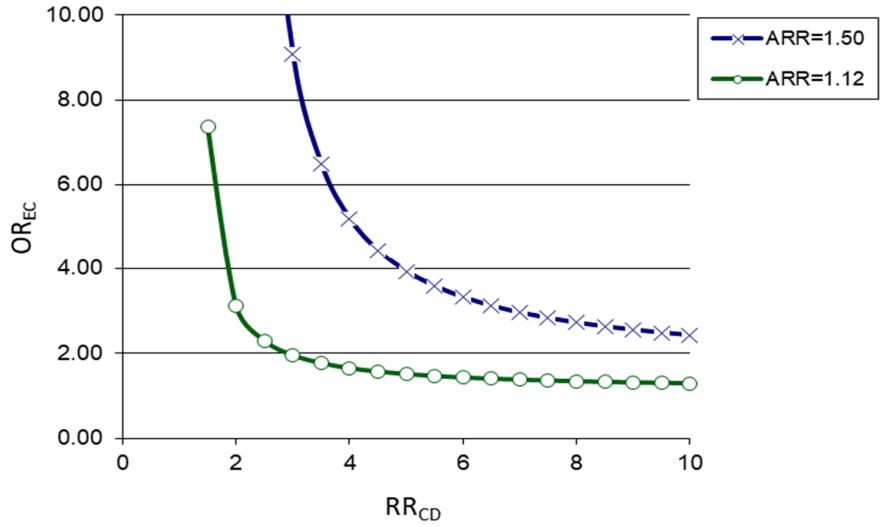
RRCD = Association between confounder and disease outcome (i.e. hospitalization for heart failure)
OREC = Association between exposure (i.e. receipt of carfilzomib-containing regimen) and confounder
ARR = Apparent (or observed) exposure relative risk

Figure 15-11.2. Sensitivity analysis of residual confounding on the estimated association between the receipt of carfilzomib-containing regimens and the risk of hospitalization for heart failure at third-/fourth-line therapy among white patients in Medicare: Rule Out approach

a. Assuming prevalence of confounder of 0.05



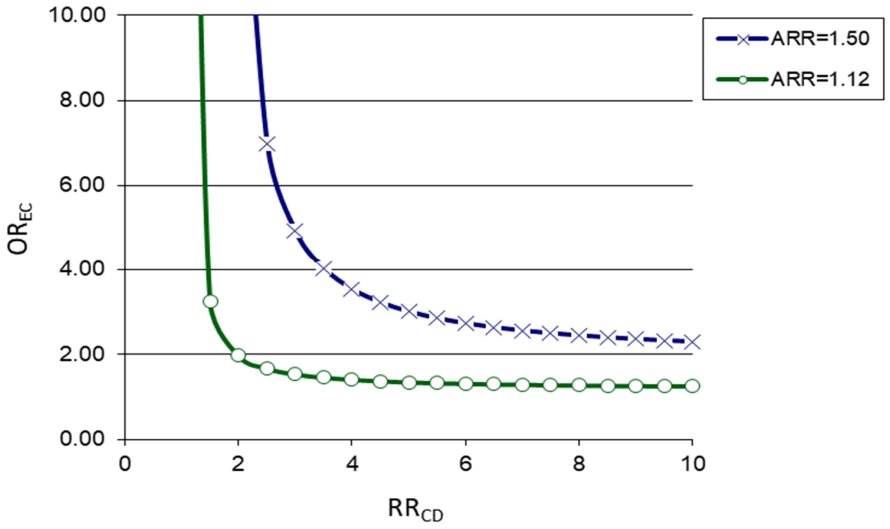
b. Assuming prevalence of confounder of 0.1



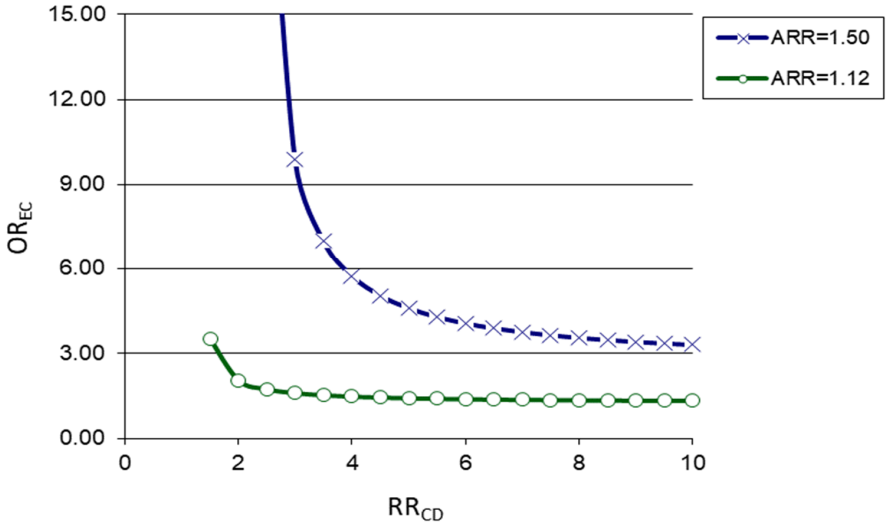
RRCD = Association between confounder and disease outcome (i.e. hospitalization for heart failure)
OREC = Association between exposure (i.e. receipt of carfilzomib-containing regimen) and confounder
ARR = Apparent (or observed) exposure relative risk

Figure 15-11.2. Sensitivity analysis of residual confounding on the estimated association between the receipt of carfilzomib-containing regimens and the risk of hospitalization for heart failure at third-/fourth-line therapy among white patients in Medicare: Rule Out approach

c. Assuming prevalence of confounder of 0.3



d. Assuming prevalence of confounder of 0.5



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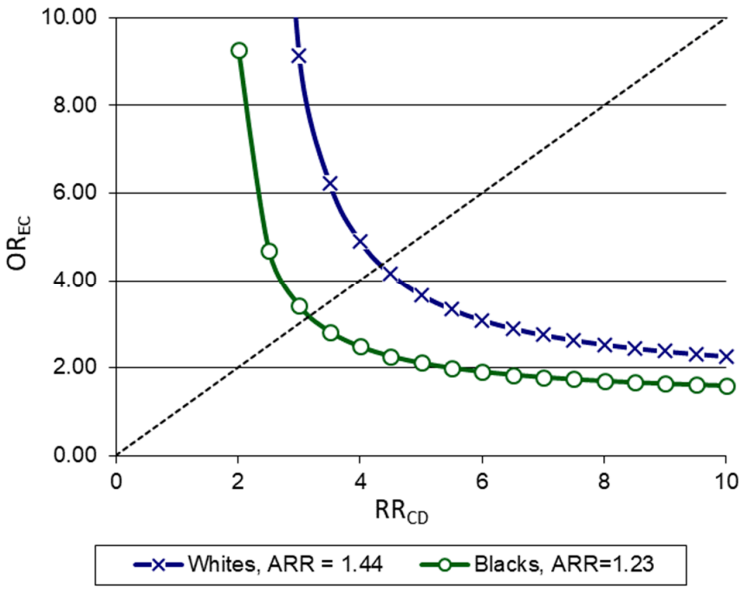
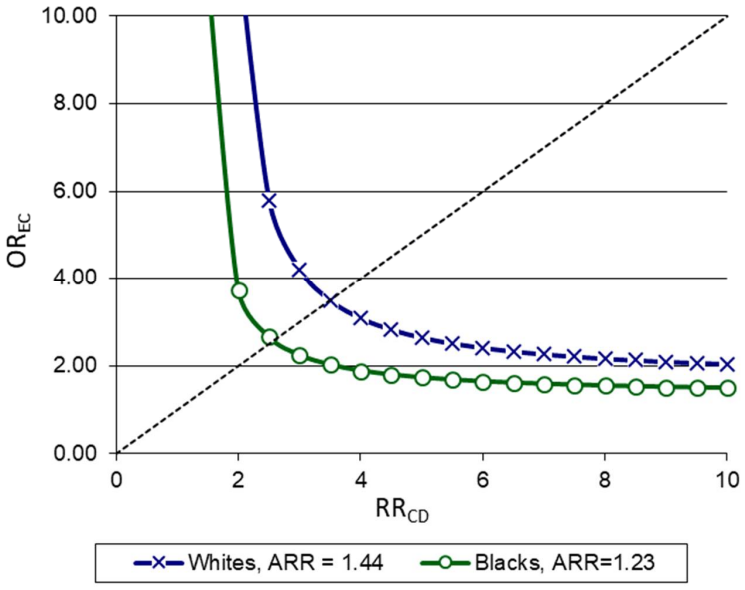
RRCD = Association between confounder and disease outcome (i.e. hospitalization for heart failure)
OREC = Association between exposure (i.e. receipt of carfilzomib-containing regimen) and confounder
ARR = Apparent (or observed) exposure relative risk

Figure 15-11.3. Sensitivity analysis of residual confounding on the estimated association between the receipt of carfilzomib-containing regimens and the risk of hospitalization for heart failure among in Humana: Rule Out approach

a. Assuming prevalence of confounder 0.1 and prevalence of exposure 0.25



b. Assuming prevalence of confounder 0.25 and prevalence of exposure 0.25



RRadjusted = "True" or fully adjusted exposure relative risk, ARR = Apparent (or observed) exposure relative risk, RRCD = Association between confounder and disease outcome, PC = Prevalence of confounder PC1 = Prevalence of confounder in the exposed, PC0 = Prevalence of confounder in the unexposed PE = Prevalence of drug exposure, OREC = Association between drug use category and confounder prevalence

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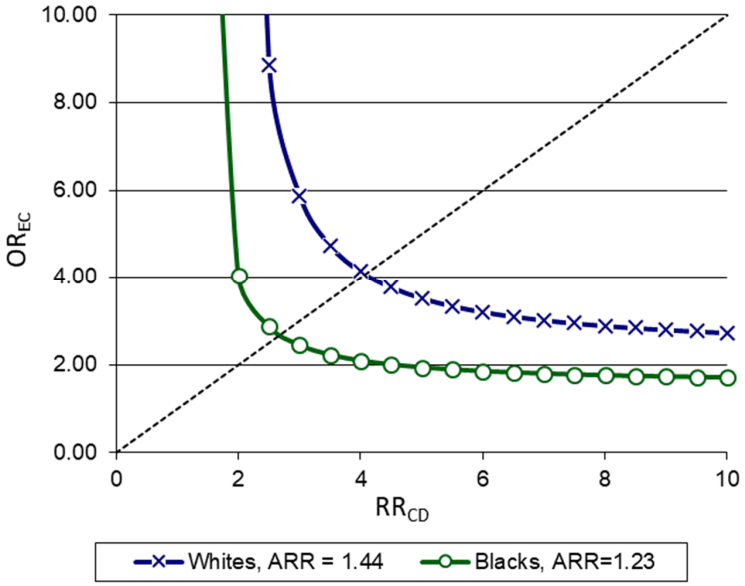
Figure 15-11.3. Sensitivity analysis of residual confounding on the estimated association between the receipt of carfilzomib-containing regimens and the risk of hospitalization for heart failure among in Humana: Rule Out approach

c. Assuming prevalence of confounder 0.50 and prevalence of exposure 0.25



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RRadjusted = "True" or fully adjusted exposure relative risk, ARR = Apparent (or observed) exposure relative risk, RRCD = Association between confounder and disease outcome, PC = Prevalence of confounder PC1 = Prevalence of confounder in the exposed, PC0 = Prevalence of confounder in the unexposed PE = Prevalence of drug exposure, OREC = Association between drug use category and confounder prevalence

16. ANNEXES

Annex 1. List of Stand-alone Documents

Not Applicable

Annex 2. Study Protocol and Amendments

Summary Table of Study Protocol

Title	An Observational Study to Estimate Incidence Rates of Heart Failure Among US Racial and Ethnic Minority Patients With Multiple Myeloma Treated or Not Treated With Carfilzomib
Protocol version identifier	20190012 Amendment 1
Date of last version of the protocol	03 April 2019
EU Post Authorization Study (PAS) Register No	TBD
Active Substance	Carfilzomib
Medicinal Product	Kyprolis
Product Reference	NA
Procedure Number	NA
Joint PASS	*No*

Research Question and Objectives	Primary objectives 1. Estimate the incidence rates of cardiac failure in US racial and ethnic populations of patients with multiple myeloma treated with carfilzomib 2. Estimate the incidence rates of cardiac failure in US racial and ethnic populations of patients with multiple myeloma not treated with carfilzomib Secondary objectives 1. Describe demographic, clinical characteristics and cardiac failure risk factors in US racial and ethnic populations of patients with multiple myeloma treated with carfilzomib. 2. Describe demographic, clinical characteristics and cardiac failure risk factors in US racial and ethnic populations of patients with multiple myeloma not treated with carfilzomib. Exploratory objectives 1. Assess comparability between patients with multiple myeloma of African American race treated with carfilzomib and those treated with other treatments for multiple myeloma, after propensity score matching, using standardized mean differences 2. If the assessment indicates sufficient post-matching comparability, compare the risk of cardiac failure between patients with multiple myeloma of African American race treated with carfilzomib and those treated with other treatments for multiple myeloma 3. Assess comparability between patients with multiple myeloma of White race treated with carfilzomib and those treated with other treatments for multiple myeloma, after propensity score matching, using standardized mean differences 4. If the assessment indicates sufficient post-matching comparability, compare the risk of cardiac failure between patients with multiple myeloma of White race treated with carfilzomib and those treated with other treatments for multiple myeloma
Country of Study	United States
Author	Akeem Yusuf, PhD, Amgen Inc. Alan Fu, PhD, Amgen Inc. (RAE)

