Summary Table of Study Protocol

Title	Topological Analysis of the baseline characteristics of relapsed and/or refractory multiple myeloma (R/R MM) patients treated with carfilzomib in clinical trials to identify cohorts that represent levels of risk of select cardiovascular adverse events (CV AEs)
Protocol version identifier	Superseding Amendment, Version 1.0
Date of last version of the protocol	20 February 2020
EU Post Authorization Study (PAS) Register No	NA
Active Substance	carfilzomib
Medicinal Product	Kyprolis (carfilzomib)
Device	NA
Product Reference	5340019.01
Procedure Number	NA
Joint PASS	Yes
Research Question and Objectives	Develop and characterize risk profiles for select cardiovascular adverse events in patients with relapsed and/or refractory (R/R) multiple myeloma (MM) treated with carfilzomib across four clinical trials through an analysis of baseline characteristics
Countries of Study	North America, Australia, Asia and Western Europe
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Marketing Authorization Holder

Marketing authorization holder(s)	NA
MAH Contact	NA

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Study Design Schema

The objective of this study is to develop and characterize risk profiles for select cardiovascular adverse events in patients with relapsed and/or refractory (R/R) multiple myeloma (MM) treated with carfilzomib across four clinical trials through an analysis of baseline characteristics. The cardiovascular adverse events of interest are: cardiac failure, hypertension, ischemic heart disease, cardiac arrhythmias, and pulmonary hypertension. The four clinical trials are A.R.R.O.W, ASPIRE, ENDEAVOR, and FOCUS. This fundamentally is a binary classification problem. Because of the class imbalance (there are considerably more non-adverse-event patients than adverse-event patients) and the wide diversity (in terms of patient characteristics) among each of the two classes, we will transform the problem into a multi-class classification problem by topological data analysis. The main goal of this transformation is to identify coherent subgroups among non-adverse-event patients. This transformation and the downstream analysis (network clustering and single decision tree learning) is expected to produce interpretable cohorts with high, medium or low risk for the adverse events.

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2. List of Abbreviations

AE Adverse Event

CV Cardiovascular

MM Multiple Myeloma

R/R Relapsed and/or Refractory

TDA Topological Data Analysis

3. Responsible Parties

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4. Abstract

- **Study Title**

  A retrospective study to identify cohorts of relapsed and/or refractory multiple myeloma (R/R MM) patients treated with carfilzomib by baseline characteristics and levels of risk of select cardiovascular adverse events (CV AEs)

- **Study Background and Rationale**

  Multiple myeloma, a plasma cell neoplasm, is the second most common hematologic malignancy and responsible for approximately 80,000 annual deaths worldwide (1% of all cancer deaths). Carfilzomib has been shown to improve outcomes including overall survival in multiple myeloma when used in combination with dexamethasone (Kd) as in the ENDEAVOR trial and when used in combination with Lenalidomide (KRd) as in the ASPIRE trial. Multiple myeloma is a disease of older adults: median age at diagnosis of 69 years, a predominantly elderly patient population, with a high prevalence of pre-existing cardiovascular disease and a high frequency of CV AEs Higher rates of cardiovascular adverse events have were observed for carfilzomib treated subjects in key pivotal trials, typically dyspnea, hypertension and cardiac failure. However, attempts to define which pre-existing conditions are clinical predictive factors for cardiovascular events have been unsuccessful. The goal of this study is to explore if there are baseline characteristics common to those patients who went on to experience a serious CVAE during the study so that high or non-high risk subjects can be characterized before those events occurred. Serious CV AE, are those that cause symptoms in the patient, possibly requiring hospitalization (grade 3), or may be life threatening requiring urgent intervention (grade 4) or, even result in death (grade 5) (CTCAE v4.03, 2009) (CTCAE v5.0,2017)

  In the ASPIRE study, the rate of grade ≥ 3 cardiac failure, hypertension, dyspnea and ischaemic heart disease in the carfilzomib arm versus the control arm were 3.8% v 1.8%; 5.8% v 2.1%; 3.1% v 2.1% and 3.3% v 2.1% respectively. In the ENDEAVOR study, the same figures were 4.8% v 1.8%; 9.5% v 2.6%; 5.6% v 2.2%; and 1.7% v 1.5% respectively. Across both studies between 40% and 50% of subjects had prior

hypertension, 1% to 4% had a history of cardiac failure and 5% to 11% had arrhythmias at study entry.

Despite evidence that cumulative weekly dose over a specific threshold correlates with better myeloma outcome and the benefit of weekly dosing for efficacy and safety versus twice weekly, cardiovascular concerns may limit adoption and optimal dosing of carfilzomib. Healthcare providers are uncertain how to identify which patients harbor a high risk of a CV adverse event and which patients are unlikely to encounter such an event and can be safely treated. The question of how to detect these high risk patients and how to differentiate them from the majority who do not develop a serious CVAE has been attempted in the past but without success. Short of this, there have also been attempts to identify what monitoring methods might allow earlier detection of evolving complications before they arise, also without success. The ENDEAVOR cardiac sub-study did not show any benefit of increased frequency of echocardiogram testing during carfilzomib to detect abnormalities of function. It also showed that the anytime occurrences of a fall left-ventricular ejection fraction (LVEF) were the same whether treated with carfilzomib or no not and such falls were largely reversible.

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor (PI) that binds selectively and irreversibly to the 20S proteasome, the proteolytic core particle within the 26S proteasome. Consequently, proteasome function after therapy can only be regained by de novo proteasome synthesis. Specifically, carfilzomib inhibits the chymotrypsin-like catalytic activity of the β5 subunit over the caspase-like catalytic activity of the β1 subunit or the trypsin-like catalytic activity of the β2 subunit, resulting in the accumulation of proteasome substrates and ultimately growth arrest and apoptosis (Hoy, 2016). Carfilzomib extensively penetrates all tissues, except the brain. An intact ubiquitin proteasome system (UPS) is critical if constantly active cardiac myocytes are to manufacture new proteins and degrade damaged or misfolded proteins. UPS dysfunction is found in human heart failure as evidenced by histopathologic findings of ubiquinated proteins, soluble protein aggregates and autophagic cell death in end-stage failing human hearts is highly suggestive that UPS dysfunction may be responsible.[1] It has therefore been thought that carfilzomib's effective inhibition of UPS is the likely mechanism behind carfilzomib induced cardiac failure although Greek investigators have published an alternative hypothesis based on rodent data involving the autophagy pathway, inactivation of AMPKa and upregulation of PP2A phosphatase activity[2].

- **Research Question and Objective(s)**

  This study will undertake an analysis of pooled data from A.R.R.O.W , ASPIRE, ENDEAVOR and FOCUS, all phase 3 trials of carfilzomib with the objective of partitioning the carfilzomib-treated population into cohorts defined by baseline attributes (demographics, vital signs, cardiac assessments, results of bedside clinical and laboratory testing and medical comorbidities) and presenting high, medium or low levels of risks of select cardiovascular adverse events.

