Statistical Analysis Plan

Protocol Title:	Phase 1b Study of Carfilzomib Administered Once Weekly in Combination With Lenalidomide and Dexamethasone in Subjects With Multiple Myeloma
Short Protocol Title:	Weekly KRd
Protocol Number:	20140241 (CFZ013)
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	10 July 2018	
Amendment 1 (v2.0)	15 October 2019	1. Section 2.1 Objectives and Endpoints: • Update MRD[-]CR definition "… MRD[-] at CR" to "… MRD[-] at CR or better" 2. Section 3.1 Study Design: • updated number of subjects in NDMM cohorts in Figure 1 and Table 1 • added superscripts in Table 1. 3. Section 3.2 Sample Size: • add the summary for sample size justification 4. Section 5 Definitions: • removed 'and time' in Baseline definition • updated FISH risk group definition (central lab data): '>10%' to '>=10%', '>20%' to '>=20%' • add FISH risk group definition based on local lab data • add R-ISS per local lab FISH data • updated TEAE definition based on DES 6.0. 5. Section 6 Analysis Sets: deleted MRD Analysis Set. Rationale: MRD[-] analyses will not be included in CSR. 6. Section 9 Statistical Methods of Analysis: • updated number of subjects in NDMM cohorts in 9.1 General Considerations • removed 'Number of screened subjects' but added 'Number of enrolled subjects' in 9.2 Subject Accountability. Rationale: not able to separate number of subjects screened for RRMM and NDMM subjects • deleted definition and the 'not done' category for FISH in 9.4.3 Disease Characteristics. Rationale: FISH is already defined in section 5 Definitions, and 'not done' can be categorized into 'unknown'; add FISH risk group per local lab data • updated categorization for baseline beta2 microglobulin to '<3.5', '3.5 - <5.5', '≥5.5' in 9.4.3 Disease Characteristics

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
		• added 'unknown' category to ISS and RISS at baseline in 9.4.3 Disease Characteristics; add RISS per local FISH lab data • corrected the conditions for PFS censoring: deleted 'post' in 'no post baseline disease assessments' in 9.5.2 Progression-free Survival • updated the AEs determined to be DLTs included in the listings: deleted 'during the first cycle' in 9.6.1 Adverse Events and Disease-related Events. Rationale: AEs determined to be DLTs were found being evaluated in other cycles other than the cycles specified in Protocol • updated EOI list in 9.6.1 Adverse Events and Disease-related Events • removed 'Examination of cardiovascular and respiratory systems' in 9.6.4 Physical Measurements. Rationale: heart rate, BP and respiratory rate are presented in vital sign section for examination of cardiovascular and respiratory system • removed summaries at unscheduled visits in 9.6.6 Echocardiogram • added '+1' to the definition of duration of treatment in weeks; and added number of treatment cycles received prior to SCT for subjects who had SCT and number of treatment cycles received for subjects who did not have SCT in 9.6.7 Exposure to Investigational Product • updated 9.7.2 Analyses of Minimal Residual Disease Negative Rate Endpoints: deleted detailed analyses and added 'The analysis of MRD[-] rate will not be included in the clinical study report (CSR). The MRD analyses will be summarized in a separate analysis plan by Clinical Biomarkers & Diagnostics group'. • updated 9.7.3 Analyses of Patient Reported Outcomes and Other Health Related Quality of Life Endpoints by adding the specifications for denominator for percentage • updated 9.7.4 Analyses of Biomarker Endpoints: deleted detailed analyses and added 'will not be included in CSR'.

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Description/Explanation
AE	Adverse Event
AMQ	Amgen MedDRA Queries
ANC	Absolute Neutrophil Count
ASCT	Autologous Stem Cell Transplant
ATC	Anatomical Therapeutic Class
BSA	Body Surface Area
CA	Chromosomal Abnormalities
CDM	Clinical Data Management
CI	Confidence Interval
cm	Centimeter
CR	Complete Response
CRR	Complete Response Rate
CSR	Clinical Study Report
CSRC	Cohort Safety Review Committee
d	Dexamethasone
DMC	Data Monitoring Committee
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOI	Event of Interest
EOT	End of Treatment
FDA	Food and Drug Administration
FISH	Fluorescence in situ Hybridization
GSO-DM	Global Study Operations-Data Management
HLT	High Level Term
HRQOL	Heath-related Quality of Life
ICF	Informed Consent Form
IMWG-URC	International Myeloma Working Group Uniform Response Criteria
ISS	International Staging System for Multiple Myeloma
K	Kyprolis® (carfilzomib)

Abbreviation or Term	Description/Explanation
kg	Kilogram
KM	Kaplan-Meier
KRd	Kyprolis (carfilzomib), Revlimid (lenalidomide), and dexamethasone
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
m^2	Square Meter
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
MRD	Minimal Residual Disease
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NDMM	Newly Diagnosed Multiple Myeloma
ORCA	Onyx Response Computational Assessment
ORR	Overall Response Rate
PBMC	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PDn	Pharmacodynamics
PFS	Progression-free Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
QT Interval	The time between the start of the Q wave and the end of the T wave in the heart's electrical cycle; QTc is corrected QT
R	Revlimid® (lenalidomide)
R-ISS	Revised ISS
RRMM	Relapsed and Refractory Multiple Myeloma
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sCR	Stringent Complete Response
SD	Stable Disease; Standard Deviation
SFLC	Serum Free Light Chain
SIFE	Serum Immunofixation
SMQ	Standardized MedDRA Queries
SOC	System Organ Class

Abbreviation or Term	Description/Explanation
SPEP	Serum Protein Electrophoresis
TEAE	Treatment-Emergent Adverse Event
UIFE	Urine Immunofixation
UPEP	Urine Protein Electrophoresis
VGPR	Very Good Partial response
WBC	White Blood Cell
WES	Whole Exome Sequencing
WGS	Whole Genome Sequencing
WHO-DD	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 carfilzomib study 20140241 (CFZ013) amendment 3.0 dated 13 December 2016. 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. PK/PDn analyses and biomarker analyses will be provided by the Department of Clinical Pharmacology, Modeling & Simulation (CPMS) and Clinical Biomarkers & Diagnostics, respectively.