Marketing Authorization Holder

Marketing authorization holder(s)	Amgen Inc.
MAH Contact	Alan Fu, PhD afu01@amgen.com 805-447-2291 Amgen Inc. 1 Amgen Center Drive MS-27 3A Thousand Oaks, CA

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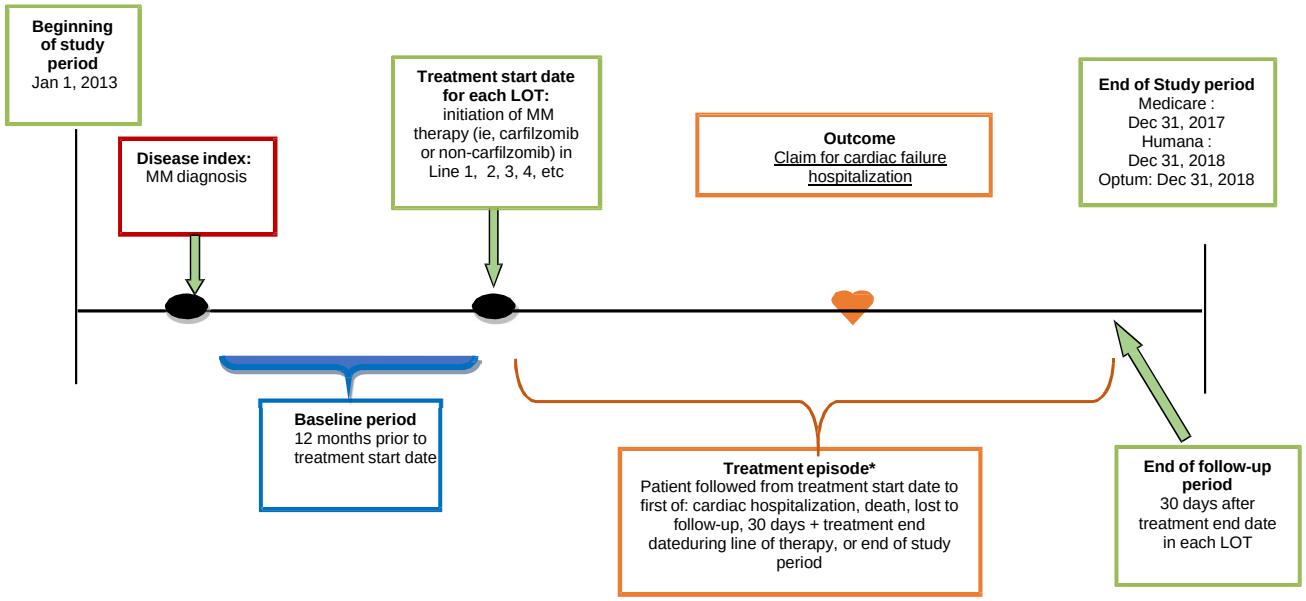
Study Design Schema



LOT : Line of therapy MM : Multiple myeloma

* Only one treatment episode is shown in this study design schema. Each patient can contribute multiple treatment episodes.

1. Table of Contents

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List of Tables

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2. List of Abbreviations

Abbreviation	Definition/Explanation
CI	Confidence interval
CDM	Clinformatics® Data Mart
CDRG	Chronic Disease Research Group
CHI	Comprehensive Health Insights Inc
CPT	Current Procedural Terminologies
EHR	Electronic Health Records
FDA	Food and Drug Administration
HCPCS	Healthcare Common Procedure Coding System
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
LOT	Line of therapy
NDC	National Drug Code
US	United States

3. Responsible Parties

Contact:

Alan Fu, PhD

Manager, Observational Research

Amgen Inc.

Thousand Oaks, CA

afu01@amgen.com

Phone: +1 (805) 490-3575

Zandra Klippel, MD

Medical Director Global Development Amgen Inc.

Thousand Oaks, CA

zklippel@amgen.com

Phone: +1 (805) 447-4897

Shuling Li, PhD

Chronic Disease Research Group Minneapolis, MN

SlLi@cdrg.org

4. Abstract

- Study Title: An observational study to estimate incidence rates of heart failure among US racial and ethnic minority patients with multiple myeloma treated or not treated with carfilzomib
- Study Background and Rationale: On 14 June 2018, Amgen submitted to the Food and Drug Administration (FDA) a labeling supplement which proposed an update to the Kyprolis US Prescribing Information indicating that the risk of developing cardiac failure is higher among Asian patients. This increased risk was identified following analysis of data from Amgen sponsored clinical trials and postmarketing reports. On 14 December 2018, the FDA issued a complete response letter, which highlighted the lack of sufficient evidence to support that there is an increased risk of cardiac failure in US Asian patients. In addition, based on the submission of this supplement, the Agency stated the concern of the potential differential risk of cardiac failure among racial and ethnic minorities. To address these issues, Amgen agreed to conduct a postmarketing requirement in the form of an observational study to estimate incidence rates of heart failure among US racial and ethnic minority patients with multiple myeloma treated or not treated with carfilzomib.
- Research Question and Objective(s)
  - Primary Objectives
    1. Estimate the incidence rates of cardiac failure in US racial and ethnic populations of patients with multiple myeloma treated with carfilzomib
    2. Estimate the incidence rates of cardiac failure in US racial and ethnic populations of patients with multiple myeloma not treated with carfilzomib
  - Secondary Objectives
    1. Describe demographic, clinical characteristics and cardiac failure risk factors in US racial and ethnic populations of patients with multiple myeloma treated with carfilzomib.
    2. Describe demographic, clinical characteristics and cardiac failure risk factors in US racial and ethnic populations of patients with multiple myeloma not treated with carfilzomib.
  - Exploratory Objectives
    1. Assess comparability between patients with multiple myeloma of African American race treated with carfilzomib and those treated with other treatments for multiple myeloma, after propensity score matching, using standardized mean differences
    2. If the assessment indicates sufficient post-matching comparability, compare the risk of cardiac failure between patients with multiple myeloma of African American race treated with carfilzomib and those treated with other treatments for multiple myeloma

3. Assess comparability between patients with multiple myeloma of White race treated with carfilzomib and those treated with other treatments for multiple myeloma, after propensity score matching, using standardized mean differences
4. If the assessment indicates sufficient post-matching comparability, compare the risk of cardiac failure between patients with multiple myeloma of White race treated with carfilzomib and those treated with other treatments for multiple myeloma

– Hypothesis/Estimation

This is an estimation study. Thus, no formal hypothesis will be tested.

- Study Design/Type

  This will be a retrospective observational study.

- Study Population or Data Resource

  This study will examine patients with multiple myeloma of specific racial/ethnic identifications using existing administrative databases. The data sources for this study include US fee-for-service Medicare, Optum research database and the Humana integrated databases. The primary and secondary objectives will be evaluated separately in each data source. In addition, these objectives will also be evaluated in a sub-group of patients identified in the Optum claims that are linkable to the Optum electronic health record (EHR) database.

- Summary of Patient Eligibility Criteria
  - Multiple myeloma diagnosis: Multiple myeloma diagnosis will be determined utilizing an algorithm based upon presence of a combination of ICD-9-CM and ICD-10-CM diagnosis codes, Current Procedural Terminology (CPT) codes for diagnosis tests or National Drug Codes (NDC) and HCPCS codes for treatments.
  - Age > = 18 years
  - Receipt of carfilzomib or other treatments for multiple myeloma in at least 1 line of therapy (LOT).
  - Continuously enrolled in medical and pharmacy insurance coverage for 12 months prior to the treatment start date.
  - Non-missing race/ethnicity
- Follow-up

  For each treatment episode within LOT, study follow-up begins on the treatment start date (ie, initiation of carfilzomib or non-carfilzomib-based regimens) and continue through the earliest date of first cardiac failure hospitalization, death, loss of insurance coverage, 30 days after treatment end

date within the LOT, or end of study period. Patients can contribute data to multiple treatment episodes across LOTs.

- Variables

– Outcome Variable

The outcome in this study is a hospitalization for cardiac failure requiring an overnight stay at an inpatient facility.

– Exposure Variable(s)

The exposure in this study is the use of carfilzomib-based regimens or non-carfilzomib-based regimens, assessed by LOT.

– Other Covariate(s)

Included demographics, myeloma-related comorbid condition, other comorbidities and lifestyle factors.

- Study Sample Size

For the three databases, we anticipate including an estimated 3,689 carfilzomib-treated patients with multiple myeloma. We assumed a cardiac failure incidence of 5-20 per 100 person-years and estimated the number of events and 90% confidence interval for the incidence rates for each racial/ethnic group among patients with multiple myeloma treated with and not treated with carfilzomib in each database (See Table 1-Table 6).

- Data Analysis

Separate analysis will be conducted in each data source used in this study. Incidence of cardiac failure will be estimated for each race/ethnicity (ie, white, black, Hispanic and Asian) separately in each data source for all observed treatment episodes. Incidence rate of cardiac failure (and corresponding 95% confidence intervals) will be estimated in each study cohort by dividing the total number of events by the total person-time at risk from which the events arose. Demographic characteristics, myeloma-related clinical characteristics, other clinical comorbidity measures, concomitant medications as well as lifestyle characteristics will be summarized for the study cohorts using descriptive statistics.

Within the cohorts of patients of African American and White race, we will attempt to create cohorts of patients with balanced covariates using

propensity score matching. Differences in baseline patient characteristics between the treatment cohorts (carfilzomib and other treatments for multiple myeloma) will be assessed in the initial study population and the propensity-score matched population using the standardized mean difference (SMD). If the assessment indicates sufficient post-matching comparability, we will evaluate the association between treatment with carfilzomib versus other treatments for multiple myeloma and risk of cardiac failure by line of therapy using a Cox proportional hazards model.

5. Milestones

Milestone	Planned date
Registration in the EU PAS Register	July 26, 2019
Start of data collection	August 1, 2019
End of data collection	Jan 31, 2020
Final report of study results	April 30, 2020
Submission of final report of study results	June 30, 2020

6. Rationale and Background

6.1 Disease and Therapeutic Area

Multiple myeloma is a common hematological cancer and accounts for approximately 1% of all incident cancer cases in the US [National Cancer Institute 2015]. Multiple myeloma is an incurable but treatment-responsive disease, and many patients achieve long-term asymptomatic remission [Bianchi et al 2014]. The prognosis of patients with multiple myeloma has improved in the last two decades with almost 47% of diagnosed patients surviving 5-years or longer [Kurtin et al 2013]. 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, lenalidomide, bortezomib and carfilzomib [NCCN 2014].

Carfilzomib is a second-generation proteasome inhibitor that irreversibly binds to the proteasome. [McBride et al 2015] In the US, carfilzomib It is approved in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy. Carfilzomib is also indicated for use as a single agent for the treatment of multiple myeloma inpatients with relapsed or refractory disease who have received one or more lines of therapy.

6.2 Rationale

In pivotal phase 2 and 3 studies, there has been a reported increase in cardiovascular adverse events (including cardiac failure) in patients treated with carfilzomib. [Dimopoulos et al 2016, Stewart et al 2015, Hajek et al 2015] In a recently published pooled analysis of carfilzomib trials, the investigators concluded that despite increased incidence of cardiovascular events, relative risk of these events with carfilzomib is low and manageable. [Chari et al 2018]

On 14 June 2018, Amgen submitted to the Food and Drug Administration (FDA) a labeling supplement which proposed an update to the Kyprolis US Prescribing Information indicating that the risk of developing cardiac failure is higher among Asian patients. This increased risk was identified following analysis of data from Amgen sponsored clinical trials and postmarketing reports. On 14 December 2018, the FDA issued a complete response letter, which highlighted the lack of sufficient evidence to support that there is an increased risk of cardiac failure in US Asian patients. In addition, based on the submission of this supplement, the Agency stated the concern of a differential risk of cardiac failure among racial and ethnic minorities. To address these issues, Amgen agreed to conduct a postmarketing requirement in the form of an observational study to evaluate incidence rates of heart failure among US racial and ethnic minority patients with multiple myeloma treated or not treated with carfilzomib.

6.3 Statistical Inference

This is an estimation study for the primary analysis and thus, no formal hypothesis will be tested. Comparison of incidence rates of cardiac failure within African American and white race will be conducted as exploratory analysis.

7. Research Question and Objectives

7.1 Primary

1. Estimate the incidence rates of cardiac failure in US racial and ethnic populations of patients with multiple myeloma treated with carfilzomib
2. Estimate the incidence rates of cardiac failure in US racial and ethnic populations of patients with multiple myeloma not treated with carfilzomib

7.2 Secondary

1. Describe demographic, clinical characteristics and cardiac failure risk factors in US racial and ethnic populations of patients with multiple myeloma treated with carfilzomib.
2. Describe demographic, clinical characteristics and cardiac failure risk factors in US racial and ethnic populations of patients with multiple myeloma not treated with carfilzomib.