Objectives	Endpoints
Primary	
• Identify cohorts of carfilzomib-treated R/R MM patients defined by baseline characteristics that confer different levels of risks for serious selectedCV AEs	• Rate of ≥3 CVAEs in cohorts of patients identified as having high, intermediate or low risks for the select CVAEs
Secondary	
None	
Exploratory	
• Explore the impact on cohort definition and AE rates of patient medical history records vs. measured baseline characteristics (demographics, vital signs, cardiac signs, and labs)	• Assessment of whether or not patient medical history records improve the quality of patient classification

- Hypothesis(es)/Estimation

  This is a descriptive study to cluster R/R Multiple Myeloma population treated with Kyprolis to determine their risk of developing a cardiovascular adverse event.

- Study Design/Type

  Retrospective cohort study

- Study Population or Data Resource

The study population consists of subjects with relapsed and/or refractory Multiple Myeloma enrolled in one of four phase 3 clinical trials. All studies where global and recruited at multiple sites across several continents.

FOCUS (20130396), *A Randomized, Open-label, Phase 3 Study of Carfilzomib vs Best Supportive Care in Subjects with Relapsed and Refractory Multiple Myeloma*, was a multi-center study, with 81 sites screening subjects for participation; 77 sites enrolled at least 1 subject from countries in Eastern and Western Europe, Israel, Australia, New Zealand, and South Korea enrolling 315 subjects between 06 September 2010 (first subject enrolled date) and and 10 Jul 2014 (data cut-off date). Subjects had had 1 to 5 prior regimens and were refractory to the most recent therapy.

In the ASPIRE study (20130395), *A Randomized, Multi-center, Phase 3 Study Comparing Carfilzomib, Lenalidomide, and Dexamethasone (CRd) vs Lenalidomide and Dexamethasone (Rd) in Subjects With Relapsed Multiple Myeloma*, recruited 792 subjects at 155 centers in 20 countries in Eastern and Western Europe, North America,

and Israel between 14 July 2010 (first subject enrolled) to 28 April 2017 (data cut-off date).

In ENDEAVOR (20130398) a study of Carfilzomib and dexamethasone was compared to bortezomib and dexamethasone for patients with relapsed and/or refractory multiple myeloma in a multicentre study of 929 subjects enrolled between 20 June 2012 (first subject enrolled date) and 30 June 2014 (data cut-off date) across 198 sites across Western and Eastern Europe, South America and Australia.

In ARROW, a study of once weekly versus twice weekly carfilzomib dosing in patients with relapsed and/or refractory multiple myeloma, recruited 578 patients from 118 sites in North America, Europe and Asia between September 2015, and August 2016. All subjects were patients (aged 18 years and older) refractory to most recent therapy (including bortezomib or ixazomib)

- Summary of Subject Eligibility Criteria

R/R MM patients that were enrolled in four Amgen clinical trials and received treatment with carfilzomib in these trials. Eligibility in all four trials required subjects to be > 18 years of age with relapsed and/or refractory multiple myeloma, measurable disease, Eastern Cooperative Oncology Group performance status of not more than 2 (0- 1 in A.R.R.O.W), at least one previous treatment, and at least a partial response to at least one previous treatment. Studies differed in the number of prior lines of therapy permitted and the interval between the most recent proteasome inhibitor treatment and study enrollment. In both FOCUS and A.R.R.O.W , subjects had to be refractory to the most recent line of therapy.

- Follow-up

For this study, patients will be censored at the end of their respective trial end dates, all qualifying patients who do not have a record of CV event within the observation window will be treated equivalently in the analysis

- Variables
  - Outcome Variable(s) ≥ Grade 3 cardiovascular adverse events:
    - Cardiac Failure
    - Hypertension
    - Ischemic Heart Disease
    - Cardiac Arrhythmias
    - Pulmonary Hypertension

- Exposure Variable(s)

  NA
- Other Covariate(s)
  - Demographics
    - Sex
    - Race
    - Age
    - Vital signs
    - Weight
    - Height
    - Body Surface Area
    - Systolic Blood Pressure
    - Diastolic Blood Pressure
    - Respiratory Rate
  - Cardiac signs
    - Summary Mean Ventricular Rate
    - Summary Mean PR Duration
    - Summary Mean QRS Duration
    - QTcF Fridericia's Correction Formula
    - ECG Interpretation
    - Left Ventricular Ejection Fraction
  - Labs
    - Hemoglobin
    - Glucose
    - Activated Partial Thromboplastin Time
    - Bilirubin
    - Cockcroft-Gault Calculated Creatinine Clearance
    - Uric Acid
    - Basophils
  - Presence of comorbidity conditions
    - Myocardial infarction
    - Congestive heart failure
    - Peripheral vascular disease
    - Cerebrovascular accident or transient ischemic attack

  - Diabetes mellitus
  - Moderate to severe chronic kidney disease
- Kyprolis regimen

- Study Sample Size

  This analysis will be of Carfilzomib-treated subjects enrolled in the following four trials, all of which are closed and have reported their findings.

    - ARROW: 235 and 238 subjects in the two (Carfilzomib) arms
    - ASPIRE: 392 subjects in the Carfilzomib arm
    - ENDEAVOR: 463 subjects in the Carfilzomib arm
    - FOCUS: 157 subjects in the Carfilzomib arm

- Data Analysis

  The analysis uses three techniques in sequence:

  Topological data analysis to produce network representations of data;

  Network clustering known as cold-spot detection to identify coherent sets of non-AE subjects; and

  Multi-class single-decision-tree learning to discover groups of subjects and conditions on variables that explain them.

  The sequence may be repeated more than once. A more detailed description of the analysis is in Section 8. An even more elaborate description is in Section 8.7.2.

5. Amendments and Updates

None

6. Rationale and Background

6.1 Diseases and Therapeutic Area

Multiple myeloma (MM), a plasma cell neoplasm, is the second most common hematologic malignancy and responsible for approximately 80 000 annual deaths worldwide (1% of all cancer deaths). Multiple myeloma is a disease of older adults, with a median age at diagnosis of 69 years (Noone et al, 2018). Despite improved treatment options for MM and outcomes over the last decade with the advent of immunomodulatory agents (thalidomide, lenalidomide and pomalidomide) and proteasome inhibitors (eg, bortezomib, carfilzomib) and therapies directed at CD-38, MM remains an incurable hematologic malignancy (Laubach et al. 2009; Lonial et al. 2011; Pulte et al. 2014; Richardson et al. 2007).

Carfilzomib has been shown to improve outcomes in multiple myeloma when used in combination with dexamethasone (Kd) as in the ENDEAVOR trial (Dimopoulos et al, 2016) at a dose of 56mg/m2 including superior progression free

survival for carfilzomib/dexamethasone compared to bortezomib/dexamethasone (18.7 months vs. 9.4 months; P<0.0001).(Dimopoulos et al. 2016) and clinically meaningful improvements in overall survival (Dimopoulos, 2017). Carfilzomib also delivers superior progression free and overall survival when used in combination with Lenalidomide (KRd) as in the ASPIRE Carfilzomib (Stewart et al, 2015).

