Statistical Analysis Plan

Protocol Title:	An Open-label Phase 2 Study of Carfilzomib Plus Dexamethasone to Assess Tolerability and Adherence in Subjects with Relapsed or Refractory Multiple Myeloma at US Community Oncology Centers
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List of Abbreviations and Definition of Terms

Term or Abbreviation	Description
ACE	Angiotensin-Converting Enzyme
AE(s)	Adverse Event(s)
[redacted]	
BNP	Brain Natriuretic Peptide
BSA	Body Surface Area
CDM	Clinical Data Management
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EuroQOL	European Quality of Life
EQ-5D-5L	European Quality of Life-5 Dimensions
EOI	Event of Interest
EOT	End of Treatment
GFR	Glomerular Filtration Rate
FDA	Food and Drug Administration
GSO-DM	Global Study Operations-Data Management
HRQoL	Health-related quality-of-life
IMWG-URC	International Myeloma Working Group-Uniform Response Criteria
IP	Investigational Product
IPD	Important Protocol Deviation
ISS	International Staging System
IXRS	Interactive Voice/Web Response System
Kd	Carfilzomib and Dexamethasone
Kd56	Kd 56 mg/m2 twice weekly
Kd70	Kd 70 mg/m2 once weekly
KM	Kaplan-Meier
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities

Term or Abbreviation	Description
MR	Minimal Response
MRI	Magnetic Resonance Imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	Not Evaluable
NT-ProBNP	N Terminal of the Prohormone Brain Natriuretic Peptide
NYHA	New York Heart Association
ORR	Overall Response Rate
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-free Survival
PO	Orally
PR	Partial Response
QLQ-C30	Quality of Life Core Module
QLQ MY20	Quality of Life Multiple Myeloma Module 20
QTc	corrected QT-interval
RDI	Relative Dose Intensity
RRMM	Relapsed or Refractory Multiple Myeloma
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
sCR	Stringent Complete Response
SD	Stable Disease
SFLC	Serum Free Light Chain
SMQ	Standardized MedDRA Queries
VGPR	Very Good Partial Response
VQ Scan	Pulmonary Ventilation/Perfusion Scan
WHO DRUG	World Health Organization Drug dictionary

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study 20170596, AMG 981 dated 06 Mar 2018. The scope of this plan includes the final analysis that is planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
Describe tolerability and treatment safety of a Kd regimen (Kd 56 mg/m^2 [Kd56] twice weekly for cycles 1-6 followed by Kd 70 mg/m^2 [Kd70] once weekly for cycles 7-12) in subjects with relapsed or refractory multiple myeloma with 1-3 prior lines of therapy at study entry.	• Proportion of subjects completing 12 cycles of treatment • Dose intensity defined as total actual dose divided by planned dose through cycle 12 or up to disease progression • Treatment-emergent adverse events and serious adverse events
Secondary	
Describe treatment adherence by the Kd regimen (Kd56 twice weekly and Kd70 once weekly).	• Dose intensity in cycles 1-6 and cycles 7-12 defined as total actual dose divided by planned dose through cycle 6 or 12 or up to disease progression • Dose reductions in cycles 1-6 and cycles 7-12 • Treatment discontinuation for all reasons in cycles 1-6 and cycles 7-12
Assess subject health-related quality-of-life (HRQoL) with Kd56 twice weekly and Kd70 once weekly.	• European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire (EORTC QLQ) Core 30 (C30) and EORTC QLQ Multiple Myeloma Module (MY20) scores through cycle 12 or up to disease progression • EORTC QLQ-C30 and EORTC QLQ-MY20 scores for cycles 1-6 and cycles 7-12 in subjects completing 12 cycles of treatment

Objectives	Endpoints
Assess response to the Kd regimen.	• Response rate (minimal response [MR], partial response [PR], very good partial response [VGPR], complete response [CR], and stringent complete response [sCR]). • Landmark response rate (MR, PR, VGPR, CR and sCR) after 6 and 12 cycles. • Progression-free survival (PFS) at 1 year • Response rate and PFS by line of prior therapy 1 vs ≥ 2
Exploratory	
[redacted]	

2.2 Hypotheses and/or Estimations

Carfilzomib plus dexamethasone twice weekly followed by carfilzomib plus dexamethasone once weekly is tolerable in subjects with RRMM in a community-based setting.