2. Objectives,Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of a once-weekly carfilzomib, lenalidomide, and dexamethasone (KRd) regimen in relapsed and refractory multiple myeloma (RRMM) and newly diagnosed multiple myeloma (NDMM) subjects	• Safety and tolerability of carfilzomib administered once weekly in combination with lenalidomide and dexamethasone, as defined by the type, incidence, and severity of Adverse Events (AEs) and changes from baseline in key laboratory analyses, including vital signs, and the extent and duration of exposure to study drugs
Secondary	
• To evaluate the pharmacokinetics (PK) of carfilzomib when administered once weekly in a KRd regimen in RRMM and NDMM subjects separately. • To evaluate the clinical activity (efficacy) of a once-weekly KRd regimen in RRMM and NDMM subjects separately	• Pharmacokinetics (PK) of carfilzomib • Overall Response Rate (ORR), defined as the proportion of subjects who achieve a best overall response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) in accordance with IMWG-URC (Rajkumar et al. 2011) • Complete Response Rate (CRR), defined as the proportion of subjects who achieve a best overall response of sCR or CR in accordance with IMWG-URC • Progression-free Survival (PFS), defined as the time from the first day of study treatment to the earlier of disease progression or death due to any cause • Duration of Response (DOR), defined as the time from the first evidence of confirmed PR or better to disease progression or death due to any cause among subjects who respond
Exploratory	
• To explore the genomic and transcriptional biomarkers that might predict response and resistance to a once-weekly KRd regimen • To characterize the pharmacodynamics (PDn) of proteasome inhibition with a once-weekly KRd regimen in RRMM and NDMM subjects • To assess minimal residual disease (MRD) status with a once-weekly KRd regimen in RRMM and NDMM subjects • To assess subject convenience and satisfaction with a once-weekly KRd regimen using subject questionnaire in RRMM and NDMM subjects	• Pharmacodynamics (PDn) of proteasome inhibition by carfilzomib measured in whole blood • MRD[-] rate, defined as the proportion of subjects who are negative for MRD at Cycle 8 Day 1 • MRD[-]CR rate, defined as the proportion of subjects who are MRD[-] at CR **or better** • Subject convenience and satisfaction with the carfilzomib dosing schedule • WGS, WES, whole transcriptome sequencing, and other nucleic acid and protein quantification data and immunoglobulin levels in tumor cells

2.2 Hypotheses and/or Estimations

No formal hypothesis testing is planned for this study. The number (%) of subjects with Dose Limiting Toxicities (DLTs) and AEs at each dose level will be summarized. Point and interval estimates will be provided for specific efficacy summary statistics. Point estimates for overall response rate (ORR), complete response rate (CRR), along with their exact 2-sided 95% confidence intervals will be calculated. Summary statistics for DOR and PFS, including 95% confidence intervals for quartiles and probability estimates, will be calculated using the Kaplan-Meier method. **More details for the efficacy analyses are provided in section 9.5.**

3. Study Overview

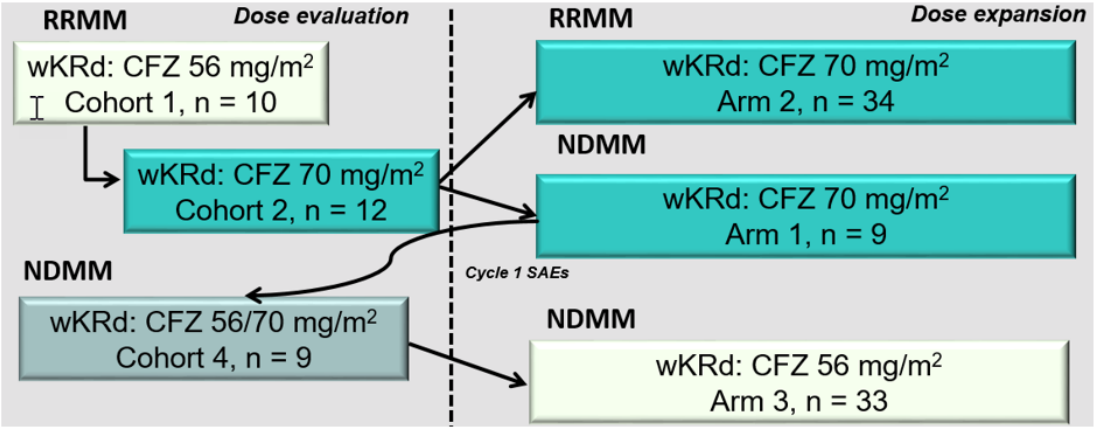
3.1 Study Design

This is an open-label, multicenter, Phase 1b, dose-finding study of carfilzomib administered once weekly in combination with lenalidomide and dexamethasone (KRd) in 28-day cycles to subjects with multiple myeloma. Subjects may continue to receive study treatment for up to 18 cycles or until 1 or more of the following events occurs: disease progression; allogeneic stem cell transplant, initiation of non-protocol MM therapy (including maintenance KRd therapy beyond cycle 18), withdrawal from the study for any reason, study termination by the sponsor, death. Subjects who discontinued study therapy (for any reason other than progressive disease, **allogeneic stem cell transplant, death, or withdrawal of consent**) could enter active follow up for up to one year.

The study included dose-evaluation and dose-expansion, and was amended three times. The final study schema is shown in Figure 1.

Figure 1. Study Schema

CFZ013 Study design (Amendment 3, Active)



Approximately 8 dose-limiting toxicity (DLT) evaluable subjects were **planned to be** enrolled into each opened dose-evaluation cohort. Dose-expansion arms 2 and 3 for RRMM and NDMM were planned to enroll approximately 30 subjects each. **The cohort safety review committee (CSRC) would review all available safety data and make recommendations regarding ongoing enrollment and opening of subsequent cohorts during the dose-evaluation components and would also select the KRd**

regimens to be evaluated in the dose-expansion components. After 3 amendments to the protocol, 6 dosing groups were enrolled, as seen in Table 1.