MM is predominately a disease of the elderly with a median age of 69 nearly half of whom are over 70 years of age at diagnosis (Pulte et al. 2014) This is an age group with a high prevalence of CV risk factors and/or pre-existing CV disease. The elderly MM patient population has a high prevalence of pre-existing cardiovascular disease, estimated as upwards of 50% (Cornell, RF et al). Accordingly, cardiovascular events occur as frequently as 70% in MM clinical trials, chiefly as arrhythmias and cardiac failure (Kistler et al, 2012). CV risk factors likely predispose to carfilzomib-related CV AEs. For example, a pre-treatment history of hypertension increases the likelihood of developing carfilzomib-related hypertension (Lendvai et al. 2014). Similarly, pre-treatment history of anthracycline exposure, hypertension, hyperlipidemia, and smoking history are prevalent among patients who develop carfilzomib-related heart failure (Lendvai et al. 2014). The relative contribution of MM, prior treatments, underlying CV disease and/or risk factors, or any combination of these factors, to the overall incidence of CV adverse events among patients receiving treatment for MM is uncertain.

Carfilzomib treated subjects typically experience an increased number of cardiovascular adverse events over the control arm but without an overall increase in fatalities or discontinuations (Chiari, Ajai et al). Pooling data in an analysis focusing on CV AEs of carfilzomib treated subjects in the phase 3 ASPIRE, ENDEAVOR, and FOCUS, studies, dyspnea, hypertension and cardiac failure were the most frequent with any-grade incidences of 31.9%, 18.5% and 6.7% respectively with grade ≥ 3 incidences of 4.5%, 5.9% and 4.4%. To date, attempts to define which pre-existing conditions are clinical predictive factors for cardiovascular events and/or symptomatic have been unsuccessful (Moreb 2019).

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor (PI) that binds selectively and irreversibly to the 20S proteasome, approved by the US Food and Drug Administration (FDA) in July 2012 for the treatment of patients with progressive MM who have received at least two prior therapies, including bortezomib and an immunomodulatory agent, lenalidomide (Herndon et al. 2013). Since 2015, carfilzomib has also been approved for use in combination with lenalidomide and dexamethasone in

relapsed MM based on the results of the ASPIRE study, (Stewart et al 2015). In 2016, carfilzomib was approved in combination with dexamethasone at a dose of 56mg/m2 based on the basis of results from the ENDEAVOR trial (Dimopoulos et al. 2016).

Cardiac myocytes require an intact ubiquitin proteasome system (UPS) to manufacture new proteins and degrade damaged or misfolded proteins is evidenced by histopathological findings in human heart failure of ubiquinated proteins, soluble protein aggregates and autophagic cell death (Predmore, 2010). Inhibition of this pathway by Carfilzomib may be a theoretical explanation for cardiac failure events reported during carfilzomib treatment.

There remains uncertainty around the CV safety data available for carfilzomib. Cardiac safety data for single-agent carfilzomib is available for 526 patients with relapsed and/or refractory MM (RRMM) who took part in one of four phase II studies. These data indicate that any cardiac adverse event occurred in 22.1% of patients, hypertension in 14.3%, cardiac arrhythmia in 13.3%, and ischemic heart disease in 3.4% (Siegel et al. 2013). Aggregated cardiac failure events including congestive heart failure, pulmonary edema and decreased left ventricular ejection fraction (LVEF) were reported in 7.2% of patients; with the majority of events classified as grade 3 (severe) or 4 (life threatening) in severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (Siegel et al. 2013). Additionally, several deaths due to cardiac events reportedly occurred within hours or a few days of carfilzomib administration (Herndon et al. 2013). Overall, cardiac adverse events appear to have contributed to death in 8 of these 526 (1.5%) patients (Siegel et al. 2013). The nature of this acute and fatal CV AEs is unclear. Cardiac adverse events of any type occur after just one dose of carfilzomib in 11.8% of patients and ultimately lead to drug discontinuation in 4.4% (Siegel et al. 2013). Although not exclusively cardiac in etiology, it is important to note that dyspnea is a common adverse effect of carfilzomib, reported in 19-42% of patients (Papadopoulos et al. 2013; Siegel et al. 2013; Stewart et al. 2015), which may have resolved without any change in carfilzomib therapy in 61% of patients (Siegel et al. 2013).

It is unclear what relationship if any exists between carfilzomib dose and cardiac failure. Recently the phase 3 A.R.R.O.W. study comparing once-weekly dosing of Kyprolis an dexamethasone (Kd) at (70 mg/m2) with twice-weekly Kd (27 mg/m2) demonstrated that the incidence of cardiac failure events was not increased in the subjects receiving the higher weekly dose of 70mg/m2). Results were as follows: all grades: Kd 20/70 mg/m2

once-weekly: 3.8%, Kd 20/27 mg/m2 twice-weekly: 5.1%; grade ≥ 3 adverse events: Kd 20/70 mg/m2 once-weekly: 2.9%, Kd 20/27 mg/m2 twice-weekly: 4.3%. [6]

Not all cardiotoxicities are a direct consequence of carfilzomib treatment. Prior chemotherapy treatments such as anthracyclines used in older myeloma regimens may predispose to future CV events during subsequent carfilzomib treatment including cardiac failure. MM disease itself can cause adverse effects on the CV system unrelated to treatment such as heart failure secondary to cardiac amyloidosis, hyper viscosity syndrome, or high-output failure (Allegra et al. 2010). Coronary microvascular dysfunction, even in the absence of epicardial coronary disease, is highly prevalent in patients with light chain cardiac amyloidosis and can complicate MM or predispose patients to further CV AE (Dorbala et al. 2014).

6.2 Rationale

There is a lack of data about which risk factors and if the number of risk factors per patient predispose cardiovascular adverse effects during treatment with carfilzomib. There is also no sense of what a typical high- risk patient looks like in terms of baseline attributes that clinicians might be able to recognize amongst the commonly performed patient assessments before a new treatment is initiated such as blood work (laboratory assessments of organ function), structural and functional cardiac assessments, vital signs and physical measurements). Having this information would help identify patients at risk and support clinicians when selecting patients for treatment with carfilzomib-based regimens. It may not only help cluster patients but could potentially improve physician confidence when selecting patients for carfilzomib treatments if more is known about which specific patient characteristics associated with CVAE and which are not.

6.3 Statistical Inference (Estimation or Hypothesis[es])

N/A

7. Research Question and Objectives

The aim of the study is to develop a risk clustering of carfilzomib-treated patients for selected cardiovascular adverse events by using baseline characteristics available in pivotal carfilzomib trials. The objective is to develop a predictive risk model that has clinical utility and is parsimonious in the number of characteristics.

7.1 Primary

The primary objective of this study is to cluster carfilzomib-treated refractory multiple myeloma (R/R MM) patients into cohorts defined by baseline characteristics and conferring different levels of risks for select cardiovascular adverse events of a serious nature (≥ Grade 3)

8. Research Methods

Identifying patients who are or are not at risk for a CV AE is fundamentally a binary classification problem. In this instance, two aspects make this a significant challenge and may explain the lack of success with prior attempts. One aspect is the class imbalance: there are considerably more non-AE patients than AE patients. Another aspect the wide diversity (in terms of patient characteristics) among each of the two classes: there are no readily-identifiable characteristics that differentially drives risk. Under such circumstances, it can be beneficial to intelligently convert the binary classification problem into a multi-class classification problem that may identify similar levels of risk but for different reasons. The method to be employed achieves this through the following three macro-steps.