3. Study Overview

3.1 Study Design

This is a phase 2, multicenter, open-label study in subjects with RRMM in US community oncology centers. Subjects with 1-3 prior lines of therapy at study entry are eligible to be screened for participation. Subjects refractory to their last line of treatment are eligible to participate as long as their last line of treatment did not include an IP. The study will consist of a screening period of up to 28 days, up to 12 cycles of treatment, and a 30-day safety follow-up period following the last dose of study drug.

During the treatment period, all subjects will be treated with Kd 20/56 mg/m^2 twice weekly for up to six 28-day cycles followed by up to Kd 70 mg/m^2 once weekly for another six 28-day cycles. After discontinuation of study drugs, subjects will be followed for 30 days for adverse events.

3.2 Sample Size

The study is descriptive in nature. Approximately 75 subjects will be enrolled in the study. A sample size of 75 will provide an estimate for the percent of subjects completing 12 cycles of Kd treatment with an expected precision (half-width of the 95% CI) of 11.3%, assuming an expected proportion of 50%. The expected precision will be 9.8% for an expected proportion of 75%.

3.3 Adaptive Design

Not applicable.

4. Covariates and Subgroups

4.1 Planned Covariates

Not applicable.

4.2 Subgroups

Proportion of subjects completing 12 cycles of treatment, proportion of subjects completing 6 cycles of treatment, relative dose intensity, causes of discontinuation, overall response rate, greater than or equal to grade 3 non-hematology AEs, cardiovascular AEs by Standardized MedDRA Queries (SMQ) narrow term will be examined in subgroups. If the numbers of subjects in certain category of subgroups are less than 10% of total sample size, relevant subgroups may be rationally combined or subgroup analysis may not be carried forward.

Proportion of subjects completing 12 cycles of treatment, proportion of subjects completing 6 cycles of treatment, relative dose intensity and causes of discontinuation will be analyzed in the following subgroup:

- commute distance to treatment center: 0-10, 11-25, > 25 miles

Overall response rate, greater than or equal to grade 3 non-hematology AEs, cardiovascular AEs by SMQ narrow search will be analyzed in the following subgroup:

- hypertension history (include use of anti-hypertensive medications) (yes, no)
- history of ischemic heart disease (myocardial infarction or coronary artery disease), congestive heart failure (NYHA class ≤ 2), stroke, or history of peripheral vascular disease (yes, no)
- family history of coronary artery disease in first degree relatives with onset < 65 years of age for female relative or < 55 years of age for male relative (yes, no)
- smoking history (yes, no)
- history of hyperlipidemia (yes, no)

- history of diabetes (yes, no)
- revised international staging system stage (stage 1 vs stage 2 vs stage 3 vs unknown)
- progressive disease on lenalidomide during or within 60 days of treatment (yes, no)

5. Definitions

Study Treatment

Study treatment of this study includes carfilzomib and dexamethasone.

First Dose Date

The first dose date is the date on which a subject is administered the first dose of any study treatment.

Last Dose Date

The last dose date is the date on which a subject is administered the last dose of any study treatment.

End of Study Date for a Subject

The end of study date is the date recorded on the End of Study page for an enrolled subject.

Baseline

When analyzing progression-free survival time (PFS), baseline will be defined as the day of enrollment. When analyzing all other analysis endpoints for subjects who received study treatment, baseline is the closest recorded measurement prior to the first dose of any study treatment. If a subject doesn't receive any study treatment, baseline is defined as the latest measurement on or prior to enrollment date. If multiple valid records are observed at the same date and time, the average of these values will be used.

Study Day 1

The first day of study treatment administration or the enrollment date for subjects who are not administered any dose of study treatment.