Table 1. KRd Dose Level Combinations

Study treatment	Cohort 1 RRMM N = 10	Cohort 2 RRMM N = 12	Arm 2 RRMM N = 34	Arm 1 NDMM N = 9	Cohort 4 [b] NDMM N = **9**	Arm 3 NDMM N = **33**
Carfilzomib mg/m^2, cycle 1 [a]	56	70	70	70	56	56
Carfilzomib mg/m^2, cycles 2+	56	70	70	70	70	56
Lenalidomide (mg)	25	25	25	25	25	25
Dexamethasone (mg) [c]	40	40	40	40	40	40

[a] All subjects received carfilzomib 20 mg/m^2 on Day 1 Cycle 1.

[b] Carfilzomib will be given at 56 mg/m^2 on Day 8 and 15 of Cycle 1; 70 mg/m^2 on Days 1, 8, and 15 of Cycle 2 and beyond.

[c] IV or oral; Day 22 dexamethasone required only in Cycles 1–8; subjects receiving IV dexamethasone on Day 1, 8, 15 may receive dexamethasone orally on Day 22.

3.2 Sample Size

Sample sizes are determined to provide preliminary information on safety, clinical activity, PDn, and PK. **The study has 2 parts: enrolling approximately 8 DLT evaluable subjects in each opened dose-evaluation cohort, and then expanding the selected doses by enrolling approximately 30 more subjects. Before opening dose-expansion arms, it must be determined that there are not more than 2 dose-limiting toxicities in 8 DLT-evaluable subjects at the dose selected for Dose-expansion. With combined number of subjects in both dose evaluation and expansion components, 38 subjects will allow an approximately 86% probability to detect an occurrence of an adverse event (AE) with 5% incidence rate.**

Assuming beta (0.5, 0.5) prior distribution for the DLT rate, 95% credible intervals for the DLT rate and the posterior probability of DLT rate being larger than 0.33 for each toxicity scenario are provided in Table 2. For example, when 3 out of 8 subjects have DLTs, the posterior probability of the DLT rate being >0.33 is 0.62.

Table 2. 95% Credible Intervals for the Dose-limiting Toxicity Rate and Probabilities of Dose-limiting Toxicity Rate Being Larger Than 0.33

Cohort Size	# DLTs Observed	95% Credible interval for the DLT Rate		[redacted]
8	0	0	0.26	
8	1	0.01	0.45	
8	2	0.06	0.59	
8	3	0.12	0.71	
8	4	0.20	0.80	
8	5	0.29	0.88	
8	6	0.41	0.94	
8	7	0.55	0.99	
8	8	0.74	1	

After the safety evaluation of the first 4 DLT evaluable subjects in each opened Cohort, CSRC recommended enrollment of an additional 4 subjects for up to 8 dose-evaluable subjects in total. Upon the safety evaluation of the opened dose-evaluation cohorts, dose-expansion Arm 1 (KRd 70 mg/m2 QW) for NDMM and Arm 2 (KRd 70 mg/m2 QW) for RRMM were planned to enroll approximately 30 subjects each. However, among 9 NDMM subjects enrolled in Arm 1, 2 serious adverse events (SAE) were observed and the enrollment stopped. The CSRC determined to add a 2-step-up KRd regimen in Cohort 4 NDMM (KRd 56/70 mg/m2 QW) in the Dose-evaluation component. Following the DLT rules above, the CSRC elected to open the second NDMM dose-expansion arm (Arm 3: KRd 56 mg/m2 QW) where approximately 30 NDMM subjects (upon protocol amendment 3) were planned to be enrolled.

4. Covariates and Subgroups

4.1 Planned Covariates

Not Applicable.

4.2 Subgroups

No subgroup analyses are planned in this study.

5. Definitions

Baseline

The baseline value is the closest recorded measurement prior to the first dose of study drug. If there are multiple valid records on an individual at the same date, then the record closest to cycle 1 day 1 will be used.

Best overall response by computational assessment

Best overall response will be derived using the Onyx Response Computational Assessment (ORCA) for multiple myeloma disease assessments based on the International Myeloma Working Group Uniform Response Criteria (IMWG-URC) (Durie et al. 2006, with revisions, Rajkumar, et al. 2011). The detailed algorithm is documented in a separate document.

Best overall response by investigator assessment

Best overall response by investigator assessment is the best confirmed response by the analysis trigger date based on the responses by visit collected on myeloma response assessment CRF. The following confirmatory assessments are required for all response categories (sCR, CR, VGPR and PR) and PD:

- All laboratory-based progressive disease and all responses require two consecutive assessments made at any time before initiation of any new therapy. Confirmatory lab samples should be separated by at least one calendar day.
- Progressive disease by non-laboratory-based assessment (ie, plasmacytoma or skeletal lesion) does not require confirmatory report.
- All response categories also require no evidence of progression including new bone lesion, if radiographic studies are performed.
- Confirmation of CR or sCR requires local pathology review of a bone marrow biopsy or aspirate (a repeat confirmatory bone marrow sample is not required)
- Extramedullary plasmacytoma evaluation is required to confirm PR, CR, or sCR (if present at baseline)

Best overall response will be decided in the following order of confirmed responses: sCR, CR, VGPR, PR, SD, PD starting from the best to the worst.

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.

First Dose Date

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

Fluorescent in Situ Hybridization (FISH) Risk Group

Subjects in this study had FISH analysis performed by a central study laboratory and local laboratory.

For central laboratory FISH: Subjects with chromosomal abnormalities (CA) t (4;14) or t (14;16) in >=10% of screened plasma cells, and/or deletion 17p in >=20% of screened plasma cells are in high risk group. Subjects with other CA or normal cytogenetics are in standard risk group.

For local laboratory FISH (captured on eCRF): Subjects with chromosomal abnormalities (CA) t (4; 14) or t (14;16) and/or deletion 17p detected on FISH are in high risk group. Subjects with other CA or normal cytogenetics are in standard risk group.

Investigational Product (IP)

IP for this study refers to Kyprolis® (carfilzomib).

Informed Consent Date

The informed consent date is the date on which a subject signs the informed consent for this study.

International Staging System (ISS) Stage at Baseline

ISS stage at baseline will be calculated using serum beta-2 microglobulin and serum albumin value collected at baseline based on the criteria published by the International Myeloma Working Group (Greipp 2005).