7.3 Exploratory

1. Assess comparability between patients with multiple myeloma of African American race treated with carfilzomib and those treated with other treatments for multiple myeloma, after propensity score matching, using standardized mean differences
2. If the assessment indicates sufficient post-matching comparability, compare the risk of cardiac failure between patients with multiple myeloma of African American race treated with carfilzomib and those treated with other treatments for multiple myeloma
3. Assess comparability between patients with multiple myeloma of White race treated with carfilzomib and those treated with other treatments for multiple myeloma, after propensity score matching, using standardized mean differences
4. If the assessment indicates sufficient post-matching comparability, compare the risk of cardiac failure between patients with multiple myeloma of White race treated with carfilzomib and those treated with other treatments for multiple myeloma

8. Research Methods

8.1 Study Design

We propose a retrospective cohort study of patients with multiple myeloma of specific racial/ethnic identifications using existing administrative databases. The data sources for this study include:

- US fee-for-service Medicare, including Parts A, B, and D
- Optum Clinformatics Data Mart (administrative claims and integrated claims-EHR)
- Humana integrated databases

The analysis will focus on US racial and ethnic groupings of patients with multiple myeloma treated or not treated with carfilzomib. Cardiac failure will be identified using a validated algorithm based on International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) diagnosis codes. The study period will include up to 5 years of follow-up in Medicare FFS database and up to 6 years in the Optum and Humana databases. The analysis of the primary and secondary objectives will be evaluated using the Medicare FFS database, the Optum claims database and the Humana claims database. In addition, patients identified in the Optum claims database that are linkable to the Optum EHR will be the focus of a sub-group analysis evaluating the same primary and secondary study objectives.

Occurrence of the study outcome (defined as hospitalization for cardiac failure events requiring an overnight stay at an inpatient facility) will be assessed during treatment

episodes delineated by LOT. Each patient can contribute multiple exposures corresponding to the number of observed LOT in the data source during the study period.

8.2 Setting and Study Population

8.2.1 Study Period

For Medicare fee-for-service (FFS) database, the study period will be 01 January 2013 through 31 December 2017. For Optum and Humana databases, the study period will be 01 January 2013 through 31 December 2018.

8.2.2 Patient Eligibility

8.2.2.1 Inclusion Criteria

For the Medicare FFS databases, included patients will be those who satisfy the following criteria between 2013 and 2017:

- Multiple myeloma diagnosis: Multiple myeloma diagnosis will be determined utilizing an algorithm based upon presence of a combination of ICD-9-CM and ICD-10-CM diagnosis codes, Current Procedural Terminology (CPT) codes for diagnosis tests or National Drug Codes (NDC) and HCPCS codes for treatments. (See Appendix C for details).
- Age > = 18 years.
- Receipt of carfilzomib or other multiple myeloma treatments listed in Appendix D in at least 1 line of therapy (LOT) between January 1 2014 and June 30 2017.
- Continuously enrolled in Medicare fee-for-service Parts A, B and D date (for the Medicare FFS) and in medical and pharmacy insurance coverage (for Optum and Humana) for 12 months prior to the treatment index.

For the Optum and Humana claims databases, included patients will be those who satisfy the following criteria between 2013 and 2018:

- Multiple myeloma diagnosis: Multiple myeloma diagnosis will be determined utilizing an algorithm based upon presence of a combination of ICD-9-CM and ICD-10-CM diagnosis codes, CPT codes for diagnosis tests or NDC and HCPCS codes for treatment. (See Appendix C for details).
- Age > = 18 years.
- Receipt of carfilzomib or other treatments listed in Appendix D in at least 1 line of therapy (LOT) between January 1 2014 and June 30 2018.
- Continuously enrolled in medical and pharmacy insurance coverage for 12 months prior to the first observed treatment episode.

Eligible patients will be able to contribute data to multiple LOT.

8.2.2.2 Exclusion Criteria

Patients with missing or unknown race/ethnicity variable will be excluded.

8.2.3 Baseline Period

The baseline period for covariate assessment will be inclusive of the 12 months prior to the patient's treatment index date. Treatment index date is defined as the initiation of carfilzomib or non-carfilzomib-based regimens in each LOT.

8.2.4 Study Follow-up

Time at risk for occurrence of the study outcome is observed during each LOT. For each LOT, follow-up for occurrence of study outcome will begin on the treatment start date (ie, initiation of carfilzomib or non-carfilzomib-based regimens within that LOT) and continues through the earliest date of first cardiac failure hospitalization, death, loss of insurance coverage, 30 days after treatment end date within the LOT, or end of study period.

8.3 Variables

8.3.1 Exposure Assessment

The exposure in this study will be the use of carfilzomib-based regimens or non-carfilzomib-based regimens. Exposure will be assessed for each LOT (ie, LOT 1, 2, 3,4 etc). Within each LOT, patients will be considered as exposed from the treatment start date until 30 days after treatment end date. Patients can contribute exposures in more than one LOT during the study period. Carfilzomib and other drug treatments will be identified using NDC codes and HCPCS codes. (See Appendix A for a list of codes).

Treatment episodes will then be further classified as belonging to one of the following exposure cohorts :

Carfilzomib-treated : Treatment episodes in which patients initiated a carfilzomib-containing treatment regimen.

- Whites
- Blacks
- Asians
- Hispanic

Non-carfilzomib-treated : Treatment episodes in which patients initiated a multiple myeloma regimen not containing carfilzomib.

- Whites
- Blacks
- Asians
- Hispanic

For analysis of the Medicare FFS database, treatment episodes of multiple myeloma patients of North American natives race treated with carfilzomib containing and non-carfilzomib containing treatments will also be identified and included in the analysis.

8.3.2 Outcome Assessment

The outcome in this study is a hospitalization for cardiac failure events requiring an overnight stay at an inpatient facility. These events will be defined as any inpatient claim in the study databases carrying a relevant ICD-9-CM or ICD-10-CM diagnosis for cardiac failure. The diagnosis codes used to identify cardiac failure from claims are listed in Appendix E. These codes are widely used to define cardiac failure from medical claims in literature and their performance for this purpose have been previously validated in several databases and health systems. [Saczynski et al 2012]

8.3.3 Covariate Assessment

Baseline patient characteristics and comorbidities will be determined from claims in the 12-month baseline period for each treatment episode.

The following baseline characteristics will be determined:

Demographics

- Age
- Sex
- Calendar year of multiple myeloma diagnosis (disease index date)
- Geographic region

Myeloma-related factors

- Renal disease
- Hypercalcemia
- Anemia
- Stem cell transplantation

Other clinical comorbidities:

- Prior Cardiovascular history (hypertension, heart failure, cardiomyopathy, cardiac arrhythmias, and conduction disorders)
- Ischemic heart disease
- Peripheral artery disease
- Hypercholesterolemia
- Chronic obstructive pulmonary disease
- Diabetes

- Liver disease
- Gastrointestinal disease
- Inflammatory diseases

Lifestyle risk factors:

- Smoking
- Obesity
- Alcohol consumption

Treatments and concomitant medications:

- Antihypertensives
- Cholesterol lowering medications
- Antidiabetics
- LOT

See Appendix A for the list of ICD-9-CM, ICD-10-CM, CPT codes, HCPCS codes and case identification algorithms for identifying these variables in the study databases.

8.3.4 Validity and Reliability

Diagnosis of multiple myeloma

The ICD-9-CM diagnosis codes (203.0x) have been used previously to identify patients with multiple myeloma in administrative data. Epidemiologic studies in which patients are identified by only ICD-9-CM codes (patients identified by at least one inpatient or two outpatient ICD-9-CM codes) may contain many false positive patients without multiple myeloma. In this study, patients with multiple myeloma will be identified using a claims-based algorithm developed and validated by Princic et al 2016 As described in Appendix C, this algorithm includes the use of diagnosis codes, CPT codes for certain tests and procedures and presence of claims for myeloma treatments. In the validation study for this algorithm, Marketscan claims data were compared to electronic medical records in a study of 2,179 patients, and the algorithm yielded sensitivity of 83%, specificity of 94% and positive predictive value of 93%.

Validation information for cardiac failure

In this study, cardiac failure will be ascertained from any claim that is submitted by an inpatient facility and includes ICD-9-CM diagnosis code 428.xx (Heart failure) and ICD-10-CM diagnosis code I50.xx (Heart failure) in any code position. The ICD-10-CM diagnosis codes were mapped from the corresponding ICD-9-CM diagnosis codes.

Among codes designating heart failure, these were the codes generally reported to have the highest positive predictive value in a systematic review by Saczynski et al 2012 of studies that evaluated the validity of diagnosis codes and algorithms developed using administrative health plan data to identify heart failure. This review was conducted as part of the US FDA's Mini-Sentinel program.

Accuracy of racial and ethnicity information variable

The Medicare program obtains information on beneficiaries' race and ethnicity for its administrative record from the Social Security Administration. The Social Security Administration collects this data at the time of application for a social security number and then transfers it to the Medicare Program's enrollment database upon enrollees eligibility.

Zaslavsky et al 2012 investigated the relationships between the race/ethnicity as reported in the Medicare enrollment databases and self-reported race information from the 2010 Medicare Consumer Assessments of Healthcare Providers and Systems (CAHPS) surveys. [Zaslavky et al 2012] Sensitivity, specificities and positive predictive values of Medicare enrollment database identification for Whites and Blacks were high (exceeding 90%). Specificities and positive predictive values for Hispanics and Asians were also high, but sensitivities for was moderate.

8.4 Data Sources

8.4.1 US Fee-for-service Medicare

US Medicare is a comprehensive, nationally representative, population-based data system of US patients ≥ 65 years of age, persons with certain disabilities or receiving dialysis (or kidney transplant) for permanent kidney damage. Patients included in the US Medicare data system for this study are those with full fee-for-service (traditional) Medicare. Patient information is documented from initial enrollment in Medicare until the date of death with minimal loss to follow up. Essentially all billable medical transactions are captured in the Medicare data system. Because these data are subject to federal audit, data quality for these variables is generally high.

The 100% Medicare multiple myeloma (MM) files from 2013 through 2017 will be used in this study. Data are from CMS Chronic Conditions Data Warehouse. The 100% MM data files include the annual denominator file and the annual claims-based standard analytic files (SAFs) from 2013 through 2017 for all Medicare beneficiaries with at least one ICD-9/10-CM diagnosis code for MM in any position from Part A or Part B claims between 2013 and 2017.

8.4.2 Optum Clinformatics® Data Mart (CDM)

Optum Clinformatics® Data Mart (CDM) is a medical claims database which represents the medical experience of insured employees and their dependents from both affiliated commercial and Medicare Advantage plans. Patients must have both medical and pharmacy coverage to be included in the database. The underlying insured population from which the data are drawn spans across all 50 US states and is racially/ethnically diverse. The database contains fully adjudicated eligibility, pharmacy, procedure, and medical claims data for subjects enrolled in a large US health plan (UnitedHealth Group). The health plan provides coverage for physician, hospital, and prescription drug services, and captures medical claims or encounter data from all available health care sites (inpatient hospital, outpatient hospital, emergency room, physician's office, surgery center, etc.) for virtually all types of provided services. Each facility inpatient admission record contains information on diagnoses (recorded using ICD-9-CM and ICD-10-CM diagnosis codes), procedures (recorded with ICD-9-CM and ICD-10-CM procedure codes, CPT codes, or HCPCS codes), and Present on Admission codes. Data are linked at the patient level by a unique identifier that is consistent across services, health plans, and time, so patients can be tracked over multiple years even if they switch health plans.

The Optum EHR consist of electronic medical records of patients receiving care at health care partners who are major health systems and integrated delivery networks.

Optum EHR data can be deterministically linked at the patient level to a subset of Optum CDM.

8.4.3 Humana Integrated Databases

The Humana Integrated Research Database contains claims data for Humana's research eligible fully-insured commercial and Medicare membership. Humana Inc. is a large US health insurance company; most members reside in the Midwestern and Southern regions of the United States; the West and Northeast are sparsely represented. The data sources for this study may include Humana member enrollment, medical and pharmacy data from Humana's claims database. Information from these different data sources can be linked reliably for each member using a unique member identifier which is included in all data sources. Race/ethnicity information is available for Medicare members and is based on information provided directly by the Centers for Medicare and Medicaid Services (CMS).

8.5 Study Size

For the Medicare FFS database, estimated person-years of observation among patients with multiple myeloma of different race and ethnicities treated and not treated with carfilzomib that will be available for calculation of cardiac failure incidence rates are extrapolated from a previous analysis covering 3 years of Medicare FFS data

(2013-2015). For the Humana and Optum databases, person-years of observation are estimated from preliminary patient counts (for the years 2013-2018) and assuming a follow-up of 2 years. We assumed a cardiac failure incidence of 5-20 per

100 person-years and estimated the number of events and 90% confidence interval for the incidence rates for each racial/ethnic group among patients with MM treated with and not treated with Kyprolis in each database (Table 1-Table 6). The actual numbers of events and cardiac failure incidence will depend on the true person-years accrued for each racial/ethnic group in the databases.