Study Day

The number of days from the study day 1 to a date of interest, inclusive:

$$\text{Study day } n = (\text{date of interest} - \text{date of study day 1}) + 1.$$

Unless otherwise specified, the timing of all study-related events, assessments, and interventions will be calculated relative to study day 1. Study day −1 will be the day before study day 1, and in general for assessments prior to study day 1, study day is defined as:

Study Day *n* = (date of interest – date of Study day 1)

Relative Dose Intensity (%)

Relative Dose Intensity (%) of carfilzomib/dexamethasone is defined as

$$\text{Relative Dose Intensity} = 100 \text{ x } \frac{\text{Actual Dose Intensity}}{\text{Intended Dose Intensity}}$$

Actual dose intensity is the actual cumulative dose (mg/m2 for carfilzomib, mg for dexamethasone) divided by the duration of exposure (week). Intended dose intensity is the planned cumulative dose (mg/m2 for carfilzomib, mg for dexamethasone) divided by the protocol specified treatment duration (week). Specifically,

- Actual cumulative dose is the sum of actual doses that a subject received. For carfilzomib, it is the sum of received doses (mg) divided by baseline BSA (m^2). If BSA is > 2.2 m^2, then 2.2 will be used in the calculation. For dexamethasone, it is the sum of received doses (mg).
- Duration of exposure (week) is calculated as (Last Dose Date – First Dose Date + Interval (days) to next planned treatment) / 7. Depending on the cycle and day of the last infusion, Interval (days) to next planned treatment is specified in following table:

Last Cycle	Cycle Day of the Last Administration	Interval (days) to Next Planned Carfilzomib Administration	Interval (days) to Next Planned Dexamethasone Administration
1 - 6	Day 1 or Day 8	7	7
	Day 2 or Day 9	6	6
	Day 15	14	7
	Day 16	13	6
	Day 22	-	7
	Day 23	-	6
7-12	Day 1 or Day 8	7	7
	Day 15	14	14

- Planned cumulative dose (mg/m^2 for carfilzomib, mg for dexamethasone) is the sum of protocol specified doses of the subject. Protocol specified doses are summarized in following table:

Cycle	Cycle Day	Carfilzomib Dose (mg/m^2)	Dexamethasone Dose (mg)
1	1, 2	20	20
1	8, 9, 15, 16	56	20
1	22, 23	-	20
2 – 6	1, 2, 8, 9, 15, 16	56	20
2 – 6	22, 23	-	20
7 – 12	1, 8, 15	70	40

- Number of protocol specified treatment weeks is calculated as 4 x number of completed cycles + the number of weeks in the last cycle according to following table.

Last Cycle Day of the last Infusion	Number of weeks for carfilzomib	Number of weeks for dexamethasone
Day 1 or Day 2	1	1
Day 8 or Day 9	2	2
Day 15 or Day 16	4	3
Day 22 or Day 23	-	4

Dose Reduction

The occurrence that actual dose a patient received in one treatment administration is less than the protocol specified dose.

Best Overall Response

Response category will be assessed by investigator according to International Myeloma Working Group Uniform Response Criteria (IMWG-URC) per standard procedure. Best overall response will be derived for multiple myeloma disease assessments based on the International Myeloma Working Group Uniform Response Criteria (IMWG-URC). Best overall response will be decided in the following order of confirmed responses: stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), MR, SD, PD starting from the best to the worst. Determine stable disease (SD) as best overall response requires a duration of at least 6 weeks. If a subject's best overall response is none of above, the patient's best overall response is not evaluable (NE).

Overall Response Rate

Overall response rate is the proportion of subjects whose best overall response is sCR, CR, VGPR, or PR.

Progression-free survival (PFS)

PFS is defined as the time (months) from First Dose Date until the earliest date of disease progression or death due to any cause, whichever occurs first.