ISS Stage I: Serum beta-2 microglobulin < 3.5 mg/L and serum albumin ≥ 3.5 g/dL

ISS Stage II: Serum beta-2 microglobulin < 3.5 mg/L and serum albumin < 3.5 g/dL or serum beta-2 microglobulin 3.5–<5.5 mg/L irrespective of the serum albumin

ISS Stage III: Serum beta-2 microglobulin ≥ 5.5 mg/L

Revised International Staging System (R-ISS) Stage at Baseline

R-ISS stage at baseline will be calculated using ISS (serum beta-2 microglobulin and serum albumin value collected at baseline, with ISS calculated as above), cytogenetic

risk group by FISH (central lab data, local lab data), and LDH, based on the criteria published by the International Myeloma Working Group (Palumbo, 2015):

R-ISS Stage I: Serum beta-2 microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL and standard risk CA by FISH and normal LDH

R-ISS Stage II: Not R-ISS I or III

R-ISS Stage III: ISS III and either high risk CA by FISH or greater than normal LDH

Last Dose Date

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

Refractory to prior multiple myeloma therapy

Subject is refractory to a drug received in prior regimens if the data collected on prior multiple myeloma therapy CRF indicates that any of the following criteria is met:

a. Best Response to any regimen containing the drug is stable disease or progressive disease
b. Reason the drug was stopped is progression in any regimen
c. Date of relapse/progression is after start date and within 60 days after stop date of the drug in any regimen

Study Day 1

Study day 1 is the earliest date when carfilzomib, lenalidomide, or dexamethasone is given for subjects who receive at least one dose of study drug, enrollment date for subjects who are enrolled but not treated.

Study Day

The number of days from the study day 1 to a date of interest, inclusive: Study day = (date of interest – 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)

Subject Incidence Rate

The subject incidence rate for a given event is defined as the number of subjects with one or more reported occurrence of the event divided by the number of subjects who had the opportunity to experience the event.

Treatment-emergent Adverse Event

Treatment-emergent adverse events are **defined as any** adverse events **starting on or after** the first dose **of any study drug**, and **up to including** 30 days after the last dose of any study drug **or End of Study date, whichever is earlier**.

6. Analysis Sets

6.1 Safety Analysis Set

The safety analysis set includes all subjects who received at least one dose of study drug.

6.2 Response-Evaluable Analysis Set

The response-evaluable analysis set is defined as subjects who are included in the safety analysis set, have a baseline disease assessment and at least 1 post-baseline disease assessment, or dropped out due to AE prior to the first post-baseline disease assessment.

6.3 Pharmacokinetic Analysis Set

The pharmacokinetic analysis subset includes subjects in the safety analysis set that have sufficient carfilzomib exposure and plasma concentration versus time data for the estimation of PK parameters by a non-compartmental analysis on Day 8 of Cycle 1.

6.4 Pharmacodynamic Analyses Set

The pharmacodynamic analysis subset includes subjects in the safety analysis set that have at least one measurable PDn endpoints. Proteasome activity for the chymotrypsin-like, trypsin-like and caspase-like activities from whole blood will be reported for the collected time points to determine if carfilzomib treatment produces a pharmacodynamic reduction in proteasome activity relative to baseline activity levels.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

A Cohort Safety Review Committee (CSRC) comprised of the lead investigator, selected additional investigators, the sponsor's study medical monitor, and sponsor's drug safety representative will review all available safety data and make recommendations regarding ongoing enrollment and opening of subsequent cohorts during the Dose Evaluation Component. The CSRC will also select the KRd regimens to be evaluated in the Dose-expansion Component.

No formal interim analyses with the purpose of stopping the study early for efficacy or futility will be conducted for this study.

7.2 Primary Analysis

No primary analysis is planned for this study.

7.3 Final Analysis

The final analysis will occur when last subject completes the last assessment in the study (last subject last visit).

Approximately 6 months will be required to enroll subjects in the RRMM Dose evaluation component of the study. Approximately 9 months will be required to enroll subjects in the RRMM dose-expansion component of the study. Subjects will be followed for up to 17 months in order to complete primary safety and efficacy evaluation with up to an additional 12 months of Active follow-up.

It will take up to approximately 12 months to enroll NDMM subjects into Dose-evaluation Cohort 4, review the safety data, and enroll NDMM subjects into the NDMM Dose-expansion Arm 3. Subjects will be followed for up to 17 months on treatment (with an allowed interruption of up to 4.5 months for ASCT), and for up 12 months for Active Follow-up.

Based on the assumption, it is estimated that the final analysis will occur approximately 60 months after the first subject is enrolled.

In preparation for this analysis, data will be subject to ongoing checks for integrity, completeness and accuracy in accordance with the Data Management Plan with the expectation that all outstanding data issues are resolved ahead of the snapshot. The data will be locked to prevent further changes, and a snapshot of the locked database will be used in the analysis.

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. The database will be subject to edit checks outlined in the data management plan (DMP) by Amgen Clinical Data Management (CDM) department. Data inconsistencies and suspicious values will be reviewed and resolved before the database is locked.

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. PK, FISH, MRD and biomarker data will be evaluated by central laboratory transferred to Amgen GSO-DM. The data handling and electronic transfer of data are described in the DMP.

8.3 Handling of Missing and Incomplete Data

Missing and incomplete data will be identified through programmatic checks and a review of the tables and listings created within Biostatistics. Missing and incomplete data will be identified for investigation, and possible resolution, by DM and Global Study Management prior to each planned data snapshot and final database lock.

The handling of dropouts and missing disease status assessments for the efficacy variables is described in the description of the analyses. In general, data will be analyzed as retrieved from the study database and no imputation for missing data will be performed. Exceptions to this rule are detailed as below.

Missing or incomplete dates for adverse events, concomitant medications will be imputed as outlined by the algorithms below.