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Table 1. Estimated Patient-years of Multiple Myeloma Patients Exposed to Kyprolis in the Medicare FFS Database (2013-2017) and 90% Confidence Intervals for Different Cardiac Failure Incidence Rates

	Estimated accrual of carfilzomib-treated patients*		CF rate: 5 per 100 patient-years			CF rate: 10 per 100 patient-years			CF rate: 15 per 100 patient-years			CF rate: 20 per 100 patient-years		
	Number of patients	Patient-years	CF events	90% CI		CF events	90% CI		CF events	90% CI		CF events	90% CI	
White	1753	2644	132	4.3	5.77	264	9	11.06	397	13.8	16.32	529	18.6	21.5
Black	248	374	19	3.33	7.45	37	7.38	13.01	56	11.84	18.71	75	16.4	24.3
Asian	33	49	2	0.73	12.85	5	4.02	21.46	7	6.7	26.83	10	11.07	34.62
Hispanic	33	49	2	0.73	12.85	5	4.02	21.46	7	6.7	26.83	10	11.07	34.62

CF = cardiac failure, CI = confidence interval
* Accrual of carfilzomib-treated patients is estimated based on a previous analysis of Medicare data covering 2013-2015.

Table 2. Estimated Patient-years of Multiple Myeloma Patients not Exposed to Kyprolis in the Medicare FFS Database (2013-2017) and 90% Confidence Intervals for Different Cardiac Failure Incidence Rates

	Estimated accrual of non-carfilzomib-treated patients*		CF rate: 5 per 100 patient-years			CF rate: 10 per 100 patient-years			CF rate: 15 per 100 patient-years			CF rate: 20 per 100 patient-years		
	Number of patients	Patient-years	CF events	90% CI		CF events	90% CI		CF events	90% CI		CF events	90% CI	
White	86 856	131072	6554	4.9	5.1	13107	9.86	10.14	19661	14.82	15.18	26214	19.8	20.2
Black	9111	13750	688	4.69	5.33	1375	9.56	10.46	2062	14.46	15.55	2750	19.38	20.64
Asian	1191	1799	90	4.17	5.96	180	8.81	11.32	270	13.54	16.6	360	18.31	21.83
Hispanic	1483	2238	112	4.25	5.85	224	8.93	11.18	336	13.69	16.43	448	18.49	21.64

CF = cardiac failure, CI = confidence interval
* Accrual of carfilzomib-treated patients is estimated based on a previous analysis of Medicare data covering 2013-2015.

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Table 3. Estimated Patient-years of Multiple Myeloma Patients Exposed to Kyprolis in the Optum Research Database (2013-2018) and 90% Confidence Intervals for Different Cardiac Failure Incidence Rates

	Estimated accrual of carfilzomib-treated patients*		CF rate: 5 per 100 patient-years			CF rate: 10 per 100 patient-years			CF rate: 15 per 100 patient-years			CF rate: 20 per 100 patient-years		
	Number of patients	Patient-years	CF events	90% CI		CF events	90% CI		CF events	90% CI		CF events	90% CI	
White	743	1182	59	3.97	6.2	118	8.52	11.63	177	13.17	16.96	236	17.88	22.24
Black	204	325	16	3.09	7.48	33	7.43	13.58	49	11.72	19.13	65	16.1	24.59
Asian	31	49	2	0.73	12.85	5	4.02	21.46	7	6.7	26.83	10	11.07	34.62
Hispanic	104	165	8	2.41	8.75	17	6.56	15.45	25	10.53	21.16	33	14.64	26.74

CF = cardiac failure, CI = confidence interval
* Accrual of patient-years assumed an average follow-up of 2 years in commercial insurance databases

Table 4. Estimated Patient-years of Multiple Myeloma Patients not Exposed to Kyprolis in the Optum Research Database (2013-2018) and 90% Confidence Intervals for Different Cardiac Failure Incidence Rates

	Estimated accrual of non-carfilzomib-treated patients*		CF rate: 5 per 100 patient-years			CF rate: 10 per 100 patient-years			CF rate: 15 per 100 patient-years			CF rate: 20 per 100 patient-years		
	Number of patients	Patient-years	CF events	90% CI		CF events	90% CI		CF events	90% CI		CF events	90% CI	
White	10389	16539	827	4.72	5.3	1654	9.6	10.41	2481	14.51	15.51	3308	19.43	20.58
Black	2656	4228	211	4.44	5.59	423	9.22	10.84	634	14.03	16.01	846	18.89	21.18
Asian	440	700	35	3.7	6.63	70	8.12	12.2	105	12.68	17.64	140	17.3	23.01
Hispanic	1631	2597	130	4.31	5.79	260	9.01	11.09	390	13.79	16.33	519	18.56	21.49

CF = cardiac failure, CI = confidence interval
* Accrual of patient-years assumed an average follow-up of 2 years in commercial insurance databases

Table 5. Estimated Patient-years of Multiple Myeloma Patients Exposed to Kyprolis in the Humana Database (2013-2018) and 90% Confidence Intervals for Different Cardiac Failure Incidence Rates

	Estimated accrual of carfilzomib-treated patients*		CF rate: 5 per 100 patient-years			CF rate: 10 per 100 patient-years			CF rate: 15 per 100 patient-years			CF rate: 20 per 100 patient-years		
	Number of patients	Patient-years	CF events	90% CI		CF events	90% CI		CF events	90% CI		CF events	90% CI	
White	358	569	28	3.5	6.75	57	7.94	12.49	85	12.38	17.89	114	17.05	23.41
Black	161	256	13	3	8.07	26	7.12	14.09	38	11.12	19.46	51	15.57	25.16
Asian	10	15	1	0.34	31.63	2	2.37	41.97	2	2.37	41.97	3	5.45	51.69
Hispanic	11	17	1	0.3	27.91	2	2.09	37.03	3	4.81	45.61	3	4.81	45.61

CF = cardiac failure, CI = confidence interval
* Accrual of patient-years assumed an average follow-up of 2 years in commercial insurance databases

Table 6. Estimated Patient-years of Multiple Myeloma Patients not Exposed to Kyprolis in the Humana Database (2013-2018) and 90% Confidence Intervals for Different Cardiac Failure Incidence Rates

	Estimated accrual of non-carfilzomib-treated patients*		CF rate: 5 per 100 patient-years			CF rate: 10 per 100 patient-years			CF rate: 15 per 100 patient-years			CF rate: 20 per 100 patient-years		
	Number of patient	Patient-years	CF events	90% CI		CF events	90% CI		CF events	90% CI		CF events	90% CI	
White	4876	7762	388	4.59	5.44	776	9.41	10.61	1164	14.28	15.74	1552	19.17	20.85
Black	2194	3493	175	4.4	5.68	349	9.13	10.92	524	13.94	16.13	699	18.78	21.3
Asian	142	226	11	2.73	8.06	23	6.96	14.42	34	11.07	20.03	45	15.29	25.53
Hispanic	200	318	16	3.16	7.64	32	7.33	13.52	48	11.7	19.2	64	16.17	24.78

CF = cardiac failure, CI = confidence interval
* Accrual of patient-years assumed an average follow-up of 2 years in commercial insurance databases

8.6 Data Management

8.6.1 Obtaining Data Files

This study will use the Medicare FFS data, Optum Clinformatics Data Mart and the Humana research database. Chronic Disease Research Group (CDRG) will obtain the Medicare FFS data under a data use agreement. Comprehensive Health Insights Inc. (CHI), a Humana company, has direct access to the Humana Research Database, which contains all claims data for Humana's fully-insured commercial and Medicare membership. The data sources for this study will include Humana member enrollment, as well as medical and pharmacy claims data, from the Humana Research Database. Amgen has access to the Optum research database, which includes enrollment data, demographics, pharmacy claims, all medical and facility claims and data on services, procedures, and their accompanying diagnoses; as well as linkage to EHR for a subset of multiple myeloma patients. Data are received from Optum CDM via download using Amazon WorkSpace S3 buckets. Data may be encrypted with a password sent separately. A manifest detailing contents (list of tables, fields, and number of rows) is also included in the transfer to enable Amgen to verify that the transfer completed successfully.

8.6.2 Linking Data Files

The Medicare FFS data files include a unique identifier that allows claims and enrollment data to be linked to an individual beneficiary over time. Information from the different data sources in the Humana research database can be linked reliably for each patient using a unique member identifier that is included in all data sources. The Optum research database includes a patient-specific identifier that is used to link tables, and there are internal data disclosure processes to examine the use of various combinations of variables to control the risk of re-identification. In addition, Optum offers a link between administrative claims and the clinical specificity of EHR for a subset of identified patients with multiple myeloma.

8.6.3 Review and Verification of Data Quality

Medicare has its own quality control process and accuracy assessment programs. CDRG has an existing quality assurance protocol that is routinely implemented with Medicare data they receive. Each file is examined in detail, and consistency across years is assessed to evaluate data completeness and accuracy and to identify any change in variable names or addition of new variables.

CHI's Data Offerings team performs quality checks on the Humana Research Database. The Research Scientist will perform quality data checks at certain stages of the research process (eg, data extraction, programming). All datasets, including the analytical file, will be quality-checked to ensure that data appear to be correct. This will involve checking for missing values, ensuring that minimum and maximum values are within acceptable ranges, and that frequency counts, means, and other quantitative results are reasonable.

The Optum CDM is a de-identified, Health Insurance Portability and Accountability (HIPAA) compliant, closed system of claims, which undergo audits and quality control procedures by the insurer at regular intervals. The coding of medical claims conforms to insurance industry standards, including the use of designated claims forms (eg, physicians use the Health Care Financing Agency [HCFA]-1500 format and hospitals use the UB-92 format). Data received from Optum CDM are checked against the vendor-provided manifest to verify that every table, field and row was received by Amgen. Amgen runs additional data quality checks, including custom data checks comparing prior refreshes to the current data.

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8.7 Data Analysis

8.7.1 Planned Analyses

Administrative data will be utilized to evaluate all study objectives. Separate analyses will be conducted for each of the data sources employed in this study. Pre-index study variables and exposures will be analyzed descriptively. Counts and percentages will be provided for dichotomous and polychotomous variables. Means, standard deviations, and medians will be provided for continuous variables. Cardiac failure outcome will be evaluated descriptively as incidence rates per person year for each exposure cohort within each data source. Comparison of incidence rates of cardiac failure within African American and white race will be conducted as exploratory analysis.

8.7.2 Planned Method of Analysis

8.7.2.1 General Considerations

This analysis focuses on describing the characteristics of US patients with multiple myeloma of different race/ethnicities treated and not treated with carfilzomib, examining the risk factor for heart failure in these cohorts and estimating the incidence of cardiac failure. Included patients can contribute exposures and observations across multiple LOT. The cohorts will be described in terms of demographic and clinical characteristics, and outcome will be assessed as inpatient hospitalization events for cardiac failure.

Analyses will be conducted among separate cohorts identified by treatment episodes (carfilzomib containing regimens and non-carfilzomib containing regimens) for each race/ethnic group. This study utilizes an observational research approach and study analysis for primary objectives is estimation rather than hypothesis testing. Comparison of incidence rates of cardiac failure within African American and white race will be conducted as exploratory analysis.

8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

For variables with missing or incomplete data, flags will be created to denote the number of patients with unknown values. No data imputation or other methods will be performed. Because of the way that the claims data are generated, lack of evidence of a diagnosis, procedure, or medication will be considered to be evidence that the diagnosis, procedure, or medication does not apply to the patient. Follow-up of participants will be censored if insurance coverage is lost because events will not be detectable during periods without coverage.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Study Enrollment

Separate analysis will be conducted in each data source used in this study. An attrition table will be generated to illustrate how the study cohorts were derived from the source data. Excluded participant counts will be provided for each inclusion and exclusion criterion applied, as specified in **section 8.2.2.1** and **section 8.2.2.2**.

8.7.2.3.2 Description of Patient Characteristics

Demographic characteristics, including age, gender, and geographic region will be summarized for the overall cohort. Myeloma-related clinical characteristics, other clinical comorbidity measures, concomitant medications, as well as lifestyle characteristics will be summarized for the study cohorts. Mean and standard deviation (SD) will be reported for continuous measures, and frequency and percent will be reported for categorical measures.

8.7.2.4 Analysis of the Primary Endpoints

Separate analysis will be conducted in each data source used in this study. Incidence of cardiac failure will be estimated for each race/ethnicity (ie, white, black, Hispanic and Asian) separately in each data source for all observed treatment episodes(ie, across all lines of therapy). Incidence rate of cardiac failure will be estimated by dividing the total number of events by the total person-time at risk from which the events arose. Ninety-five percent confidence intervals (CIs) for the incidence rates will be calculated

using Byar's formula [Breslow et al 1987]. For the estimation of incidence rates, study follow-up begins on the treatment start date (ie, initiation of carfilzomib or non-carfilzomib-based regimens) within each LOT and continue through the earliest date of first cardiac failure hospitalization, death, loss of insurance coverage, 30 days after treatment end date within the LOT, or end of study.

8.7.2.5 Analysis of the Secondary Objectives

As previously described in **section 8.7.2.3.2**, demographic characteristics, myeloma-related clinical characteristics, other clinical comorbidity measures, concomitant medications as well as lifestyle characteristics will be summarized for the study cohorts using descriptive statistics.