PFS = (PD / death date – first dose date +1)/30.4

Progression-free survival will be right-censored for subjects who met one of the following conditions: 1) no baseline disease assessments, 2) non-protocol anti-myeloma therapy started before documentation of disease progression or death, 3) death or disease progression immediately after more than 1 consecutively missed disease assessment visit, or 4) alive and does not have documentation of disease progression before a data analysis cutoff date. These conventions are based on the May 2007 FDA Guidance for Industry, 'Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics' (https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf), The censoring rules for the primary analysis of PFS are described in Table 5-1. Additionally, if the last disease assessment date is after the date that triggers the analysis, the subject will be censored at the analysis trigger date.

Table 5-1 Conventions for Censoring for PD dates

Situation	Date of Progression or Censoring	Outcome
No baseline disease assessments	Date of first dose	Censored
New anti-myeloma therapy started before documentation of PD or death	Date of last disease assessment prior to start of new anti-myeloma therapy	Censored
Death or PD immediately after more than 1 consecutively missed disease assessment visit	Date of last disease assessment visit without documentation of PD that is before the first missed visit	Censored
Alive and without PD documentation (including lost to follow-up without PD)	Date of last disease assessment	Censored
Death or PD between planned disease assessments	Date of death or first disease assessment showing PD, whichever occurs first	Progressed
Death before first disease assessment	Date of death	Progressed

Treatment-emergent Adverse Event

AEs starting on or after first dose of investigational product as indicated by field "*Did event start before first dose of investigational product?*" in Events page and up to 30 days, inclusive, after the last dose of study treatment.

6. Analysis Sets

6.1 Full Analysis Set

The full analysis set will include all enrolled subjects who received at least 1 dose of any study treatment (ie, carfilzomib or dexamethasone).

6.2 Safety Analysis Set

The safety analysis set is the same as full analysis set.

6.3 Interim Analyses Set(s)

Not Applicable.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

Not Applicable.

7.2 Primary Analysis

Not Applicable.

7.3 Final Analysis

The final analysis will occur after all subjects have completed therapy, disease assessment and safety follow-up.

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database.

8.3 Handling of Missing and Incomplete Data

The descriptive statistics will identify the extent of missing data. Rules for handling missing data related to endpoints are described in the endpoint definitions or in the description of analyses. The handling of incomplete and partial dates for adverse events and concomitant medications are described in Appendix A.

8.4 Detection of Bias

Not Applicable.

8.5 Outliers

Any suspected outliers will be investigated by the study team and will be included in the database unless determined to be an error or there is supporting evidence or explanation to justify the exclusion. Any outliers excluded from the analysis will be discussed in the Clinical Study Report (CSR), including the reasons for exclusion and the impact of their exclusion on the study.

8.6 Distributional Characteristics

The statistical assumptions for analysis methods will be assessed. If the assumptions for the distributional characteristics are not met, these will be described and further analyses may be carried out using data transformations or alternative analysis methods. The use of transformations or alternative analysis methods will be justified in the final study report.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

In general, safety analysis set will be utilized to generate summary statistics for different dosing regimen, including Kyprolis in combination with dexamethasone (Kd) 56 mg/m^2 [Kd56] twice weekly and Kd 70 mg/m^2 [Kd70] weekly.

Continuous variables will be summarized by the non-missing sample size (n), mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by the n and percentage in each category. Time to event endpoints will be summarized with Kaplan-Meier (KM) curves (Kaplan and Meier, 1958), KM proportions at select time points, KM quartiles (when estimable), the number of subjects with events, the number of subjects censored, and censoring reasons. Point estimates for efficacy endpoints will be accompanied by 2-sided 95% confidence intervals including estimates of KM quartiles (Klein and Moeschberger, 1997), KM proportions (Kalbfleisch and Prentice, 1980), and binomial proportions (Clopper CJ and Pearson, 1934).

9.2 Subject Accountability

The number and percent of subjects who were screened, enrolled, and received study treatment will be summarized. The number and percent of subjects who discontinued study treatment and study will also be tabulated, along with the reason for

discontinuation. Key study dates for the first subject enrolled, last subject enrolled, and data cut-off date for analysis will be presented.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

9.4 Demographic and Baseline Characteristics

Descriptive statistics for demographic and baseline characteristics will be summarized.