- Topological data analysis (TDA) to produce network representations of data;
- Community detection on TDA-produced networks by cold-spot analysis to obtain coherent and significant sets of non-AE subjects; and
- Multi-class single-decision-tree learning seeded by the outcome of cold-spot analysis to discover cohorts and conditions on variables that explain them.

A distinct feature of topological data analysis in data science is the absence of overt or covert presumptions on both the shape of the predicting data and the manner in which the predicting data relate to the predicted data. The method is expected to lead to clustering with comprehensive multivariate explanation, not merely a number that one must ascribe a meaning to. Thus, the method addresses the need for interpretability, a fundamental requirement of this project.

8.1 Study Design

This is a retrospective study utilizing existing clinical trial datasets to develop patient risk cohorts for cardiovascular adverse events. The study will seek to identify groups that are defined by clinically recognizable baseline characteristics and possess high, intermediate or low AE incidence rates. The best success would be to arrive at groups whose defining characteristics are few in number and clinically interpretable, and whose incidence rates are either high or low, but not intermediate. Whilst clearly separating and

defining characteristics that cluster high and low rate groups represents a useful outcome, if this analysis yields a large intermediate risk group there would still be learnings from such as a result

The study would be unsuccessful if it produces groups defined by characteristics that are not clinically interpretable. The possibility of that outcome is unlikely due to the variable preparation described in section 8.3. Whether the incidence rate of a discovered group is labeled as high, intermediate or low could be regarded as subjective, a key factor is that a group with an incidence rate similar to that of the overall population would be deemed to have an intermediate incidence rate. The incidence ratio (risk ratio) could be used to substantiate the high/intermediate/low qualifier. For instance, incidence ratios of 5.17, 1.02 and 0.23 would obviously justify the high, intermediate and low qualifiers, respectively.

8.2 Setting and Study Population

The study population consists of both (Kyprolis treatment) arms of the ARROW study (Moreau 2018) and the Kyprolis treatment arms of the ASPIRE (Stewart 2015), ENDEAVOR (Dimopoulos 2016) and FOCUS studies (Hajek 2017).

8.2.1 Study Period

The study period for this analysis is comprised of the respective study periods of the individual trials. For the purposes of this protocol, the CVAEs analyzed are all adverse events observed by the investigator or reported by the subject that occur after signing of the ICF through the 30 (+3) days after the last dose of all study drug(s) are reported using the Event eCRF. The four clinical trials were conducted between 2010 and 2014.

8.2.2 Subject/Patient/Healthcare Professional Eligibility

8.2.2.1 Inclusion Criteria

The subjects in this study are the individuals who participated in the ARROW, ASPIRE, ENDEAVOR and FOCUS studies and were treated with carfilzomib.

8.2.2.2 Exclusion Criteria

N/A

8.2.3 Baseline Period

Baseline values were established during the screening period prior to exposure to carfilzomib.

8.2.4 Study Follow-up

The follow-up period starts with initiation and ends with censoring, a terminating adverse event or death.

8.3 Variables

The following variables, all baseline, were selected through expert medical judgement and taking into account their actual availability in the study data and expected availability in clinical practice.

- **Demographics**
  - Sex
  - Race
  - Age
- **Vital signs**
  - Weight
  - Height
  - Body Surface Area
  - Systolic Blood Pressure
  - Diastolic Blood Pressure
  - Respiratory Rate
- **Cardiac signs**
  - Summary Mean Ventricular Rate
  - Summary Mean PR Duration
  - Summary Mean QRS Duration
  - QTcF Fridericia's Correction Formula
  - ECG Interpretation
  - Left Ventricular Ejection Fraction
- **Labs**
  - Hemoglobin
  - Glucose
  - Activated Partial Thromboplastin Time
  - Bilirubin
  - Cockcroft-Gault Calculated Creatinine Clearance
  - Uric Acid
  - Basophils

- **Presence of comorbidity conditions**
  - Myocardial infarction
  - Congestive heart failure
  - Peripheral vascular disease
  - Cerebrovascular accident or transient ischemic attack
  - Diabetes mellitus
  - Moderate to severe chronic kidney disease
- **Kyprolis regimen**

Those variables that are inherently continuous will be turned into categorical variables according to ranges specified through expert medical judgement. This is expected to lead to increased clinical interpretability but may result in clustering with reduced contrast between high and low AE incidence levels.

8.3.1 Exposure Assessment

All subjects in this study were exposed to carfilzomib at different doses, schedules, and combinations in one of the following trials: ARROW, ASPIRE, ENDEAVOR and FOCUS. In this study, a coded (categorical) variable will identify regimens and its impact will be evaluated along with that of the other variables. There are a total five possible codes: two for ARROW and three for ASPIRE, ENDEAVOR and FOCUS.

8.3.2 Outcome Assessment

The adverse events of interest, in order of priority, are:

- Cardiac Failure
- Hypertension
- Ischemic Heart Disease
- Cardiac Arrhythmias
- Pulmonary Hypertension

8.3.3 Adverse Events Will be Identified Using Standard MedDRA Queries (Narrow Scope). Grade ≥ 3 Event Classification Will be as per CTCAE Version at the Time the Study was Conducted. Covariate Assessment

Variables are listed in Section 8.3. For each AE, the model will eliminate a variable if it fails to meet the following requirement: there must be at least one AE subject with non-null value, and there must be at least one non-AE subject with non-null value. No imputation is performed.

8.3.4 Validity and Reliability

The variables were selected by the medical sub team on the project based on a review of known clinical risk factors.

8.4 Data Sources

The data sources are as follows.

- ARROW study
  https://clinicaltrials.gov/ct2/show/NCT02412878
- ASPIRE study
  https://clinicaltrials.gov/ct2/show/NCT01080391
- ENDEAVOR study
  https://clinicaltrials.gov/ct2/show/NCT01568866
- FOCUS study
  https://www.clinicaltrialsregister.eu/ctr-search/trial/2009-016840-38/results

8.5 Study Size

Data was available for all subjects enrolled across the four phase 3 trials. Only data from the Carfilzomib treatment arm will be included in the analysis of baseline risk factors and adverse event prediction.

- ARROW: 235 and 238 subjects in the two (Carfilzomib) arms
- ASPIRE: 392 subjects in the Carfilzomib arm
- ENDEAVOR: 463 subjects in the Carfilzomib arm
- FOCUS: 157 subjects in the Carfilzomib arm

The total number of subjects is 1485.

8.6 Data Management

8.6.1 Obtaining Data Files

Data will be obtained from the clinical trials previously specified. Unit conversion will be performed where required.

8.6.2 Linking Data Files

Data will be linked and pooled in data engineering.

8.6.3 Review and Verification of Data Quality

The data engineering code will be reviewed by a selected DH&I data scientist.

8.7 Data Analysis

8.7.1 Planned Analyses

8.7.1.1 Primary Analysis

The analysis will generate groups of subjects according to risk of CV AE: high, medium and low. Patients will be grouped according to the presence of conditions on the variables listed in Section 8.3.3.