8.7.2.6 Analysis of the Exploratory Objectives

Given that covariates in this study may differ between patients treated with carfilzomib and other treatments, we will attempt to create cohorts of patients with balanced covariates using propensity score matching separately for African American and White patient cohorts. For the propensity score matching strategy, we will calculate propensity scores using a logistic regression model to estimate the predicted probability of exposure to a carfilzomib treatment episode. The logistic regression model will include covariates listed in section 8.3.3. Each carfilzomib treatment episode will be matched to a non-carfilzomib treatment episode on the propensity score using a greedy algorithm with a 5-digit match. For the mechanics of matching, we will set the smaller group as the referent group and the larger group as the comparator group.

Differences in baseline patient characteristics between the treatment cohorts (carfilzomib and other treatments for multiple myeloma) will be assessed in the initial study population and the propensity-score matched population using the standardized mean difference (SMD). A SMD greater than 0.1 (10%) will represent residual imbalance for any covariate. The overlap of the propensity score distribution will also be visualized to assess possible positivity violations. If the assessment indicates sufficient post-matching comparability, we will evaluate the association between treatment with carfilzomib versus other treatments for multiple myeloma and risk of cardiac failure by line of therapy using a Cox proportional hazards model.

Follow-up for occurrence of study outcome will begin on the treatment start date (ie, initiation of carfilzomib or non-carfilzomib-based regimens within that LOT) and continues through the earliest date of first cardiac failure hospitalization, death, loss of insurance coverage, 30 days after treatment end date within the LOT, or end of study

period. The proportionality assumption of the Cox model will be checked by including time-dependent covariates (generated by creating interactions of the explanatory variables and a log function of survival time) in the model,

Despite the attempt to balance covariates using a propensity score matching strategy, the possibility exists for residual bias due to unmeasured confounding. Thus, we will apply quantitative bias analyses to assess the extent of unmeasured confounding that would be required to refute an observed difference in outcome incidence between cohorts. The rule-out method has been described previously [Schneeweiss et al 2006) is publicly available (www.drugepi.org) and has been applied extensively in the literature. [Weintraub et al 2012] An alternative method of evaluating unmeasured confounding involves assessing the strength of the measured confounders by removing each confounder individually from the model to develop a distribution of the point estimate of the hazard ratios to display the strength of the measured confounding. Assuming the unmeasured confounders fall within this distribution, the distribution can be used to inform the potential magnitude and direction of the unmeasured confounders on the validity of the effect estimate. One or more of these methods will be explored, as appropriate.

8.7.2.7 Sensitivity Analysis

For the analysis of the primary objectives, we will calculate incidence rates by race, including all data sources (ie, Medicare fee-for-service, Optum claims data and Humana claims data) and lines of therapy. This analysis will be done separately for cohorts of patients treated with carfilzomib treatment and those receiving other treatments. Due to data use agreement restrictions, we are unable to pool individual patient level data across data for this analysis. Thus, we will calculate estimates of incidence rates by race across all data sources from aggregated person-time and number of outcomes for each race from each data source. We may not be able to do this calculation for race/ethnicities with very few outcome counts as CMS rules mandate that event counts less than 11 should be suppressed in data tables.

8.7.2.7.1 Subgroup Analysis

Among the subset of patients identified from the Optum claims database linkable to the Optum EHR database, the planned analysis for the primary and secondary objectives as previously described in **section 8.7.2.4** and **section 8.7.2.5** will be evaluated.

8.7.2.7.2 Stratified Analysis

Analysis stratified by LOT will be conducted for the study objectives.

8.7.2.7.3 Sensitivity Analysis for Residual Confounding and Bias

Not applicable.

8.7.2.7.4 Other Sensitivity Analysis

Not applicable.

8.7.3 Analysis of Safety Endpoint/Outcome

Cardiac failure outcome will be analyzed.

8.8 Quality Control

Independent production and quality control programming will be performed for all analyses.

8.9 Limitations of the Research Methods

This retrospective cohort study is designed to estimate the incidence of cardiac failure in multiple myeloma patients of various race and ethnic identification treated with and not treated with carfilzomib. As this is an estimation study, the findings are descriptive and no causal hypothesis is being tested or implied.

8.9.1 Internal Validity of Study Design

8.9.1.1 Measurement Error/Misclassifications

The possibility of misclassification exists in all studies that rely on administrative claims. These data are collected for billing purposes, not research. As a result, evidence of conditions and events based on reported ICD-9-CM and ICD-10-CM diagnosis codes are primarily for reimbursement and may not reflect confirmed diagnoses. In addition, while codes of pharmacy claims indicate filled prescriptions, they do not confirm that the medication was taken as prescribed. Thus, use of administrative claims to evaluate exposures, outcomes, and covariates may introduce measurement error or misclassification. This will be emphasized in the reporting of this study.

8.9.1.2 Information Bias

Claims databases only include information on subjects while covered by the health plan. As a result, a complete medical history may not be fully captured in an administrative claims database. Care sought and paid for outside of the health insurance plan will not be captured. However, this is expected to be very minimal for the cardiac failure outcome in this study.

8.9.1.3 Selection Bias

Subject selection is based on ICD-9-CM and ICD-10-CM diagnosis codes which may be incomplete or missing as previously described. This study will also include subjects who

meet minimum enrollment criteria. This approach will exclude subjects with shorter or intermittent insurance coverage. This limitation will be acknowledged in the final study report.

8.9.1.4 Confounding

For the primary analysis, this study will not assess potential causal relationships, and therefore confounding will not be relevant. For the exploratory analysis, there exists the possibility of confounding in measured and unmeasured covariates. However, we will mitigate against confounding by applying a propensity score approach to balance baseline covariates and employ quantitative bias analysis to assess the extent of unmeasured confounding that would be required to refute an observed difference in outcome incidence between cohorts.

8.9.2 External Validity of Study Design

This study will include patients enrolled in different health insurance options (Medicare FFS, Optum and Humana). Thus, this study will represent the experience of patients with multiple myeloma in these settings. Caution should be used when generalizing the study findings to outcomes in patient populations with other (or no) health insurance coverage.

8.9.3 Analysis Limitations

Not applicable

8.9.4 Limitations Due to Missing Data and/or Incomplete Data

Subjects may be missing insurance claims for medical or pharmacy encounters for which they did not use their insurance. This is not expected to be common issue for this study population. ICD-9-CM and ICD-10-CM diagnosis codes for lifestyle factors (smoking, obesity, alcohol consumption) are known to be under-utilized. Thus, underestimation of the number of patients with these factors is expected.

9. Protection of Human Subjects

This study will use de-identified data and the research process will be conducted in strict compliance with all state, local and federal regulatory requirements.

9.1 Informed Consent

This is a retrospective database analysis, and therefore does not require informed consent.

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

The study concept and proposal has been submitted to and received approval (expedited review) from the Hennepin County Medical Center/Hennepin Healthcare System, Inc. Office for Human Subjects Research and the Humana's Protected Health Information and Vendor Ethics (PHIVE) and Research Review (RRC) committees.

9.3 Patient Confidentiality

This study will comply with all applicable laws, regulations, and guidance regarding patient protection including patient privacy. No personally identifying patient data will be submitted to Amgen, only aggregate data summarized at the cohort-level. No direct participant contact will occur in this retrospective study using previously collected de-identified claims data.

10. Collection, Recording, and Reporting of Safety Information and Product Complaints

This study is analyzing secondary data from Medicare FFS database, Humana research database and Optum research database. The safety outcome listed in section 8.3.2 will be documented in the study report and analyzed in this study. These will be reported in aggregate in the final study report as incidence rates. See section 8.3.2 for safety outcomes and definitions. Submission of safety outcomes as individual safety reports to Amgen is not required. Safety events suspected to be related to any medicinal product should be reported to the local authority in line with the local country requirements.

11. Administrative and Legal Obligations

11.1 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 relevant ethical review board must be informed of all amendments and give approval. The Investigator **must** send a copy of the approval letter from the relevant ethical review board 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 relevant ethical review board in writing of the study's completion or early termination and send a copy of the notification to Amgen.

12. Plans for Disseminating and Communicating Study Results

12.1 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:

1. 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.

Approved

13. References

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14. Appendices

Appendix A. Codes for Identifying Multiple Myeloma Treatments and Comorbid Conditions

No.	Document Reference Number	Date	Title
1	Multiple myeloma treatment codes	4 March 2019	NDC Codes to identify MM treatments in claims  Codes for identifying
2	Multiple myeloma comorbid codes	4 March 2019	ICD-9-CM, ICD-10-CM, CPT and HCPCS codes to identify comorbid conditions  Codes for MM

Appendix B. ENCePP Checklist for Study Protocols

Study title:
An observational study to estimate incidence rates of heart failure among US racial and ethnic minority patients with multiple myeloma treated or not treated with carfilzomib

Study reference number:
TBD

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5
1.1.2 End of data collection[2]	☐	☐	☐	5
1.1.3 Study progress report(s)	☐	☐	☒	5
1.1.4 Interim progress report(s)	☐	☐	☒	5
1.1.5 Registration in the EU PAS register	☒	☐	☐	5
1.1.6 Final report of study results.	☒	☐	☐	5

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6.2 7
2.1.2 The objective(s) of the study?				
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	6.3
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	6.3

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (eg, cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	8.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.4

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.3 Does the protocol specify measures of occurrence? (eg, incidence rate, absolute risk)	☒	☐	☐	8.3.2
3.4 Does the protocol specify measure(s) of association? (eg, relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	8.2
4.2 Is the planned study population defined in terms of:	☒	☐	☐	8.2.1
4.2.1 Study time period?	☒	☐	☐	8.2.1
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☒	☐	☐	
4.2.4 Disease/indication?	☒	☐	☐	
4.2.5 Duration of follow-up?				
4.3 Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	8.2.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.3.1
5.2 Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☒	☐	☐	8.3.4
5.3 Is exposure classified according to time windows? (eg, current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.3.2
6.3 Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	8.3.4
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (eg, HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:				
7.2.1. Selection biases (eg, healthy user bias)	☒	☐	☐	8.9.1.3
7.2.2. Information biases (eg, misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	8.9.1.2
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	8.9.4

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (eg, collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	8.4
9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient	☒	☐	☐	8.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
interview including scales and questionnaires, vital statistics, etc.) 9.1.3 Covariates?	☒	☐	☐	8.4
9.2 Does the protocol describe the information available from the data source(s) on: 8.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) 8.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event) 8.2.3 Covariates? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒ ☒ ☒	☐ ☐ ☐	☐ ☐ ☐	 8.4 8.4 8.4
9.3 Is a coding system described for: 9.3.3 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System) 9.3.2 Outcomes? (eg, International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA)) 9.3.3 Covariates?	☒ ☒ ☒	☐ ☐ ☐	☐ ☐ ☐	 8.3.1 8.3.2 8.3.2
9.4 Is a linkage method between data sources described? (eg, based on a unique identifier or other)	☒	☐	☐	8.6.2

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	8.7.2.4
10.2 Are descriptive analyses included?	☒	☐	☐	8.7.2.3
10.3 Are stratified analyses included?	☒	☐	☐	8.7.2.6.2
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	8.7.2.2
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	8.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.6.1
11.2 Are methods of quality assurance described?	☒	☐	☐	8.6.3
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	8.9.1.3
12.1.2 Information bias?	☒	☐	☐	8.9.1.2
12.1.3 Residual/unmeasured confounding? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	8.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.2
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.3

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	11.1

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.1

Comments:

Name of the main author of the protocol: Akeem A

Yusuf Date: 03/20/2019

Signature: _____

Approved

Appendix C. Algorithm for Identification of Patients With Multiple Myeloma in Claims Data

Patients with multiple myeloma with symptomatic disease in the Medicare FFS, Optum and Humana claims databases will be identified using a validated algorithm for ascertainment of patients with multiple myeloma in claims data (Princic, Gregory et al 2016).

This claims-based algorithm includes a combination of ICD-9-CM code 203.0X OR ICD-10-CM code C90.0x and diagnosis tests or treatment. To meet this algorithm a patient must have a multiple myeloma diagnosis (index diagnosis) and one of:

- 3 additional multiple myeloma 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-myeloma therapy within 180 days after one multiple myeloma diagnosis; Drug codes must be on a claim with a chemotherapy administration code. Index diagnosis is the first diagnosis to meet treatment criteria.