Baseline demographics and characteristics:

- age (as categorical variable: 18 to < 65, 65 to 75, and > 75 years)
- sex (male, female)
- race (white and other categories depending on frequency observed)
- commute distance to treatment center: 0-10, 11-25, > 25 miles

Baseline organ function and comorbid conditions:

- ECOG performance status (0 or 1)
- estimated GFR (< 50 vs ≥ 50 mL/min/1.73 m^2)
- hypertension history (include use of anti-hypertensive medications) (yes, no)
- history of ischemic heart disease (myocardial infarction or coronary artery disease), congestive heart failure (NYHA class ≤ 2), stroke, or history of peripheral vascular disease (yes, no)
- family history of coronary artery disease in first degree relatives with onset < 65 years of age for female relative or < 55 years of age for male relative (yes, no)
- smoking history (yes, no)
- history of hyperlipidemia (yes, no)
- history of diabetes (yes, no)
- history or chronic mild hepatic impairment (yes, no)

Baseline disease characteristics:

- revised international staging system stage (stage 1 vs stage 2 vs stage 3 vs unknown)
- determination of measurable disease at baseline (based on serum or urine M−protein, based on SFLC only)
- β2-microglobulin level (< 2.5, ≥ 2.5 and < 5.5, ≥ 5.5 mg/L)

- presence of soft tissue plasmacytoma (yes, no)
- progressive disease on lenalidomide during or within 60 days of treatment (yes, no)
- progressive disease on lenalidomide in combination with dexamethasone during or within 60 days of treatment (yes/no)

9.5 Efficacy Analyses

9.5.1 Analyses of Primary Efficacy Endpoint(s)

Not applicable.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

European Organization for Research and Treatment of Cancer Quality of life Questionnaire (EORTC QLQ) Core 30 (C30) and EORTC QLQ Multiple Myeloma Module (MY20) scores will be administered and collected prior to study treatment on Day 1 of each cycle. Actual values and changes from baseline of QLQ-C30 and QLQ-MY20 scores will be summarized for each cycle with non-missing sample size (n), mean, standard deviation, median, minimum, and maximum. The summary statistics will be tabulated separately for following groups: subjects who ended treatment due to disease progression before the end of Cycle 6, subjects who ended treatment due to disease progression after the end of Cycle 6 but before the end of Cycle 12, subjects who have completed all 12 cycles, subjects who ended treatment with reasons other than “Disease progression” before the end of Cycle 12. For subjects who have completed all 12 cycles of treatment, the overall QLQ-C30 and QLQ-MY20 scores will be summarized by Cycle 1-6 versus Cycle 7-12.

Best overall response rates (minimal response [MR], partial response [PR], very good partial response [VGPR], complete response [CR], and stringent complete response [sCR]) will be summarized descriptively at the end of study, end of Cycle 6 and end of Cycle 12 respectively. Overall response rate will also be summarized descriptively with 95 % CI estimated using the Clopper-Pearson method at the end of study, end of Cycle 6 and end of Cycle 12 respectively. The rate of PFS at 1 year will be estimated using the Kaplan-Meier method and with 95% CI estimated by Greenwood’s formula (Kalbfleisch and Prentice, 1980) with log-log transformation and will be summarized by number of prior lines (1 vs ≥2). Similarly, the best overall response and overall response rate will also be summarized by number of prior lines (1 vs ≥2).

All secondary efficacy endpoints will be based on full analysis set.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

[redacted]

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

The proportion of subjects completing 12 cycles of Kd treatment will be calculated and the associated 95% CI will be estimated using the Clopper-Pearson method. Per protocol, dose intensity is defined as total actual dose divided by planned dose through cycle 12 or up to disease progression. In this SAP, duration of exposure/protocol specified treatment weeks will be taken into consideration when summarizing dose intensity data. Specifically, relative dose intensity as defined in section 5, number of cycles received, duration of treatment, number of administrations and actual cumulative dose will be summarized descriptively for Cycle 1-12 and tabulated separately, with the same four groups as described in section 9.5.2.