8.7.2 Planned Method of Analysis

The analysis uses three techniques in sequence:

- Topological data analysis to produce network representations of data;
- Network clustering through community detection to identify coherent sets of non-AE and/ or AE subjects;
- Multi-class single-decision-tree learning to discover groups of subjects and conditions on variables that explain them.

Topological Data Analysis (TDA) – topology being the study of shapes, a mathematical discipline- will generate a view of the shape of the data in the form of a visual a network of) soft clusters (usually small) each node in the network is a cluster- a cluster representing subjects that share characterisitics- , and each connection indicates that the connected clusters are overlapping. This data representation is coordinate-free. The geographical positioning of the data into nodes and connections is for visual clarity and the . e; insight on the shape of the data are to be found in the connectivity structure of the network. Details of the process that generate a TDA network are described in the literature. It is an active process of scientific data generation where an observation generates an action by the scientist conducting TDA: lenses and a metric. A lens can be thought of simply as a derived numerical feature. There are some common choices as well as choices customized for specific applications. Lenses are used to create (deliberately overlapping) groups of observations – each group has in common that their lens values are within a common range. The metric is then used for hard clustering within each of these groups. These steps are anything but arbitrary. They are the discretized version of the topological steps of producing a covering of the space and producing the connected components of each covering set. These are well-established approaches in the discipline of topology to parse global complexity into overlapping instances of local insight. In an algorithm known as outcome auto-analysis, the lenses and metric are optimally selected to maximize the contrast among nodes: we seek to maximize the number of cold (fully non-AE) nodes and hot (fully AE) nodes and minimize the number of lukewarm (mixed AE and non-AE) nodes.

Communities that are topologically coherent and that are enriched for AE or non-AE subjects. It is anticipated that due to the rarity of high grade CVAE it will be more challenging to expose such communities. As a result the process will require innovative techniques including novel algorithms that will need to be developed and evolve as part of the data analysis technique is that, while subjects in two different cold spots have in common that they are non-AE subjects, topology reveals differences in their respective feature landscapes; crossing from one to another necessitates crossing path with AE subjects.

The final step uses a multi-class single-decision-tree classifier to discover descriptive conditions that use the variables. The seeds for the classifier are the retained communities. The leaves of the tree that are deemed significant by judging as follows. To ensure that is robust and meets the study objectives the analysis of the groups will be such that several conditions are met: the size of the high AE group is no more than twice the size of the AE group of the whole population, the rate of AE in the high group is more than double the rate of AE of the overall population and, the rate of AE in the low risk group is less than half the rate of AE in the whole population .

8.7.2.1 General Considerations

The challenge of identifying patients who are or are not at risk for a CV AE is classified in machine learning as a "*binary classification problem"* In this instance, two aspects make this a significant challenge and may explain the lack of success with prior attempts. One aspect is the class imbalance: there are considerably more non-AE patients than AE patients. Another aspect is the wide diversity (in terms of patient characteristics) among each of the two classes: whilst there are known clinical risk factors for cardiovascular disease in the general population, there are no readily-identifiable characteristics that differentially drives risk in the myeloma population who often contain general risk factors given the median age of this patient population. Under such circumstances, it can be beneficial to intelligently convert the binary classification problem into a multi-class classification problem that may identify similar levels of risk but for different reasons. The method we employ achieves this through the described three macro-steps.

8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

For each AE, a variable will be eliminated if it fails to meet the following requirement: there must be at least one AE subject with non-null value, and there must be at least one non-AE subject with non-null value. No imputation is performed.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Subject/Patient Characteristics

The 4 clinical trials analyzed in the study were subjects in one of four randomized phase 3 trials of carfilzomib with either dexamethasone or in combination also with lenalidomide. The dose of carfilzomib varied across the studies from 27mg/m2 twice weekly to 56mg/m2 twice weekly to 70mg/m2 once weekly. These studies were conducted over a 5-year period. Studies required pretreatment and post-treatment intravenous (IV) hydration (250 to 500 ml) during cycle 1 with some protocols allowing hydration in subsequent cycles to be at the investigator's discretion. IV hydration is no longer mandatory in cycle one of carfilzomib clinical trials. Eligibility varied with respect to the number of prior lines of therapy (a measure of pre- treatment exposure of the patient population) and refractoriness to therapy. A.R.R.O.W and ENDEAVOR required a baseline cardiac function threshold (LVEF of $\geq 40\%$). Exclusions varied regarding duration from and specifics around prior cardiac events. No study excluded patients based on a background history of hypertension or specific thresholds of BP values.

A.R.R.O.W. (R**A**ndomized, Open-label, Phase 3 Study in Subjects with **R**elapsed and **R**efractory Multiple Myeloma Receiving Carfilzomib in Combination with Dexamethasone, Comparing **O**nce-**W**eekly versus Twice-weekly Carfilzomib Dosing), a multicenter, open-label, randomized, phase 3 superiority study comparing once-weekly (70 mg/m2) versus twice-weekly carfilzomib (27mg/m2) in combination with dexamethasone (wKd70 vs Kd27) in patients with **relapsed AND refractory** multiple myeloma. This study was designed to evaluate a more convenient carfilzomib once-weekly dosing schedule, reducing the number of carfilzomib infusions for patients (from 6 to 3 infusions/cycle). The primary endpoint was progression free survival (PFS). Eligible patients had to have relapsed multiple myeloma with measurable disease and to have been previously treated with a proteasome inhibitor (except carfilzomib or oprozomib) and an immumomodulatory drug (IMiD), at least 2 but no more than 3 prior lines of therapy for myeloma, refractory to the most recent line of therapy and at least and a partial response to at least one prior line of treatment at least a partial response to at least one prior line of treatment. Patients were required to have a creatinine clearance $\geq$ 30 mL/min and a left ventricular ejection fraction (LVEF) $\geq 40\%$. Patients were excluded if they had any of the following: active congestive heart failure CHF (NYHA Class III to IV), a myocardial infarction (MI) within 6 months of enrollment or uncontrolled hypertension or diabetes mellitus. Between September 2015, and August 2016 patients

438 patient were randomized to receive wKd70 (n = 240) Kd27 (n = 238). Median age was 66 years and 54% of the wKd70 and 64% of the Kd27 were ≥ 65 years of age. Baseline co-morbidities were not reported

ASPIRE (C**A**rfilzomib, Lenalidomide, and Dexametha**S**one versus Lenalidomide and Dexamethasone for the treatment of **P**at**I**ents with **R**elapsed Multiple My**E**loma) was an international, randomized Phase 3 trial that evaluated KYPROLIS in combination with lenalidomide and dexamethasone, versus lenalidomide and dexamethasone alone, in patients with relapsed multiple myeloma exposed to one to three prior treatment regimens. The primary endpoint of the trial was PFS. In ASPIRE, patients received either Carfilzomib at a dose of 27mg/m^2 twice weekly 3 weeks of 4 (cycle 2 onwards, and 20 mg/m^2 on days 1 and 2 of cycle one) with lenalidomide (25 mg per day for 21 days on, 7 days off) and low-dose dexamethasone (40 mg per week in four-week cycles) or lenalidomide and low-dose dexamethasone alone. 792 patients were randomized between July 2010 and March 2012, 398 in the carfilzomib arm and 396 to the control arm. The median age of the overall study population was 64 years. Baseline co-morbidities were not reported.