Option 1:	**Option 2:**
3 multiple myeloma diagnoses during the 90 days prior to the index diagnosis **AND** 1 Bone Marrow Test **OR** 2 Other Diagnostic Tests a. Urine/serum protein tests b. Serum free light chain assay c. Immunoglobulin tests d. Serum albumin e. Serum beta 2-microglobulin f. X-ray skeletal survey g. Lactate dehydrogenase	1 multiple myeloma diagnosis **AND** Anti-myeloma therapy within 180 days after multiple myeloma diagnosis

Appendix D. Drug Treatments for Multiple Myeloma

Generic name	Brand name (sold as)	Type of treatment
Bendamustine	Bendeka, Treanda	Chemotherapy
Bortezomib	Velcade	Targeted therapy (Proteasome inhibitor)
Carfilzomib	Kyprolis	Targeted therapy (Proteasome inhibitor)
Cisplastin	Platinol	Chemotherapy
Cyclophosphamide	-	Chemotherapy
Daratumumab	Darzalex	Monoclonal antibody
Dexamethasone	-	Steroid
Doxorubicin	Doxil	Chemotherapy
Elotuzumab	Empliciti	Monoclonal antibody
Etoposide	Etopohos	Chemotherapy
Ixazomib	Ninlaro	Targeted therapy (Proteasome inhibitor)
Lenalidomide	Revlimid	Immunomodulator
Melphalan	Alkeran	Chemotherapy
Panobinostat	Farydak	Targeted therapy (Histone deacetylase inhibitor)
Pomalidomide	Pomalyst	Immunomodulator
Thalidomide	Thalomid	Immunomodulator
Vincristine	Vincasar PFS	Chemotherapy
Vorinostat	Zolinza	Chemotherapy

Appendix E. ICD-9-CM and ICD-10-CM Diagnosis Codes to Identify Cardiac Failure

ICD-9-CM Dx	ICD-10-CM Dx	ICD-9 Description	ICD-10 Description
"428.0"	I50.9	Congestive heart failure, unspecified	Heart failure, unspecified
"428.1"	I50.1	Left heart failure	Left ventricular failure
"428.20"	I50.20	Systolic heart failure, unspecified	Unspecified systolic (congestive) heart failure
"428.21"	I50.21	Acute systolic heart failure	Acute systolic (congestive) heart failure
"428.22"	I50.22	Chronic systolic heart failure	Chronic systolic (congestive) heart failure
"428.23"	I50.23	Acute on chronic systolic heart failure	Acute on chronic systolic (congestive) heart failure
"428.30"	I50.30	Diastolic heart failure, unspecified	Unspecified diastolic (congestive) heart failure
"428.31"	I50.31	Acute diastolic heart failure	Acute diastolic (congestive) heart failure
"428.32"	I50.32	Chronic diastolic heart failure	Chronic diastolic (congestive) heart failure
"428.33"	I50.33	Acute on chronic diastolic heart failure	Acute on chronic diastolic (congestive) heart failure
"428.40"	I50.40	Combined systolic and diastolic heart failure, unspecified	Unspecified combined systolic (congestive) and diastolic (congestive) heart failure
"428.41"	I50.41	Acute combined systolic and diastolic heart failure	Acute combined systolic (congestive) and diastolic (congestive) heart failure
"428.42"	I50.42	Chronic combined systolic and diastolic heart failure	Chronic combined systolic (congestive) and diastolic (congestive) heart failure
"428.43"	I50.43	Acute on chronic combined systolic and diastolic heart failure	Acute on chronic combined systolic (congestive) and diastolic (congestive) heart failure
"428.9"	I50.9	Heart failure, unspecified	Heart failure, unspecified

Amendment 1

Protocol Title: An Observational Study to Estimate Incidence Rates of Heart Failure Among US Racial and Ethnic Minority Patients With Multiple Myeloma Treated or not Treated With Carfilzomib

Amgen Protocol Number 20190012

Amendment Date: 18 July 2019

Rationale:

The FDA has reviewed the protocol that was conditionally approved by the ORRG on 3 April 2019 and suggested a number of additions. These include:

1. An exploratory objective to assess the comparability of African American multiple myeloma (MM) patients treated with carfilzomib- vs. non-carfilzomib-based therapies following propensity score (PS) matching (Exploratory Objective [EO] 1).
2. An exploratory objective to compare the risk for cardiac failure between African American MM patients treated with carfilzomib- vs. non-carfilzomib-based therapies following PS matching, gated by EO1 (EO2).
3. An exploratory objective to assess the comparability of white MM patients treated with carfilzomib- vs. non-carfilzomib-based therapies following PS matching (EO3).
4. An exploratory objective to compare the risk for cardiac failure between white MM patients treated with carfilzomib- vs. non-carfilzomib-based therapies following PS matching, gated by EO3 (EO4).

Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Global	Global Version date in header and Summary Table of Study Protocol	Replace: 03 April 2019 With: **16 July 2019**	To reflect the date of most recent changes to the protocol
Global	Global Exploratory Objectives	Add: **Exploratory objectives** **1.Assess comparability between patients with multiple myeloma of African American race treated with carfilzomib and those treated with other treatments for multiple myeloma, after propensity score matching, using standardized mean differences** **2.If the assessment indicates sufficient post-matching comparability, compare the risk of cardiac failure between patients with multiple myeloma of African American race treated with carfilzomib and those treated with other treatments for multiple myeloma** **3.Assess comparability between patients with multiple myeloma of White race treated with carfilzomib and those treated with other treatments for multiple myeloma, after propensity score matching, using standardized mean differences** **4.If the assessment indicates sufficient post-matching comparability, compare the risk of cardiac failure between patients with multiple myeloma of White race treated with carfilzomib and those treated with other treatments for multiple myeloma**	New exploratory objectives added by request of the FDA

Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Page 1, Summary Table of Study Protocol	Page 1, Summary Table of Study Protocol, Author	Add: **Alan Fu, PhD, Amgen Inc. (RAE)**	Updated to reflect new protocol author and study RAE
Page 2, Summary Table of Study Protocol	Page 2, Summary Table of Study Protocol, MAH Contract	Replace: Akeem Yusuf, PhD, ayusuf01@amgen.com With: **Alan Fu, PhD, afu01@amgen.com**	Updated to reflect new study RAE and MAH contact
Page 10, Section 3 Responsible Parties	Page 10, Section 3 Responsible Parties, Contact	Change: Akeem Yusuf, PhD Senior Manager, Observational Research Amgen Inc. Thousand Oaks, CA ayusuf01@amgen.com +1 (805) 447-2291 With: **Alan Fu, PhD** **Manager, Observational Research** Amgen Inc. Thousand Oaks, CA **afu01@amgen.com** +1 (805) **490-3575**	Updated with new Amgen point of contact information

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Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Page 13, Section 4 Abstract	Page 13, Section 4 Abstract, Data Analysis	Add: **Within the cohorts of patients of African American and White race, we will attempt to create cohorts…**	Updated data analysis plan to reflect intent to assess risk for heart failure in African American and white myeloma patients treated with carfilzomib- or non-carfilzomib-based therapies, as outlined in Exploratory Objectives
Page 15, Section 6 Rationale and Background	Page 15, Section 6 Rationale and Background, 6.3 Statistical Inference	Add: **Comparison of incidence rates of cardiac failure within African American and white race will be conducted as exploratory analysis.**	Updated section to reflect intent to assess risk for heart failure in African American and white myeloma patients treated with carfilzomib- or non-carfilzomib-based therapies, as outlined in Exploratory Objectives
Page 21, Section 8 Research Methods	Page 21, Section 8 Research Methods, 8.4 Data Sources, 8.4.1 US Fee-for-service Medicare	Replace: Five years of accrued Medicare claims data will be collected and analyzed (2013 – 2017) for this study. With: **The 100% Medicare multiple myeloma (MM) files from 2013 through 2017 will be used in this study…**	Added text to more thoroughly describe the Medicare data we intend to use.
Page 26, Section 8 Research Methods	Page 26, Section 8 Research Methods, 8.7 Data Analysis, 8.7.1 Planned Analyses	Add: **Comparison of incidence rates of cardiac failure within African American and white race will be conducted as exploratory analysis**	Updated section to reflect intent to assess risk for heart failure in African American and white myeloma patients treated with carfilzomib- or non-carfilzomib-based therapies, as outlined in Exploratory Objectives

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Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Page 27, Section 8 Research Methods	Page 27, Section 8 Research Methods, 8.7 Data Analysis, 8.7.2 Planned Method of Analysis, 8.7.2.1 General Considerations	Change: This study utilizes an observational research approach and study analysis is estimation rather than hypothesis testing. With: This study utilizes an observational research approach and study analysis **for primary objectives** is estimation rather than hypothesis testing.	Updated text to reflect that the estimation/descriptive portion of the protocol specifically pertain to the Primary Objectives
Page 27, Section 8 Research Methods	Page 27, Section 8 Research Methods, 8.7 Data Analysis, 8.7.2 Planned Method of Analysis, 8.7.2.1 General Considerations	Add: **Comparison of incidence rates of cardiac failure within African American and white race will be conducted as exploratory analysis.**	Updated section to reflect intent to assess risk for heart failure in African American and white myeloma patients treated with carfilzomib- or non-carfilzomib-based therapies, as outlined in Exploratory Objectives
Page 27, Section 8 Research Methods	Page 27, Section 8 Research Methods, 8.7 Data Analysis, 8.7.2 Planned Method of Analysis, 8.7.2.4 Analysis of the Primary Endpoints	Change: Incidence of cardiac failure will be estimated for each race/ethnicity (ie, white, black, Hispanic and Asian) separately in each data source for all observed treatment episodes With: Incidence of cardiac failure will be estimated for each race/ethnicity (ie, white, black, Hispanic and Asian) separately in each data source for all observed treatment episodes **(ie, across all lines of therapy)**	Clarified what is meant by “treatment episodes”

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Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Pages 28-29, Section 8 Research Methods	Page 28-29, Section 8 Research Methods, 8.7 Data Analysis, 8.7.2 Planned Method of Analysis, 8.7.2.6 Analysis of the Exploratory Objectives	Add: **8.7.2.6 Analysis of the Exploratory Objectives** **Given that covariates in this study may differ between patients…**	Added section delineating analysis plan for the Exploratory Objectives
Page 29, Section 8 Research Methods	Page 28-29, Section 8 Research Methods, 8.7 Data Analysis, 8.7.2 Planned Method of Analysis, 8.7.2.7 Sensitivity Analysis	Add: **8.7.3.7 Sensitivity Analysis** **For the analysis of the primary objectives, we will calculate incidence rates by race…**	Added section to reflect intent to perform sensitivity analyses for the Primary Objectives. This section had been intentionally left blank in the previous version of the protocol.
Page 30, Section 8 Research Methods	Page 30, Section 8 Research Methods, 8.7 Data Analysis, 8.7.2 Planned Method of Analysis, 8.7.2.7 Sensitivity Analysis, 8.7.2.7.1-4	Change: 8.7.2.6.1, 8.7.2.6.2, 8.7.2.6.3, 8.7.2.6.4 With: 8.7.2.**7**.1, 8.7.2.**7**.2, 8.7.2.**7**.3, 8.7.2.**7**.4	Changed section numbers due to addition of subsection 8.7.2.6 Analysis of Exploratory Objectives
Page 31, Section 8 Research Methods	Page 33, Section 8 Research Methods, 8.9 Limitations of the Research Methods, 8.9.1 Internal Validity of Study Design, 8.9.1.4 Confounding	Change: This study will not access potential causal relationships, and therefore confounding will not be relevant. With: **For the primary analysis, t**his study will not assess potential causal relationships, and therefore confounding will not be relevant.	Changed text to reflect that assessment of confounding will not apply to the Primary Objectives, but will be carried out for the Exploratory Objectives (see next row)

Page 5 of 6

Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Page 31, Section 8 Research Methods	Page 33, Section 8 Research Methods, 8.9 Limitations of the Research Methods, 8.9.1 Internal Validity of Study Design, 8.9.1.4 Confounding	Add: **For the exploratory analysis, there exists the possibility of confounding…**	Amended section to reflect our intent to and plan for assessing confounders for the Exploratory Objectives
Page 34, Section 13 References	Page 34, Section 13 References	Add: **14. Schneeweiss S. Sensitivity analyses and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. Pharmacoepi Drug Safety 2006;15:291–303** **15. Weintraub WS et al. Comparative Effectiveness of Revascularization Strategies. N Engl J Med. 2012 Apr 19; 366(16): 1467–1476.**	Added additional references for sensitivity and comparative analyses pertaining to the Exploratory Objectives

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Annex 3. Signature of Coordinating Investigator

Not Applicable

Annex 4. Statistical Analysis Plan

Analysis Plan for *Kyprolis FDA PMR – Heart failure risk in racial and ethnic minorities (Humana Integrated Databases)*

DAC Epidemiologist:

TA Epidemiologist:

Alan Fu (Amgen)

Other Collaborators (if any):

Brandon Suehs (Humana)

Shuling Li (CDRG)

Prepared by:

Alan Fu (Amgen)

DAC Intake Form Number:

Lead Programmer:

Document Version:

Version	Date	Summary of Version Change
1.0	12 Aug 2019	Original draft. Note: ~~Major updates and amendments of the original protocol are highlighted~~. All date ranges are inclusive unless otherwise stated.
1.1	21 Aug 2019	Integrating suggested changes from CDRG
1.2	22 Aug 2019	Integrating suggested changes from Humana
1.3	5 Sep 2019	Revised based on 3 September team meeting
1.4	11 Sep 2019	Updates highlighted
1.5	4 Oct 2019	Updates highlighted
1.6	5 Nov 2019	Updates: • Comorbidities list o "Codes for MM comorbid conditions.xlsx" replaced with "Codes for comorbidities (CDRG) – final.xlsx" • Added some references to codes in comments of Table 1 (attrition table) of table shells • Added codes for dialysis and kidney transplant ("Dialysis and kidney transplant.PNG")
1.7	5 Nov 2019	Updated criterion 2 of Table 1c (attrition flow) to include the "Other (any other race)" category