Number and proportion of subjects who had dose modifications (dose reductions, missed dose, etc), and reasons of dose modifications will be summarized for Cycle 1-12, tabulated by the same four groups as described in section 9.5.2. In addition, summary statistics of the difference between protocol specified dose and actual dose received will be provided and tabulated by reasons.

Treatment-emergent adverse events and serious adverse events will be summarized descriptively following methods specified in section 9.6.3. The profile plot for each subject, which includes both actual dose received and treatment-emergent adverse events and serious adverse events during the study will be provided. All analyses of primary safety endpoints will be based on the safety analysis set.

9.6.2 Analyses of Secondary Safety Endpoint(s)

Relative dose intensity, number of cycles received, duration of treatment, number of administrations and actual cumulative dose in Cycle 1-6 and Cycle 7-12 will be summarized respectively, with the same four groups as described in section 9.5.2. Number and proportion of subjects who had dose modifications, and reasons of dose modifications will be summarized for Cycle 1-6, and Cycle 7-12 respectively. In addition, treatment discontinuation along with reasons will be summarized descriptively for Cycle 1-6 and Cycle 7-12. Summary statistics of the difference between protocol specified dose and actual dose received will be provided and tabulated by reasons for

Cycle 1-6 and Cycle 7-12 respectively. All analyses of secondary safety endpoints will be based on the safety analysis set.

9.6.3 Adverse Events and Disease-related Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term.

Treatment-emergent adverse events are events starting on or after first dose of investigational product and up to 30 days, inclusive, after the last dose of study treatment.

The subject incidence of adverse events will be summarized for all treatment-emergent adverse events, serious adverse events, and adverse events leading to dose modifications, withdrawal of investigational product, fatal adverse events, and adverse events of interest when defined.

Subject incidence of all treatment-emergent adverse events, serious adverse events, adverse events leading to dose modifications, withdrawal of investigational product, and fatal adverse events will be tabulated by system organ class and preferred term in alphabetical order.

Subject incidence of events of interest (standardized MedDRA queries and/or Amgen customized queries) will also be summarized according to their categories and preferred term.

In addition, summaries of treatment-emergent and serious adverse events occurring in at least 5% of the subjects by preferred term in any treatment arm will be provided in descending order of frequency.

Summaries of treatment-emergent and serious adverse events will be tabulated by system organ class, preferred term, and grade.

9.6.4 Laboratory Test Results

For hematology, chemistry, and other laboratory values, descriptive statistics for the actual value at each visit and the change from baseline at each post-baseline visit during the study period will be summarized. Subjects with missing data for baseline and/or a scheduled visit will not contribute to the summary table which summarizes the change from baseline to that scheduled visit. Numeric values of each laboratory parameter will

be converted to grades according to NCI CTCAE (v4.03) and grade shit from baseline will be summarized.

9.6.5 Vital Signs

The analyses of vital signs, including systolic/diastolic blood pressure, heart rate, respiratory rate and temperature, will be summarized descriptively by scheduled time point for actual value and change from baseline.

9.6.6 Physical Measurements

Any clinically significant abnormal values noted on the physical examination will be reported by the investigator as AEs. No summary of the physical examination data will be provided.

9.6.7 Electrocardiogram

The electrocardiogram (ECG) measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QT interval corrected (QTc) effect. Because these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; neither summaries nor statistical analyses will be provided, and these data would not be expected to be useful for meta-analysis with data from other trials.

9.6.8 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to carfilzomib as described in section 9.6.1 and 9.6.2.

9.6.9 Exposure to Other Protocol-Specified Treatment

Descriptive statistics will be produced to describe the exposure to non-Amgen non-investigational products (dexamethasone). The number of cycles received, duration of treatment, number of administrations, cumulative dose, number and proportion of subjects with dose modifications, reasons for modification will be summarized descriptively.

9.6.10 Exposure to Concomitant Medication

The number and proportion of subjects receiving therapies of interest will be summarized by preferred term or category by dosing regimen period and overall as

coded by the World Health Organization Drug (WHO DRUG) dictionary. See Appendix Appendix C for a list of selected medications and their groupings.