ENDEAVOR (RandomizEd, OpeN Label, Phase 3 Study of Carfilzomib Plus DExamethAsone Vs Bortezomib Plus DexamethasOne in Patients with Relapsed Multiple Myeloma) trial evaluated Kyprolis in combination with low-dose dexamethasone, versus Velcade with low-dose dexamethasone in patients whose multiple myeloma has relapsed after at least one, but not more than three prior therapeutic regimens. The primary endpoint of the trial was PFS. Between June 20, 2012, and June 30, 2014, 929 patients were randomly assigned (464 to the carfilzomib group and 465 to the bortezomib group) to receive either carfilzomib 56 mg/m² twice weekly (after cycle 1) and dexamethasone or bortezomib and dexamethasone. Cardiac eligibility requirements were the same as A.R.R.O.W (LVEF ≥ 40% and exclusions for CCF, MI and NYHA status). Median age in both arms was 65 years. Baseline co-morbidities were not reported.

FOCUS, (Car**F**ilz**O**mib for Advan**C**ed Refractory M**U**ltiple Myeloma European **S**tudy) was conducted with the purpose of comparing the overall survival (OS) of subjects with refractory multiple myeloma relapsed after at least 3 prior regimens who were randomized to receive either carfilzomib alone (Regimen C) or best supportive care (Regimen BSC). BSC included an active control regimen of low-dose dexamethasone, or equivalent corticosteroids, plus optional cyclophosphamide. First subject was enrolled

on 06 September 2010 and the date of data cutoff was 10 July 2014. 315 were randomized (157 to carfilzomib, 158 to control). To be eligible patients were required to have the expected criteria of measurable disease, to meet specific hematology and chemistry criteria. No threshold LVEF was required. Patients were required to have both relapsed and refractory multiple myeloma and significant pre- treatment. Median age was 63 in the Carfilzomib group and 66 in the control group and the median number of prior lines of therapy was 5 in both arms.

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

Patients will be grouped into either two cohorts of high and low risk and three groups of high, medium and low risk. Each cohort may consist of two or more sub-cohorts defined by different sets of patient characteristics. The numerical attributes of a cohort will include its size relative to the study population, the AE incidence rate, and the AE incidence ratio (defined as the in-cohort to out-of-cohort ratio of incidence rates). The AE incidence ratio will be used to justify the high, medium or low qualifier.

8.7.2.5 Sensitivity Analysis

The analysis will include more than one passes of the three macro-steps described above. At each pass, all patients are assigned to a sub-cohort. A sub-cohort may be selected for a next pass because its relative size is too small or too large, or its AE incidence rate is neither low nor high. A large sub-cohort may persist at a next pass, in which case it is deem genuine and retained. The process ends when the remaining sub-cohorts collectively have either low nor high AE incidence, or persist in a new pass.

The study will explore strengthening the parsimony of the model by evaluating the impact of dropping select variables from the model. Sensitivity analysis may also be conducted to assess variances of the model across different Carfilzomib treatment regimens.

8.7.2.5.1 Subgroup Analysis

No subgroup analyses are currently planned.

8.7.2.5.2 Stratified Analysis

No stratified analyses are currently planned.

8.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

Because this is an algorithm-development study, sensitivity analyses for residual confounding and bias are not applicable.

8.7.2.5.4 Other Sensitivity Analysis

No other sensitivity analyses are planned at this time.

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

Safety data will not be collected or analyzed in this study.

8.8 Quality Control

The data is from clinical studies and was already quality-controlled according to the applicable protocols. A DH&I data scientist will review the data engineering and science code.

8.9 Limitations of the Research Methods

8.9.1 Internal Validity of Study Design

The data used in this study was collected as part of interventional clinical trials where there was clear disease identification, exposure with carfilzomib, and then follow-up for CV events with accurate baseline medical history and lab readings. The populations identified in these studies were fairly uniform as all subjects had relapsed or refractory multiple myeloma, were treated with carfilzomib and shared similar age, prior therapy and organ function thresholds for eligibility. These characteristics should lead to a result that is likely valid within this clinical trial population.

This study is one of several efforts to identify characteristics that place patients at risk of a severe CVAE and methods of assessing patients before commencing carfilzomib and what parameters may be useful to monitor patient safety during treatment. Together these will form a more comprehensive dataset that can be shared with treating HCPs.

There are limitations to the application of the findings of this specific study to patient care. The findings from this study alone could not be shared with HCPs as the definitive set of risk factors that stand alone for use when assessing patients for fitness for carfilzomib. Despite the number of patients (I,485) and the nature of the four different Carfilzomib phase 3 trials conducted in diverse geographical regions, it cannot be assumed that this clinical trial population could match all the variables inherent in a diverse real- world patient population. The investigators are aware that if a specific baseline parameter or co-morbidity within this selected population of clinical trial patients is found to be associated with an adverse CV outcome (or not) this does not mean that such information can be assumed to operate similarly in an unselected patient population. This information will need interpretation and some caution. Ultimately the physician must interpret data, understand the detail and assess which aspects apply and

which do not to the patient in question. Such limitations will be acknowledged in reports of the study findings.

8.9.1.1 Measurement Error(s)/Misclassification(s)

The data assessed in this study were collected as part of clinical trials. There is expected to be minimal measurement errors in this study as the data underwent data source verification and data monitoring as part of the routine data processing in a clinical trial. The data collection was specific to the data elements, so there is not expected to be any systematic misclassification due to use of algorithms or proxies for estimating exposures, outcomes, or covariates.

8.9.1.2 Information Bias

The data from this study were originally collected for different study design (eg, evaluating efficacy and safety of carfilzomib versus control). Despite this, there should be limited bias as the data collected on study followed similar protocols for ascertainment of all covariates, exposures, and outcomes.

8.9.1.3 Selection Bias

There is no selecting of patients aside from those enrolled into the trials. All patients are to be evaluated with valid baseline covariates, exposures, and follow-up. Thus, there is not expected to be any selection bias.

8.9.1.4 Confounding

The study objective is to identify cohorts of carfilzomib treated patients defined by baseline characteristics that confer different levels of risks for select CV AEs. No comparisons between exposure groups are planned so there will be no adjustments to address potential confounding.

8.9.2 External Validity of Study Design

Because the data collected in this study were originally ascertained on a schedule of assessments for interventional clinical trials, the identified covariates associated with the risk of developing a CV event may not be routinely collected in non-interventional routine clinical practice.

8.9.3 Analysis Limitations

Whilst the method utilized in this analysis has not previously been described for this purpose justification is provided within the protocol and the attached Appendix. The method is specifically intended to cope with the two major challenges: the class (AE vs. non-AE) imbalance and the heterogeneity of the population in each class. In addition,

the data has been prepared in such a way as to enhance the clinical interpretability of the analysis results; see section 8.3. Nevertheless, clinical interpretability is not guaranteed.