1.8	19 Nov 2019	Minor update to how to define race/ethnicity in the Optum cohort (see Table 1c shell)
1.9	4 Dec 2019	Updates highlighted: • Amended guidance on primary objectives
2.0	17 Dec 2019	Updated guidance on additional analyses for HF incidence rates based on position of diagnoses for in-patient claims (pg. 12; highlighted)
2.1	14 Jan 2020	Updates highlighted: • Guidance on analysis of Secondary Objectives (patient characteristics), pg. 15
2.2	19 Feb 2020	Updates highlighted: • Refined guidance on Exploratory Objectives
2.3	4 March 2020	Updates highlighted: • Minor corrections per email exchange with Shantel Muldrew o Add conmeds to Table 2 shell (patient characteristics table), but do not include conmeds in PS model o For Primary Objectives, person-years for the LOT 4+ analyses need to be tracked from the beginning of each LOT to the event (HF) or a censor. For the patient characteristics tables

		and PS modeling, matching, and comparative sections, we are not concerned with LOTs beyond 4.
2.4	6 March 2020	Minor guidance update for comparative analysis (highlighted, pg. 18)
2.5	12 March 2020	Updates highlighted: • Table shells for comparative analysis results • Updated guidance on quantitative analysis – to be conducted using rule-out method

Table of Contents

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I. Background

In pivotal phase 2 and 3 studies, there has been a reported increase in cardiovascular adverse events (including cardiac failure) in patients treated with carfilzomib. [Dimopoulos et al 2016, Stewart et al 2015, Hajek et al 2015] In a recently published pooled analysis of carfilzomib trials, the investigators concluded that despite increased incidence of cardiovascular events, relative risk of these events with carfilzomib is low and manageable. [Chari et al 2018]

On 14 June 2018, Amgen submitted to the Food and Drug Administration (FDA) a labeling supplement which proposed an update to the Kyprolis US Prescribing Information indicating that the risk of developing cardiac failure is higher among Asian patients. This increased risk was identified following analysis of data from Amgen sponsored clinical trials and postmarketing reports. On 14 December 2018, the FDA issued a complete response letter, which highlighted the lack of sufficient evidence to support that there is an increased risk of cardiac failure in US Asian patients. In addition, based on the submission of this supplement, the Agency stated the concern of a differential risk of cardiac failure among racial and ethnic minorities. To address these issues, Amgen agreed to conduct a postmarketing requirement in the form of an observational study to evaluate incidence rates of heart failure among US racial and ethnic minority patients with multiple myeloma treated or not treated with carfilzomib.

II. Glossary

Abbreviation/Acronym	Definition
EO	Exploratory Objective
K	Kyprolis (carfilzomib)
LOT	Line of therapy (synonymous with "treatment episode")
MM	Multiple myeloma
*n*L	*n*th line (of therapy)

PI	Proteasome inhibitor
PO	Primary Objective
SO	Secondary Objective

III. Objective(s)

- Primary Objectives
    1. Estimate the incidence rates of cardiac failure in US racial and ethnic populations of patients with multiple myeloma treated with carfilzomib
    2. Estimate the incidence rates of cardiac failure in US racial and ethnic populations of patients with multiple myeloma not treated with carfilzomib
- Secondary Objectives
    1. Describe demographic, clinical characteristics and cardiac failure risk factors in US racial and ethnic populations of patients with multiple myeloma treated with carfilzomib
    2. Describe demographic, clinical characteristics and cardiac failure risk factors in US racial and ethnic populations of patients with multiple myeloma not treated with carfilzomib
- Exploratory Objectives
    1. Assess comparability between patients with multiple myeloma of African American race treated with carfilzomib and those treated with other treatments for multiple myeloma, after propensity score matching, using standardized mean differences
    2. If the assessment indicates sufficient post-matching comparability, compare the risk of cardiac failure between patients with multiple myeloma of African American race treated with carfilzomib and those treated with other treatments for multiple myeloma

3. Assess comparability between patients with multiple myeloma of White race treated with carfilzomib and those treated with other treatments for multiple myeloma, after propensity score matching, using standardized mean differences
4. If the assessment indicates sufficient post-matching comparability, compare the risk of cardiac failure between patients with multiple myeloma of White race treated with carfilzomib and those treated with other treatments for multiple myeloma

IV. Study Design

i. Overall Research Design

Retrospective cohort study

ii. Data Source

Medicare FFS, Humana Integrated Databases, Optum Clinformatics

iii. Study Period

01 January 2013 to 31 December 2018 (31 December 2017 for Medicare FFS)

iv. Programming Definitions

<<Intentionally left blank>>

v. Inclusion Criteria

Please refer to Table 1 shell (Cohort attrition table)

vi. Exclusion Criteria

Please refer to Table 1 shell (Cohort attrition table)

vii. Index Date

MM disease index: Please see "MM and LOT algorithms_CDRG 7Aug2019.docx", pg. 1.

Treatment index: Initiation of a carfilzomib- or non-carfilzomib-based LOT therapy after MM index date and between 01 January 2014 and 30 June 2018 (30 June 2017 for Medicare FFS). Please refer to "MM and LOT algorithms_CDRG 7Aug2019.docx" for LOT rules.

viii. Baseline Period

12 months prior to initiation of each LOT (2L, 3L, 4L)

ix. Study Follow-up

Following subject identification, LOT treatment episodes among patients diagnosed with MM will be identified. Individuals may contribute more than one LOT treatment episode during the course of study follow-up. The focus of the analysis will be the follow-up time associated with each individual LOT. With each LOT episode, follow-up for the study outcome will begin on the date of LOT initiation and continue to the earliest of:

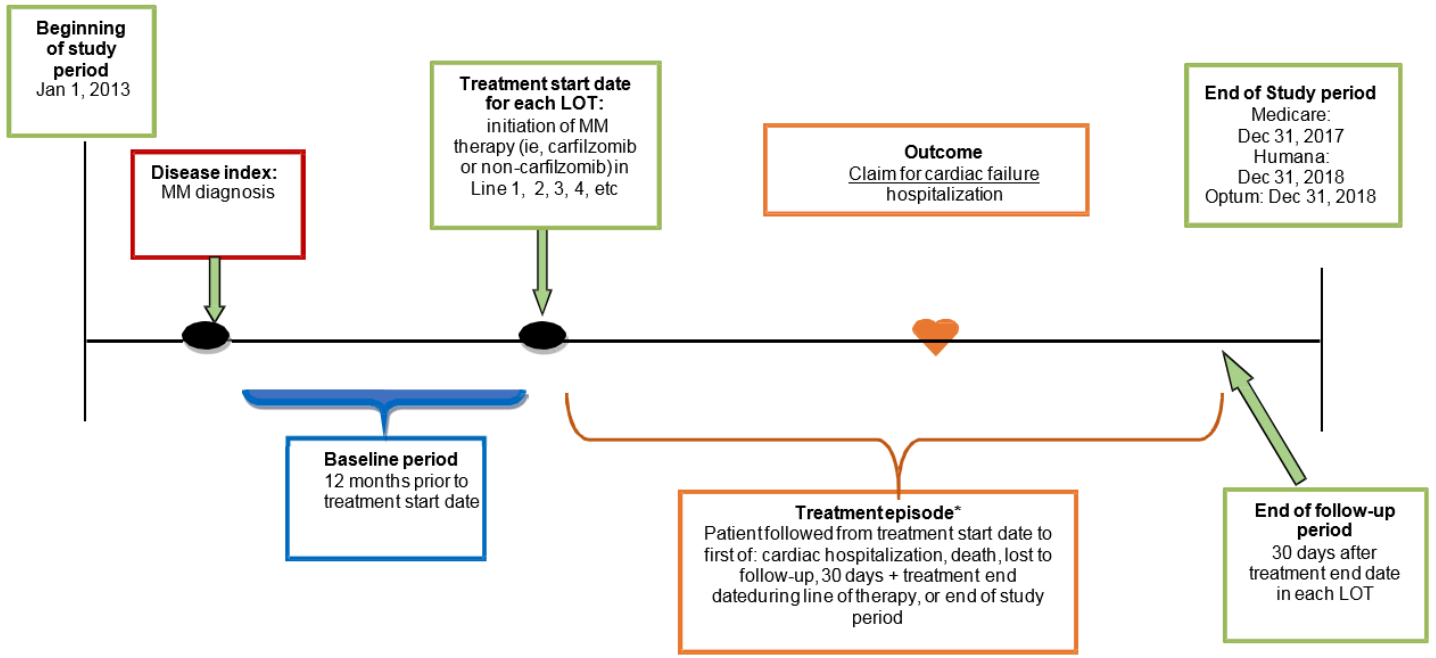
- First observed heart failure hospitalization event of the LOT

- Death
- 30 days after treatment end date
- New LOT initiation
- Change of insurance coverage status (e.g., For Medicare FFS: disenrollment from any of Medicare Part A, B, and D coverage or enrollment in a Medicare Advantage program)
- End of study period

Throughout the study period, patients will be eligible to contribute additional LOT episodes until the earliest of:

- Death
- Disenrollment
- End of study period

x. Study Design Schema



* Only one treatment episode is shown in this study design schema. Each patient can contribute multiple treatment episodes.

V. Variable Assessment

i. Exposure

- LOTs containing carfilzomib in any combination after MM index. Refer to "MM and LOT algorithms_CDRG 09092019.docx"
- LOTs not containing carfilzomib after MM index

- "MM and LOT algorithms_CDRG 09092019.docx" for LOT rules

ii. Outcome

Primary Objectives (POs): Incidence rate of hospitalizations associated with heart failure (first occurrence observed within each LOT), defined as any inpatient claim (excluding rehab and requiring an overnight stay at an inpatient facility) carrying a relevant ICD-9-CM or ICD-10-CM dx code for heart failure (see Appendix B) in:

1. The primary diagnosis position
2. Top two diagnosis positions
3. Top three diagnosis positions
4. Top give diagnosis positions

Please produce a Table 2C/3C for each of these scenarios.

Exploratory Objectives (EOs): Hazard ratio for time to first heart failure hospitalization event

iii. Covariates

Define at baseline, unless otherwise specified:

Demographics

- Age defined at LOT index date (continuous; categorical: 18-65, 66-69, 70-74, 75-79, ≥80 years)
- Sex
- Months from index MM diagnosis to treatment index
- Calendar year of treatment index
- Geographic region

Myeloma-related factors

- Renal disease (any)
- Hypercalcemia
- Anemia
- Stem cell transplantation

Other clinical comorbidities:

- Prior cardiovascular history (presence of each condition and any of the conditions combined: hypertension, heart failure, cardiomyopathy, and cardiac arrhythmias and conduction disorders)
- Ischemic heart disease
- Peripheral vascular disease
- Hypercholesterolemia
- Chronic obstructive pulmonary disease
- Diabetes
- Liver disease
- Gastrointestinal bleeding
- Inflammatory diseases

Lifestyle risk factors:

- Smoking
- Obesity
- Alcohol consumption

Treatments and concomitant medications (*4 March 2020 update: Please add conmeds to Table 2 shell*):

- Antihypertensives
- Cholesterol lowering medications
- Antidiabetics
- Index LOT

VI. Analysis plan

Study Attrition

Please refer to Table 1 shell.

Primary Objectives

1. Estimate the incidence rates of cardiac failure in US racial and ethnic populations of patients with multiple myeloma treated with carfilzomib
2. Estimate the incidence rates of cardiac failure in US racial and ethnic populations of patients with multiple myeloma not treated with carfilzomib

The incidence rate of heart failure hospitalization (units of 100 patient-years) will be summarized for "incident" MM patients treated with carfilzomib-containing or carfilzomib-free therapies by race/ethnicity (whites, blacks, Asian, Hispanic, and North American natives (Medicare FFS only)). The unit of measurement is the carfilzomib-containing or carfilzomib-free treatment episode/line of therapy (LOT) and each patient can contribute in multiple LOTs for event rate calculations. Results will be reported across all LOTs/by combining all LOTs and individually by LOT (1L, 2L, 3L, 4L+). Ninety-five percent confidence intervals will be calculated using Byar's formula (Breslow and Day 1987). Please see Table 2 and 3 shells.

Secondary Objectives

1. Describe demographic, clinical characteristics and cardiac failure risk factors in US racial and ethnic populations of patients with multiple myeloma treated with carfilzomib
2. Describe demographic, clinical characteristics and cardiac failure risk factors in US racial and ethnic populations of patients with multiple myeloma not treated with carfilzomib

Summarize baseline patient characteristics per Table 4c shell. Please refer to "Codes for MM comorbid conditions.xlsx" for diagnostic and procedural codes for myeloma-related factors, comorbid conditions, and lifestyle factors. Refer to "Amgen PMR - Drug Codes ConMeds.xlsx" for concomitant medications.