Table 3. Imputation Rules for Partial or Missing Start Dates

Start Date		Stop Date						
		Complete: *yyyymmdd*		Partial: *yyyymm*		Partial: *yyyy*		
		< 1st dose	≥ 1st dose	< 1st dose *yyyymm*	≥ 1st dose *yyyymm*	< 1st dose *yyyy*	≥ 1st dose *yyyy*	Missing
Partial: *yyyymm*	= 1st dose *yyyymm*	2	1	2	1	n/a	1	1
	≠ 1st dose *yyyymm*		2		2	2	2	2
Partial: *yyyy*	= 1st dose *yyyy*	3	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose

2 = Impute the first of the month

3 = Impute January 1st of the year

4 = Impute January 1st of the stop year

Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

Imputation Rules for Partial or Missing Stop Dates

1. Initial imputation
   - If the month and year are present, impute the last day of that month
   - If only the year is present, impute December 31 of that year
   - If the stop date is entirely missing, assume the event or medication is ongoing
2. If the stop date imputation leads to a stop date that is after the death date, then impute the stop date as the death date.
3. If the stop date imputation leads to a stop date that is before the start date, then there is a data error and do not impute the stop date. (ie, set the stop date as missing).

If a partial or complete stop date is present and the 'ongoing' or 'continuing' box is checked, then it will be assumed that the adverse event or concomitant medication is ongoing. Missing stop dates will not be imputed beyond the subject last contact date or data cutoff date.

Imputation Rules for Partial or Missing Death Dates:

1. 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.
2. If both month and day are missing for death date or a death date is totally missing, do not impute.

The imputed death date will be used in calculation of duration of response, progression-free survival.

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.

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 is < year of enrollment then impute July 1st.

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.

8.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by assessing the incidence of important protocol deviations in each cohort. The clinical study team will identify and document the criteria for important protocol deviations.

8.5 Outliers

Outlier data will not be excluded unless scientifically justified.

PK plasma concentration data will be evaluated for outliers by visual inspection and decisions to re-assay individual samples will be made in accordance with standard PKDM practices.

8.6 Distributional Characteristics

The investigation of distributional characteristics for the proposed summaries of the data is not needed for this study.

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 SAS version 9.3. or later

9. Statistical Methods of Analysis

9.1 General Considerations

In general, the data will be presented in the CSR by considering RRMM patient groups (Cohort 1, Cohort 2 and Arm 2) and NDMM patient groups (Arm 1, Cohort 4 and Arm 3) separately. The data will be presented by each assigned dose cohort and by combined dose cohort in RRMM group and NDMM group. The dose cohort grouping is as follows.

RRMM patient groups:

1. RRMM 56 mg/m^2 (n=10) – Cohort 1
2. RRMM 70 mg/m^2 (n=12) – Cohort 2
3. RRMM 70 mg/m^2 (n=34) – Arm 2
4. RRMM 70 mg/m^2 (n = 46) – Cohort 2 + Arm 2

NDMM patient groups:

1. NDMM 70 mg/m^2 (n=9) – Arm 1
2. NDMM 56/70 mg/m^2 (n=**9**) – Cohort 4 (step up dosing)
3. NDMM 70 mg/m^2 (n=**18**) – Arm 1 + Cohort 4
4. NDMM 56 mg/m^2 (n=**33**) – Arm 3

Summary statistics will be provided for selected study variables. For continuous variables, the number of subjects with non-missing data (n), mean, standard deviation, median, minimum, and maximum will be presented. For discrete variables, the frequency and percentage distribution will be presented. Unless otherwise stated, the denominator for percentages is the number of subjects in the analysis set of interest for the summary. Graphical methods will be used, as appropriate, to illustrate study endpoints.

Confidence interval, when presented, will be constructed at the 95% level. For binomial variable, exact distribution methods will be employed. The distribution of time-to-event endpoints will be summarized by Kaplan-Meier method. Quartiles including median will be estimated by Kaplan-Meier along with their 95% confidence intervals.

Individual subject data recorded on the electronic case report forms (eCRFs) and any derived data will be presented in dataset tabulations.

9.2 Subject Accountability

The following subject disposition information will be summarized as follows

- Number of **enrolled** subjects
- Number of subjects in Safety Analysis Set
- Number (%) of subjects in Response Evaluable Analysis Set
- Number (%) of subjects who discontinued treatment
- Number (%) of subjects who discontinued the study
- Primary reason for study discontinuation
- Primary reason for carfilzomib discontinuation

In addition, the number (%) of subjects who had done the following on-study procedures will be reported: stem cell collection, autologous stem cell transplant, allogeneic stem cell transplant.

The percentages are based on the number of subjects in the Safety Analysis Set.

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. All IPDs will be summarized by category and sub-category for the Safety analysis set.

9.4 Demographic and Baseline Characteristics

9.4.1 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized for the Safety analysis Set:

- Age (years) and age categorized (years) as: < 65, 65 - < 75, and ≥ 75;
- Sex (Male, Female);
- Ethnicity (Hispanic or Latino, Non-Hispanic or Latino)
- Race (White and other categories depending on frequency observed)
- ECOG performance status (0, 1, 2)
- Weight (kg)
- Height (cm)
- Body surface area (m^2)

9.4.2 Medical History

The number (%) of subjects who experienced a prior disease or disorder will be summarized by system organ class and preferred term for the Safety Analysis Set.

9.4.3 Disease Characteristics

The following disease characteristics will be summarized for the Safety Analysis Set:

- Time (months) since initial diagnosis, defined as date of informed consent signed minus date of diagnosis
- Type of measurable disease (SPEP and UPEP, SPEP, UPEP, SFLC only)
- Heavy chain and light chain status
- Plasma cell involvement (%) as assessed with bone marrow assessment (< 50%, ≥ 50%, unknown or missing)
- **Cytogenetic** risk group determined by central laboratory FISH (standard risk, high risk, unknown).
- **Cytogenetic risk group determined by local laboratory FISH (standard risk, high risk, unknown)**
- Baseline beta2 microglobulin (mg/L) (< 3.5, 3.5 - < 5.5, ≥ 5.5 mg/L)
- Baseline albumin (g/dL) (as continuous variable; <3.5, >=3.5 g/dL)
- International Staging System (ISS) stage at diagnosis (I, II, III, unknown)
- ISS stage at baseline (I, II, III, **unknown**)
- Revised ISS at baseline (I, II, III, **unknown**)**: FISH data from central laboratory**
- **Revised ISS at baseline (I, II, III, unknown): FISH data from local laboratory**

9.4.4 Prior Cancer Therapies

The following information related to prior cancer therapy will be summarized for the RRMM subjects in the Safety analysis set:

- Number (%) of subjects with at least one systemic anti-myeloma therapy, transplant, radiation or multiple myeloma-related surgery, respectively.
- Number of regimens of prior treatment (1, 2, etc.) for multiple myeloma
- Best response to most recent prior regimen
- Refractory status to any prior regimen and to most recent prior regimen (bortezomib, lenalidomide, bortezomib and lenalidomide)

9.5 Efficacy Analyses

The primary analysis of efficacy will be based on the Safety Analysis Set. Additionally, the response data (ORR, CRR) may also be analyzed based on the Response-evaluable Analysis Set.