8.9.4 Limitations Due to Missing Data and/or Incomplete Data

For each AE, a variable will be eliminated if it fails to meet the following requirement: there must be at least one AE subject with non-null value, and there must be at least one non-AE subject with non-null value. No imputation is performed.

8.10 Other Aspects

NA

9. Protection of Human Subjects

9.1 Informed Consent

This is a retrospective study utilizing data that were already collected as parts of clinical trials. No informed consent is required.

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

The conduct and data collection for these studies were reviewed by and approved by the institutional IRB are stored in the original study documentation.

9.3 Patient Confidentiality

Patients are not identified, and data cannot be traced back to the original subject in the trials.

9.4 Subjects Decision to Withdraw

These are retrospective data and no active follow-up on subjects will occur.

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

10.1 Safety Collection, Recording and Submission to Amgen Requirements

This study is analyzing secondary data from previously collected clinical trials data. The safety outcomes that are listed in section 8.3.2 will be documented on and analyzed in this study. These will be reported in aggregate in the final study report as cumulative incidence proportions. 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. Amgen reserves the right to terminate the study at any time.

12. Plans for Disseminating and Communicating Study Results

12.1 Publication Policy

The results of this study will be submitted for publication

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

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 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 (e.g., 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.

13. Compensation

Not applicable to this study.

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15. Appendices

15.1 Appendix A: Topological Data Analysis and Downstream Analysis

The shape of data is a fundamental yet seldom explicitly recognized concept in data analysis. When we do regression, we recognize that data has shape and simultaneously ascribe to it a particular shape dictated by the kind of regression we employ. When we perform clustering or other forms of unsupervised classification, we again recognize that data has shape and simultaneously ascribe to it that it is endowed with some natural hard partitioning. The shape of data as a data-science operational concept emerged from the research work in the mathematical discipline of Topology led by Prof. Gunnar Carlsson at Stanford University with major funding from the US National Science Foundation (NSF) and the US Defense Advanced Research Projects Agency (DARPA). The central proposition of Topological Data Analysis is to reveal the shape of data as a continuum that can be observed at multiple resolutions and from multiple perspectives, without preconceived notions of what that shape might be. The insight TDA provides can uncover hidden facts and can be used to inform the selection of machine learning algorithms or evaluate their performance in ways more informative than customary. TDA insights may also generate new science. As an example of how TDA identified new subtype of breast cancer tumors. This subgroup, denoted c-MYB+, is characterized by Estrogen Receptor-positive tumor cells with high expression levels of the c-MYB gene and low levels of innate inflammatory genes characterized clinically by 100% survival with no metastases (Nicolau, 2011). Hierarchical clustering did not reveal this subgroup, and in fact dispersed it over several clusters. TDA has the capacity to shed insights into entities that were not known to exist. In an unpublished example well known in the TDA community, TDA was used to analyze a human population consisting of three starkly different groups. All clustering methods attempted successfully recognized the three groups, and so did TDA. TDA additionally revealed singular aspects in one of the groups. This triggered after-the-fact investigation of the data, which revealed that the special group had been pruned to eliminate all parent-child relationships. The use of TDA and downstream analysis in this study is supported by the reported utility (unpublished to protect utility of the methodology by those who need to use this) (understandably) use of the method to detect financial fraud, a problem where the rarity of the event in relation to frequency of transactions generates a class imbalance that is more severe than with this study's adverse events analysis.

Our group conducted a satisfactory proof-of-concept using the carfilzomib-treated arm of the ASPIRE clinical trial and this example will be used to explain the analysis method

and its application in this study. The foundations of Topological Data Analysis are well established and been in use for over 10 years since a pivotal Standford mathematician's publication [Carlsson, 2009]. TDA is presented in a reduced and more accessible fashion and applications from different areas are described. As explained in the discussion on the proof-of-concept, TDA produces a network representation of data. The algorithm that generates networks is the main topic in (Singh, 2007). The use of TDA to address actual analysis problems is well described in the literature including n the biosciences area [(Nicolau, 2011), (Rivzi,2017), (Li Li, Wei-Yi Cheng, 2015) (Chan, J, 2013)]. The use of TDA to analyze rare events has been shared via personal academic communications and remains largely unpublished.

Shown on (**FIG1**) is a topological model (ie, network representation) of the carfilzomib-treated arm of the ASPIRE clinical trial colored by occurrence of the hypertension adverse event. This model was produced through TDA in the proof-of-concept. A topological model is a view of the shape of the data and the algorithm that generates such networks is well described (Singh, 2007). The algorithm is the computational embodiment of established methods in the mathematical discipline of topology to parse the global complexity of shapes into overlapping instances of local insight. It is important to note that the insight that a topological model provides lies in the connectivity structure of the network, not in where nodes appear in any particular visual rendering of the network in two or more dimensions.

The model on (**FIG1**) is a network of small soft clusters. Each node is a small group of (one to five) subjects and an edge between two nodes indicates that the corresponding groups overlap. The node colors indicate the proportion of subjects that had a hypertension adverse event. In just about all topological models in the published literature, node colors feature a continuum of visually identifiable areas that reveal most of the insight. In the case of (**FIG1**), there is no obvious identification of AE and non-AE subjects, though there is an obvious dominance of non-AE subjects. Whence the subsequent steps of cold-spot analysis and group discovery.

Cold-spot analysis is used to address the class imbalance problem: there are considerably more non-AE subjects than AE subject. Topology and network clustering are used to identify communities in the non-AE population. Every non-AE subject will fall in one community, but only communities that have at least 5% of the non-AE population are deemed significant and retained. There are numerous network clustering techniques. The communities in this work are the path-connected components within the pure

non-AE (pure blue nodes) subnetwork. The path-connected component of a node is the set of nodes it is connected to by a path (of zero or more edges). Thus, two pure non-AE (pure blue) nodes that belong to two different cold spots can be connected only by crossing path with at least one AE subject. This network clustering approach fully exploits the semantic of the topological model. (**FIG2**) shows in black color the five significant cold spots in the topological model of (**FIG1**).

The final step is explanation discovery. We started with an imbalanced binary classification problem, and we now have a multiclass problem seeded by six groups: the group of AE subjects and the five groups of non-AE subjects from cold-spot analysis. (Performing hot-spot analysis would not serve the purpose of addressing the class imbalance problem.) We use decision-tree learning, seeded by the above six groups, to assign all subjects to groups and simultaneously obtained explicit descriptions of the groups. We use the ID3 (Iterative Dichotomiser 3) algorithm (Grzymala-Busse, 1993). Groups are retained by taking into account the size of the group and the AE incidence rate (which is desired to be decidedly either high or low). For illustration, in the proof-of-concept example used here, a group described by baseline characteristics consisted of 27 subjects, 16 of which developed the hypertension adverse event, for an incidence rate of 59.3%, whereas the overall rate is 17.9%. Another group (also described by baseline characteristics, as are all groups) consisted of 104 subjects, 1 of which developed the hypertension adverse event, for an incidence rate of 0.96%.