Exploratory Objectives

1. Assess comparability between patients with multiple myeloma of African American race treated with carfilzomib and those treated with other treatments for multiple myeloma, after propensity score matching, using standardized mean differences
2. If the assessment indicates sufficient post-matching comparability, compare the risk of cardiac failure between patients with multiple myeloma of African American race treated with carfilzomib and those treated with other treatments for multiple myeloma
3. Assess comparability between patients with multiple myeloma of White race treated with carfilzomib and those treated with other treatments for multiple myeloma, after propensity score matching, using standardized mean differences

4. If the assessment indicates sufficient post-matching comparability, compare the risk of cardiac failure between patients with multiple myeloma of White race treated with carfilzomib and those treated with other treatments for multiple myeloma

Propensity Score Model and Matching (OPTUM Clinformatics)

Propensity score modeling. For the propensity score (PS) matching strategy, we will calculate propensity scores using an unconditional logistic regression model to estimate the predicted probability of exposure to a carfilzomib treatment episode. PS models will be constructed using ~~one of two~~ the following approach~~es~~:

1. Separate propensity score models by LOT (2L and 3L+4L) in the combined African American (or black) and white sample. The logistic regression model will include all covariates listed in V.**iii. Covariates** *except* alcohol consumption, conmeds, and index LOT.
2. ~~Separate propensity score models by race (whites vs. blacks) with all index LOTs combined (2L, 3L, and 4L). The logistic regression model will include all covariates listed in V.**iii. Covariates** *except* alcohol consumption and race/ethnicity.~~

The overlap of the propensity score distribution will also be visualized to assess possible positivity violations, per the example given in Appendix C (Figure 1 in Table Shell Excel file).

~~The PS modeling approach to use will depend on which approach allows for the best carfilzomib vs. non-carfilzomib-treated match.~~

Propensity score matching. Given that covariates in this study may differ between patients treated with carfilzomib and other treatments, we will attempt to create cohorts of patients with balanced covariates using propensity score (PS). PS matched cohorts will be constructed for cohorts consisting of African American and white patient cohorts separately. PS

matching will be conducted at the level of individual LOTs (2L, 3L, 4L), and patients may have multiple LOTs over the course of the study. Therefore, a single individual may contribute multiple LOTs to the matching process.

Each carfilzomib 2L+ treatment episode (2L, 3L, 4L) will be matched to up to 4 non-carfilzomib treatment episodes on the propensity score using a greedy algorithm with a 2-digit match. For the mechanics of matching, we will set the smaller group as the referent group and the larger group as the comparator group.

PS balance between and the propensity-score matched cohorts will be assessed using the standardized mean difference (SMD) (Table 5+6 shells). A SMD greater than 0.1 (10%) will represent residual imbalance for any covariate. Variables with a standardized difference less than 0.1 will be considered balanced. If a variable has a standardized difference that exceeds 0.1, these variables will be considered for adjustment in the Cox model. If the assessment indicates sufficient post-matching comparability, we will evaluate the association between treatment with carfilzomib versus other treatments for multiple myeloma and risk of heart failure by line of therapy using a Cox proportional hazards model.

Comparative Time-to-Event Analysis

- PS-matched Cox proportional hazards model
- Analysis by LOT (2L and 3+4L), separately for blacks and whites
- The proportional hazards assumption will be checked by treatment assignment (carfilzomib or non-carfilzomib) using both a formal test and visual inspection. Formal test – to be conducted by fitting a Cox PH regression model with the treatment variable and a treatment*log(time) interaction term. Visual inspection to be carried out by plotting a log-log survival curve by treatment. ~~Decision on whether to proceed with comparison will be made after consideration of output from both approaches.~~
    - To be performed for the primary ("unstratified") analysis and by LOT (2L and 3L+4L)

- As patients are can contribute to multiple LOTs, correlations across LOTs for such patients will be corrected for using the robust (sandwich) estimation method.
- Refer to Table 7, 8 shell.

Quantitative Bias Analysis

Two methods will be used to assess unmeasured confounding.

- The rule-out method is used to assess how strong a confounder (or set of confounders) would need to be to fully explain the observed association between an exposure and the outcome. This method has been described previously (Schneeweiss 2006) and an HR variant has been previously been applied in the literature (Weintraub, Grau-Sepulveda et al. 2012). For this study, the proper outcome measure is the PS-matched HR describing the association between treatment assignment (carfilzomib vs. non-carfilzomib) and the rate of heart failure hospitalization, while the confounding element is represented by a single hypothetical dichotomous confounder. The strength of the confounding required to fully explain the exposure-outcome association will be examined by varying the prevalence of the confounder.
  - To be performed for the primary ("unstratified") analysis only.
  - An example of the expected output is given in Appendix D.
- ~~An alternative method of evaluating unmeasured confounding involves assessing the strength of the measured confounders by removing each confounder individually from the model to develop a distribution of the point estimate of the hazard ratios to display the strength of the measured confounding (Lin, Logan et al. 2013). Assuming the unmeasured confounders fall within this distribution, the distribution can be used to inform the potential magnitude and direction of the unmeasured confounders on the validity of the effect estimate.~~

~~o Note: Although the comparative component will be carried out using a PS-matched model, a Cox PH regression model fitted with the covariates listed in Section V.iii. will be used to assess the magnitude and direction of potential bias from confounding.~~

VII. Table and Figure Shells

Please refer to "Table Shells_20190012 Kyprolis heart failure in racial and ethnic minorities FDA PMR.xlsx".

VIII. Appendices

Appendix A: List of referenced files

File name	Description

MM and LOT algorithms_CDRG 09092019.docx	• Line of therapy (LOT) rules
	• MM index algorithm – pg. 1
	  o MM diagnosis codes – pg. 7, Table 1
	  o Diagnostic tests – pg. 8, Table 2
	• MM treatment codes – pg. 11, Table 4
	• Chemotherapy administration codes (for criterion 1 of attrition flow) – pg. 9, Table 3

Codes for MM comorbid conditions in claims.xlsx	• Diagnostic and procedural codes for myeloma-related factors, comorbid conditions, and lifestyle factors • BMT/SCT codes (duplicate of those found in "MM algorithm_exclusion criteria (chemo, RAD, SCT) for incident MM.xlsx"
Amgen PMR - Drug Codes ConMeds.xlsx	• Concomitant medications

MM algorithm_exclusion criteria (chemo, RAD, SCT) for incident MM.xlsx	• Chemotherapy and radiotherapy codes (criterion 5 of attrition flow) • BMT/SCT codes (criterion 6 of attrition flow)
Dialysis and kidney transplant.PNG	• Codes for dialysis and kidney transplant
Table Shells_20190012 Kyprolis heart failure in racial and ethnic minorities FDA PMR.xlsx	• Table shells

Appendix B. ICD-9-CM and ICD-10-CM Diagnosis Codes to Identify Cardiac Failure

ICD-9-CM Dx	ICD-10-CM Dx	ICD-9 Description	ICD-10 Description
"428.0"	I50.9	Congestive heart failure, unspecified	Heart failure, unspecified
"428.1"	I50.1	Left heart failure	Left ventricular failure
"428.20"	I50.20	Systolic heart failure, unspecified	Unspecified systolic (congestive) heart failure
"428.21"	I50.21	Acute systolic heart failure	Acute systolic (congestive) heart failure
"428.22"	I50.22	Chronic systolic heart failure	Chronic systolic (congestive) heart failure
"428.23"	I50.23	Acute on chronic systolic heart failure	Acute on chronic systolic (congestive) heart failure
"428.30"	I50.30	Diastolic heart failure, unspecified	Unspecified diastolic (congestive) heart failure
"428.31"	I50.31	Acute diastolic heart failure	Acute diastolic (congestive) heart failure

"428.32"	I50.32	Chronic diastolic heart failure	Chronic diastolic (congestive) heart failure
"428.33"	I50.33	Acute on chronic diastolic heart failure	Acute on chronic diastolic (congestive) heart failure
"428.40"	I50.40	Combined systolic and diastolic heart failure, unspecified	Unspecified combined systolic (congestive) and diastolic (congestive) heart failure
"428.41"	I50.41	Acute combined systolic and diastolic heart failure	Acute combined systolic (congestive) and diastolic (congestive) heart failure
"428.42"	I50.42	Chronic combined systolic and diastolic heart failure	Chronic combined systolic (congestive) and diastolic (congestive) heart failure
"428.43"	I50.43	Acute on chronic combined systolic and diastolic heart failure	Acute on chronic combined systolic (congestive) and diastolic (congestive) heart failure
"428.9"	I50.9	Heart failure, unspecified	Heart failure, unspecified

Appendix C: Example of output for visual assessment of propensity score overlap

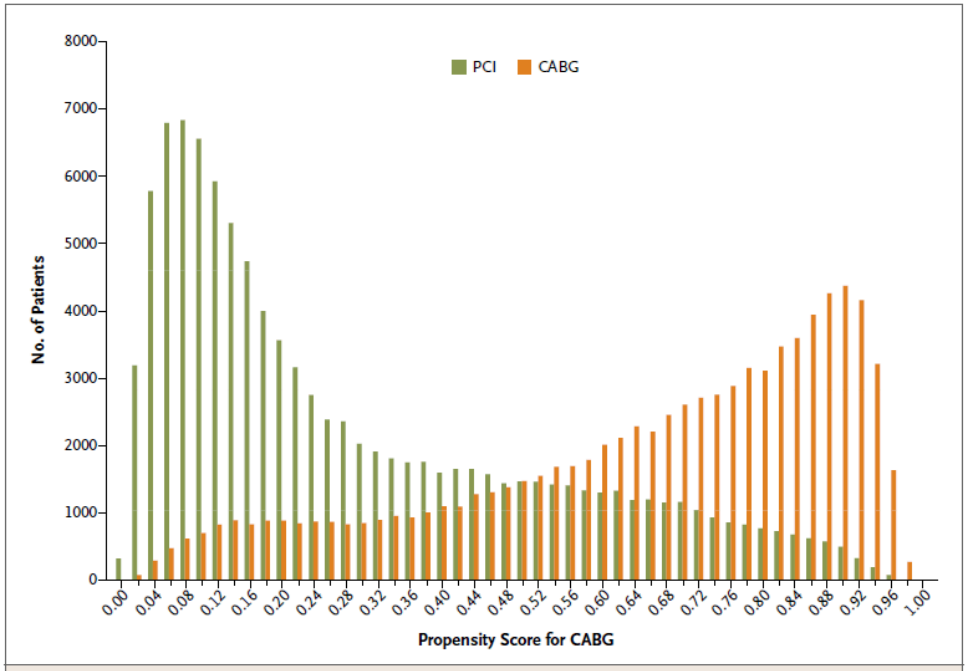


Figure 1. **Propensity Scores for Coronary Artery Bypass Grafting (CABG) in the Percutaneous Coronary Intervention (PCI) and CABG Populations.**
The propensity score for CABG is the probability given baseline variables that any patient in either group would be selected for CABG.

Source: Weintraub, Grau-Sepulveda et al. 2012

Appendix D: Example of output for rule-out method

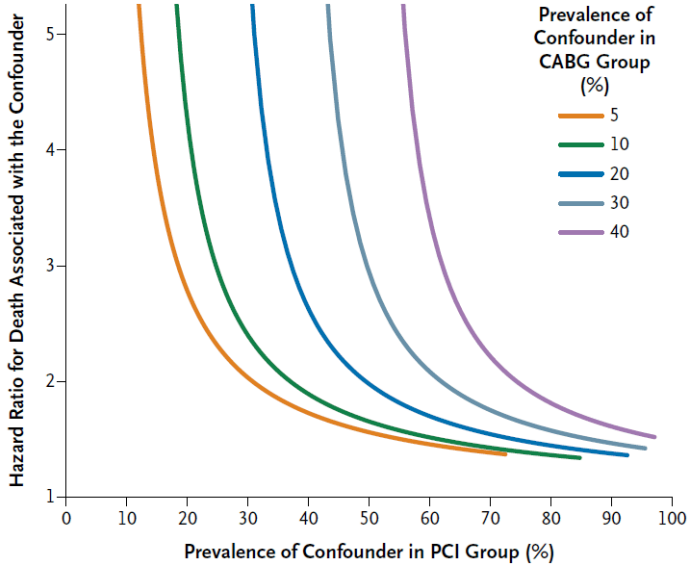


Figure 4. Effect of Unmeasured Confounding Factors.

Shown is a sensitivity analysis that illustrates how powerful a single confounder would have to be to account for the advantage of CABG over PCI that was detected in the adjusted analysis. A single unmeasured confounder could produce the observed survival differences only if it increased the long-term risk of death by a factor of approximately two or if the long-term risk of death was three to five times as high in the PCI group as in the CABG group. For example, if a confounder was present in 10% of the patients in the CABG group (green curved line) but in 35% of patients in the PCI group (x axis), and if it increased the risk of death by a factor of slightly more than two (hazard ratio, 2.09), then that confounder alone could itself account for the observed difference in mortality between the study groups.

Source: Weintraub, Grau-Sepulveda et al. 2012

References

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Lin, N. X., S. Logan and W. E. Henley (2013). "Bias and sensitivity analysis when estimating treatment effects from the cox model with omitted covariates." Biometrics **69**(4): 850-860.

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Weintraub, W. S., M. V. Grau-Sepulveda, J. M. Weiss, S. M. O'Brien, E. D. Peterson, P. Kolm, Z. Zhang, L. W. Klein, R. E. Shaw, C. McKay, L. L. Ritzenthaler, J. J. Popma, J. C. Messenger, D. M. Shahian, F. L. Grover, J. E. Mayer, C. M. Shewan, K. N. Garratt, I. D. Moussa, G. D. Dangas and F. H. Edwards (2012). "Comparative effectiveness of revascularization strategies." N Engl J Med **366**(16): 1467-1476.