9.5.1 Overall Response Rate and Complete Response Rate

The number (%) of subjects with a best response of sCR, CR, VGPR, PR, SD, PD or NE will be summarized.

Overall response rate is defined as the proportion of subjects for whom the best overall confirmed response is sCR, CR, VGPR, or PR as determined by International Myeloma Working Group Uniform Response Criteria (IMWG-URC) per investigator. The ORR along with the associated 95% exact binomial confidence interval (Clopper-Pearson method) will be determined.

The Complete Response rate (CRR), defined as the proportion of subjects with the best overall confirmed response of complete response (CR) or better, will be determined along with the 95% exact binomial confidence interval.

Same summary and analysis for ORR will be repeated based on ORCA assessments.

9.5.2 Progression-Free Survival

Progression free survival (PFS) is defined as number of months (one month = 30.4 days) between start of treatment and first evidence of documented disease progression or death (due to any cause), whichever occurs first. Disease progression will be determined using IMWG-URC and will be determined by the investigator.

- *PFS = (Earliest date of disease progression, death, or censoring – Date of first dose + 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 systemic anticancer treatment started before documentation of PD or death, 3) death or disease progression after more than 1 missed disease assessment visit, or 4) alive and does not have documentation of PD 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' (www.fda.gov/cder/guidance/7478fnl.htm). For such subjects, the primary analysis of PFS will be right-censored according to the conventions described in Table 4.

The Kaplan-Meier curves will be used to estimate the distribution of PFS and the median and other quartiles in addition to the corresponding two-sided 95% confidence intervals.

Duration of follow-up for PFS will be summarized according to the Kaplan-Meier estimate of potential follow-up also termed "reverse Kaplan-Meier" (Schemper 1996).

Same summary and analysis for PFS will be repeated based on ORCA assessments.

Table 4. Conventions for Censoring for PFS

Situation	Date of Progression or Censoring	Outcome
No baseline disease assessments	Date of first dose	Censored
New anticancer therapy started before documentation of PD or death	Date of last disease assessment prior to start of new anticancer therapy	Censored
Death or PD immediately after more than 1 consecutively missed disease assessment visit	Date of last disease assessment visit before the first missed visit	Censored
Alive and without PD documentation	Date of last disease assessment	Censored
Lost to follow up or withdrawn consent	**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

9.5.3 Duration of Response

Duration of response (DOR) will be calculated for subjects who achieve a PR or better. For such subjects, the duration of overall response is defined as the time (months) from first documentation of response to disease progression or death due to any cause. Dates of progression and censoring will be determined as described for the analysis of PFS.

DOR = (Earliest date of disease progression, death, or censoring - Date of first observation of PR or better before confirmation + 1) / 30.4

Kaplan-Meier methods will be used to estimate the distribution of DOR and the median and other quartiles in addition to the corresponding two-sided 95% confidence intervals; a figure showing the estimated DOR distribution will be provided.

9.6 Safety Analyses

All safety analyses will be based on the Safety Analysis Set.

9.6.1 Adverse Events and Disease-related Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or later will be used to code all adverse events (AEs) to a system organ class (SOC) and a preferred term (PT). The severity of AEs will be coded according to NCI-CTCAE v 4.03.

Treatment emergent adverse events will be summarized based on the number (%) of subjects experiencing events by MedDRA SOC and PT. The denominator for the percentage will be based on the number of subjects in the Safety Analysis Set.

Summaries of the subject incidence of the following TEAEs will be provided by SOC and/ or PT:

- All TEAEs
- TEAEs grade 3 or higher
- Fatal TEAEs
- Serious TEAEs
- TEAEs leading to withdrawal of carfilzomib
- Treatment-related TEAEs
- Treatment-related TEAEs grade 3 or higher
- **Treatment-related fatal TEAEs**
- **Treatment-related serious TEAEs**
- **Treatment-related TEAEs leading to withdrawal of carfilzomib**

Summaries that are displayed by SOC and PTs will be ordered by descending order of incidence of SOC and PT within each SOC for the total group. Summaries of TEAEs, and SAEs will be tabulated by SOC, PT and grade. Summaries of TEAEs, treatment-related AEs, and SAEs will also be provided by descending order of incidence of PTs in the total group

All TEAEs will be included in listings by subject. Listings of AEs determined to be DLTs, SAEs, AEs leading to discontinuation of study and AEs leading to discontinuation of investigational product will be provided.

A summary of the number of deaths and the cause of death, classified by deaths within 30 days of last dose of study drug and deaths more than 30 days after the last dose, will be provided.