9.6.11 Other Analyses

Cardiovascular events may be summarized by risk group defined by ABC score (Bulter 2008).The information of cardiovascular reasons for screen failure will be captured for exclusion criteria from the IXRS system. If warranted by the completeness of information, the proportion of failure reasons may be summarized.

The use of the dyspnea guidance instructions may be summarized by correlating the dates of reporting of dyspnea adverse events with dates of collection of brain natriuretic peptide (BNP) or N terminal of the prohormone brain natriuretic peptide BNP (NT-ProBNP), serum creatinine, echocardiograms, and evaluations for infection or pulmonary disorders as detailed in protocol Section 12.9. The proportion of subjects in whom dyspnea is reported as an adverse event and undergo each evaluation and the results of these evaluations may be summarized descriptively.

10. Changes from Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

11. Literature Citations / References

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12. Appendices

Appendix A. Technical Detail and Supplemental Information Regarding Statistical Procedures and Programs

The handing of incomplete and partial dates for adverse events and concomitant medications are described below:

Imputation rules for partial or missing AE start dates:

1) If AE start date is partial with missing day, but year and month are the same as the first dose date, then impute it with the first dose date.
2) If AE start date is partial with missing day, and year or month is not the same as the first dose date, then impute it with day 1 of the month.
3) If AE start date is partial with missing month and day, but year is the same as the first dose date, then impute it with the first dose date.
4) If AE start date is partial with missing month and day, and year is not the same as the first dose date, then impute it with January 1st of the year.
5) If AE start date is completely missing, then impute it with the first dose date.

Note: Imputation rules for partial or missing concomitant medication start date will be utilizing above algorithm by replacing “AE start date” with “Concomitant medication start date”.

Imputation Rules for Incomplete/Missing Death Dates:

- If death year and month are available but day is missing:
    - If mmyyyy for last contact date = mmyyyy for death date, set death date to the day after the last contact date.
    - If mmyyyy for last contact date < mmyyyy for death date, set death date to the first day of the death month.
    - If mmyyyy for last contact date > mmyyyy for death date, data error and do not impute.
- If both month and day are missing for death date or a death date is totally missing, do not impute.

Imputation Rules for date of initial diagnosis:

- If the day is missing and month and year < month and year of enrollment then impute 15 for the day.

- Else if the day is missing and month and year = month and year of enrollment then impute day with 15 unless the day of enrollment is < 15 then impute date of enrollment.
- If the day and month are missing and year = year of enrollment then impute July 1st.
- Else if the day and month are missing and year = year of enrollment then impute July 1st unless the day of enrollment is < July 1st then impute January 1st.

Appendix B. Reference Values/Toxicity Grades

Laboratory Values

Safety laboratory values below a distinct limit (eg. detection limit, documented as "< [limit]") will be substituted by half of the limit and values above a distinct limit (documented as "> [limit]") will be substituted by the limit itself for all analyses. A Grade will be assigned to each laboratory based on CTCAE version 4.0 [v4.03: June 14, 2010]. Depending on the toxicity definition, the same result may be assigned to two grading for deviations towards higher or lower values. Values not meeting any of the criteria will be assigned a grade 0.

Appendix C. Concomitant Medications

The following therapies of interest will be summarized. The list may be updated upon clinical discretion.

Anti-hypertensives;
Angiotensin-Converting Enzyme (ACE);
Calcium Chanel Blockers;
Cardiac Enzymes;
Diuretics;
Other cardiac medications for pulmonary hypertension: treprostinil, iloprost, bosentan, macitentan, ambrisentan, sildenafil, tadalafil, adempas;
Anticoagulants: aspirin, warfarin, low molectular weight heparin, other platelet inhibitors such as plavix.

Procedures including dialysis, CT's, MRI's, PET scans, VQ scans, pulmonary function tests, lung biopsy, cardiac procedures ECHO, heart catheterization, stress tests.