The above three steps, which we call a pass, are repeated on non-assigned patients, until a pass produces no or little change. (In the case of the proof of concepts, it took two passes both for hypertension and cardiac failure.)

The core problem in this work is the class imbalance (AE vs. non-AE) coupled with the heterogeneity (patient diversity) of the two classes. All other methods we know of involves creating fictious subjects. One style is to create several (for example 10) exact instances of each AE subject. Another style is to use purpose-built randomizers to synthesize more AE subjects. These methods impair explainability, a fundamental requirement of this work. Also, when working with a class enlarged by synthetic subjects, increased classification perform can be the result of the learner learning to recognize the synthetic subjects.

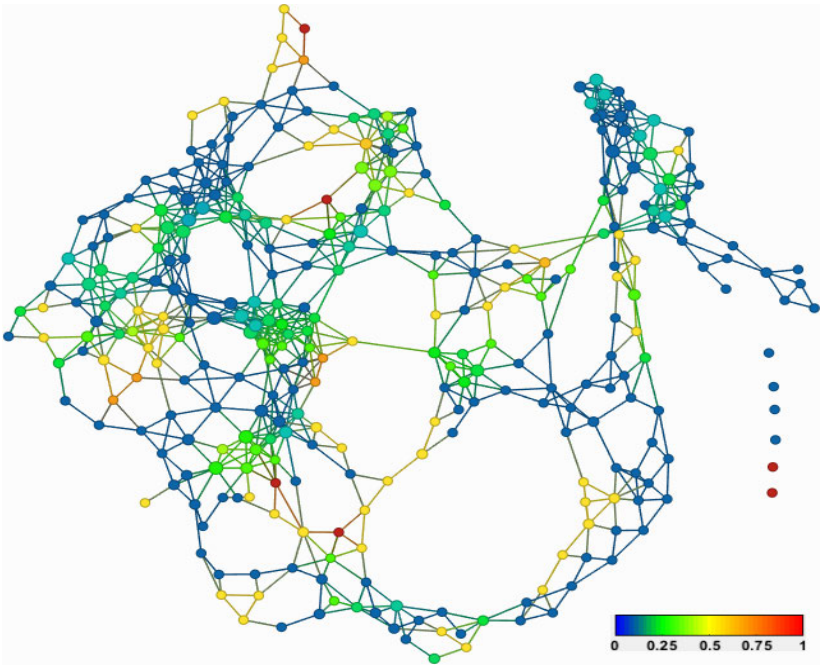

FIG1

A topological model of the carfilzomib-treated arm of the ASPIRE clinical trial colored by occurrence of the hypertension adverse event. The model is a network of small soft clusters. Each node represents a small group of (one to five) subjects and an edge between two nodes indicates that the corresponding groups overlap. The node colors indicate the proportion of subjects that had the hypertension adverse event.

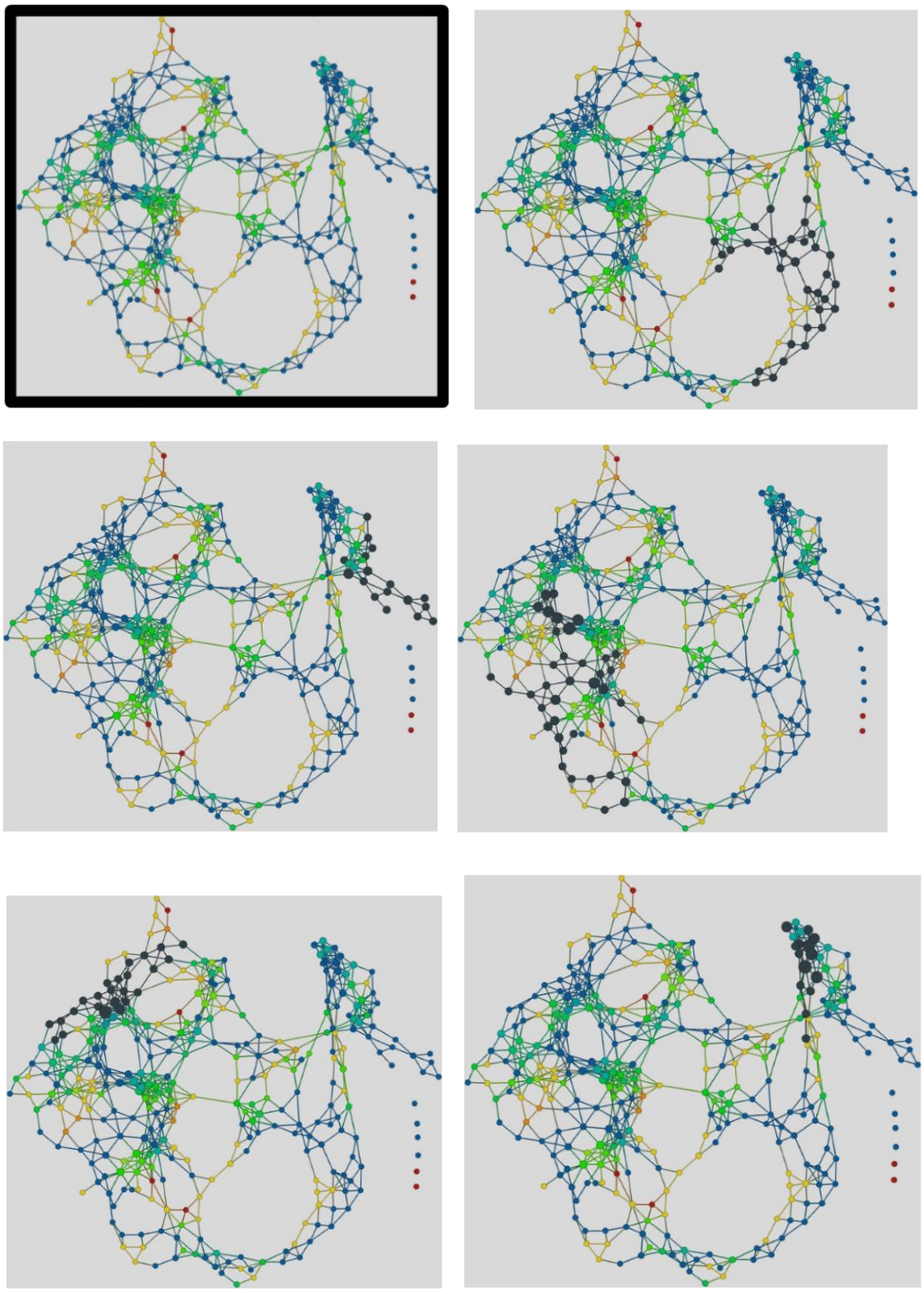

FIG2

The topological model of (FIG1) is shown here six times. The figure with the black border is exactly as on (FIG1). The other five figures highlight the five significant cold spots in black color

Approval Signatures

Document Name: Protocol-Published Original carfilzomib 20190506

Document Description:

Document Number: CLIN-000278506

Approval Date: 15 Oct 2021

Type of Study Protocol: Original

Protocol Amendment No.:

Document Approvals	
Reason for Signing: Functional Area	Name: Amy Kimball Date of Signature: 15-Oct-2021 13:11:21 GMT+0000