Subject incidence of adverse events of interest (standardized MedDRA queries (**SMQ**) and/or Amgen MedDRA queries **(AMQ)**) will also be summarized according to their categories, PTs and grade. The adverse events of interest would include

- Acute renal failure (SMQ Narrow search)
- Cardiac arrhythmias (SMQ Narrow search)
- Cardiac failure (SMQ Narrow search)
- **Cardiomyopathy (SMQ Narrow search)**

- Dyspnoeas (HLT) - MedDRA Search Strategy HLT
- Embolic and thrombotic events, venous (SMQ Narrow search)
- Haematopoietic erythropenia (SMQ Broad search)
- Haematopoietic leukopenia (SMQ Narrow search)
- Haematopoietic thrombocytopenia (SMQ Narrow search)
- Haemorrhage terms (excl laboratory terms) (SMQ Narrow search)
- Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ Narrow search)
- **Hepatitis B virus reactivation (AMQ including PTs: Hepatitis viral, Hepatitis acute, Hepatitis B, Acute hepatitis B, Hepatitis B reactivation, Hepatitis B DNA assay positive, Hepatitis B DNA increased)**
- Hypertension (SMQ Narrow search)
- Infusion reactions – (AMQ Narrow search)
  - event on same date of any Carfilzomib dosing
  - event on same date of first Carfilzomib dosing
- Interstitial lung disease (SMQ Narrow search)
- Ischaemic heart disease (SMQ Narrow search)
- Liver related investigations, signs and symptoms (SMQ Narrow search)
- Myocardial infarction (SMQ Narrow search)
- **Peripheral neuropathy (SMQ Narrow search)**
- **Progressive multifocal leukoencephalopathy (AMQ Narrow search)**
- Pulmonary hypertension (SMQ Narrow search)
- Respiratory failure (SMQ Narrow search)
- Respiratory tract infections (HLGT)
- Reversible posterior leukoencephalopathy syndrome (AMQ Narrow search)
- Torsade de pointes/QT prolongation (SMQ Narrow search)
- Tumour lysis syndrome (SMQ Narrow search)

9.6.2 Laboratory Test Results

Actual values and change from baselines for all chemistry and hematology laboratory parameters will be summarized descriptively for each scheduled visit based on the Safety Analysis Set.

Selected laboratory values will also be categorized according to their NCI-CTCAE (V4.03) toxicity grade. The laboratory parameters of interest for these summaries are:

Hematology	**Serum Chemistry**	
Hemoglobin (decrease)	Alanine transaminase (ALT) (increase)	Albumin (decrease)
Platelets (decrease)	Aspartate transaminase (AST) (increase)	Uric Acid (increase)
White Blood Cell (WBC, increase, decrease)	Alkaline Phosphatase (increase)	Sodium (increase, decrease)
Absolute Neutrophil Count (ANC, decrease)	Total Bilirubin (increase)	Phosphorus (decrease)
Absolute Lymphocyte Count (increase, decrease)	Creatinine (increase)	Potassium (increase, decrease)
	Calcium (increase, decrease)	Magnesium (increase, decrease)
	Glucose (increase, decrease)	

For hypocalcemia and hypercalcemia, serum calcium will be corrected using the formula:

- *Corrected calcium = Serum calcium + 0.8 * (4 – serum albumin) where serum calcium is recorded in mg/dL and serum albumin is recorded in g/dL.*

Shift tables will be presented for the baseline toxicity grade by the worst on-study toxicity grade and the toxicity grade at the end of treatment for the chemistry and hematology parameters with NCI-CTCAE toxicity grading.

9.6.3 Vital Signs

Actual value and change from baseline for weight and vital sign results including blood pressure, pulse, respiratory rate, and temperature will be summarized at each scheduled protocol time point. The mean pre- and post-carfilzomib SBP and DBP on C1 – 6, C12 and C18 will be presented with average change from pre-to post SBP and DBP summarized for each date. Any clinically significant values as assessed by the investigator will be reported as adverse events.

9.6.4 Physical Measurements

The following physical examination will be summarized over time

- ECOG PS
- Weight
- BSA

9.6.5 Electrocardiogram

The ECG measurements from this clinical study were performed at Screening and as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. No summary of ECG results will be provided.

9.6.6 Echocardiogram

Left ventricular ejection fraction (LVEF) as determined by MUGA Scan or Echocardiogram at baseline, during cycle 2 (for dose evaluation subjects), **and** at End of Treatment will be summarized over time. Changes in LVEF from baseline will be presented descriptively.

9.6.7 Exposure to Investigational Product

Extent of exposure to all study treatments (carfilzomib, lenalidomide, and dexamethasone) will be summarized for Safety population

- Duration of treatment (weeks) (carfilzomib in combination with lenalidomide and dexamethasone and each component)
  - Defined as the duration (in weeks) from the date of the first dose of any study drug to the date of the last dose of all study drugs **+ 1**
  - Duration of treatment with carfilzomib / lenalidomide / dexamethasone is defined as duration (in weeks) from the date of the first dose of carfilzomib / lenalidomide / dexamethasone to the date of the last dose of carfilzomib / lenalidomide / dexamethasone + 1
- Total number of treatment cycles received (carfilzomib in combination with lenalidomide and dexamethasone and each component)
  - Defined as the total number of treatment cycles in which at least one dose of any study drug is administered.
  - Number of cycles with carfilzomib / lenalidomide / dexamethasone is defined as the total number of treatment cycles in which at least one dose of carfilzomib / lenalidomide / dexamethasone is administered.
- **Number of treatment cycles received (carfilzomib in combination with lenalidomide and dexamethasone and each component) prior to stem cell transplant (SCT) for subjects who had SCT.**

- **Number of treatment cycles received (carfilzomib in combination with lenalidomide and dexamethasone and each component) for subjects who did not have SCT.**
- Number (%) of subjects dosed by cycle (carfilzomib in combination with lenalidomide and dexamethasone and each component)
- Number of doses of carfilzomib / lenalidomide /dexamethasone administered
  - Defined as the total number of non-zero doses of carfilzomib / lenalidomide /dexamethasone respectively, a subject received during the treatment period of the study.
- Cumulative dose received of carfilzomib (mg and mg/m^2), lenalidomide (mg) / dexamethasone (mg) across all cycles, defined as the cumulative dose of carfilzomib / lenalidomide / dexamethasone, respectively.
- Average dose of carfilzomib (mg and mg/m^2), lenalidomide (mg), and dexamethasone (mg) per administration, defined as the total dose received divided by the number of doses administered
- Relative dose intensity of carfilzomib / lenalidomide / dexamethasone, calculated as the ratio of actual dose intensity to planned dose intensity and expressed as a percent (Appendix A).
- Number (%) of subjects with doses missed, dose delays, dose changes, and dose interruptions for carfilzomib and dose changes and dose delays for lenalidomide and dexamethasone, respectively.

9.6.8 Exposure to Concomitant Medication

Concomitant medications are defined as medications with start date or end date on or after the date of first dose and start date before the date of the last dose + 30 days or are ongoing at the time of first dose. For the purpose of determining if a medication should be noted as a concomitant medication, the imputation rules stated in Section 8.3 will be used. The number and proportion of subjects receiving concomitant medications will be summarized by preferred name as coded by the World Health Organization Drug (WHO DRUG) dictionary. A subject is counted once if he/she reported one or more medications. The summaries will be ordered by descending frequency of preferred name in the total group.

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

PK/PDn analyses will be provided by the Department of Clinical Pharmacology, Modeling & Simulation (CPMS). Actual collection times of PK samples will be recorded to assess the plasma concentration. The PK parameter estimates for carfilzomib will be summarized. Exploratory analyses may be performed to evaluate the relationship between the estimated PK parameters and selected safety, biomarker, or clinical effect

endpoints. In addition, the population modeling program may be used to fit a nonlinear mixed effects model to estimate PK parameters. Details regarding the analyses will be provided in a separate analysis plan by CPMS.

9.7.2 Analyses of Minimal Residual Disease Negative Rate Endpoints

The analysis of MRD[-] rate will not be included in the clinical study report (CSR). The MRD analyses will be summarized in a separate analysis plan by Clinical Biomarkers **& Diagnostics** group.

9.7.3 Analyses of Patient Reported Outcomes and Other Health Related Quality of Life Endpoints

Results from the subject convenience and satisfaction questionnaire will be summarized **descriptively** at Cycle 3 Day 1 and Cycle 18 Day 1 **by presenting the number and percentage of subjects for each item of the questionnaire The denominator for percentage will be based on (1) the number of subjects in the safety analysis set; (2) the number of subjects received carfilzomib at the specified timepoint (Cycle 3 Day 1, Cycle 18 Day 1).**

9.7.4 Analyses of Biomarker Endpoints

Biomarker analyses will be performed by Clinical Biomarkers **& Diagnostics** group and will not be included in CSR.

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. Dose Intensity Calculations

Dose intensity is calculated for each drug component and expressed as an average dose per unit of time. In this study, we choose the time unit to be week.

1. The formula for Actual Dose Intensity (mg/m^2/wk or mg/wk) is defined as:

$$\text{Actual Dose Intensity } (\text{mg/m}^2/\text{wk or mg/wk}) = \frac{\text{Cumulative actual dose } (\text{mg or mg/m}^2)}{\text{Duration of exposure } (\text{wk})}$$

- Cumulative actual dose (mg or mg/m^2) received of carfilzomib and dexamethasone is defined as the cumulative dose of carfilzomib/dexamethasone, respectively, a subject received during the treatment period of the study.
- Duration of exposure (weeks) is defined as

$$\frac{(\text{last dose date} - \text{fist dose date}) + \text{planned interval to next treatment week}}{7 \text{ days}}$$

Carfilzomib dosing schedule and planned interval

Cycle	Cycle Day of Treatment	Dose (mg/m^2)	Interval (Days) to Next Planned Treatment Week (or Completion)
1	Day 1	20	7
	Day 8	56 if Cohort 1; Cohort 4; Arm 3 70 if Cohort 2; Arm 1; Arm2	7
	Day 15	56 if Cohort 1; Cohort 4; Arm 3 70 if Cohort 2; Arm 1; Arm 2	14
2 -18	Day 1	56 if Cohort 1; Arm 3 70 if Cohort 2; Cohort 4; Arm 1; Arm 2	7
	Day 8	56 if Cohort 1; Arm 3 70 if Cohort 2; Cohort 4; Arm 1; Arm 2	7
	Day 15	56 if Cohort 1; Arm 3 70 if Cohort 2; Cohort 4 ; Arm 1; Arm 2	14

Dexamethasone dosing schedule and planned interval

Cycle	Cycle Day of Treatment	Dose (mg)	Interval (Days) to Next Planned Treatment
1 - 8	Day 1	40	7
	Day 8	40	7
	Day 15	40	7
	Day 22	40	7
9 -18	Day 1	40	7
	Day 8	40	7
	Day 15	40	14

Lenalidomide dosing schedule and planned interval

Cycle	Cycle Day of Treatment	Dose (mg)	Interval (Days) to Next Planned Treatment
1 - 18	Day 1 - 7	25	7
	Day 8 – 14	25	7
	Day 15 - 21	25	7

2. The formula for Planned Dose Intensity (mg/m^2/wk or mg/wk) is defined as:

$$\text{Planned Dose Intensity } (\text{mg/m}^2\text{/wk or mg/wk}) = \frac{\text{Cumulative planned dose } (\text{mg/m}^2 \text{ or mg})}{\text{Number of protocol specified treatment weeks}}$$

- Number of protocol specified treatment weeks is the sum of treatment weeks the patient completed. It is counted by 4 weeks for a completed or skipped cycle. For the last cycle, use the following rules to count:

  Carfilzomib

  1 week if the last dose is on Day 1;
  2 weeks if the last dose is on Day 8;
  4 weeks if the last dose is on Day 15;

  Example: Patient's last carfilzomib is on cycle 2 Day 8. The number of protocol specified treatment weeks is D=4x1+2=6 weeks.

  Dexamethasone

  1 week if the last dose is on Day 1;
  2 weeks if the last dose is on Day 8;
  3 weeks if the last dose is on Day 15 in Cycle 1 to 8;
  4 weeks if the last dose is on Day 15 after Cycle 8 or Day 22;

  Lenalidomide

  1 week if the last dose is on Day 1-7;
  2 weeks if the last dose is on Day 8-14;
  4 weeks if the last dose is on Day 15- 21;

- Cumulative planned dose for each drug is the sum of protocol specified doses across the treatment weeks as determined above. Per study treatment regimen on protocol:

  Carfilzomib cumulative planned dose:

For Cohort 1; Arm 3: [20, 56, 56, 0], [56, 56, 56, 0] ……

For Cohort 2, Arm 1; Arm 2: [20, 70, 70, 70], [70, 70, 70, 0] ……

For Cohort 4: [20, 56, 56, 0], [70, 70, 70, 0] ……

Dexamethasone cumulative planned dose:

[40, 40, 40, 40], repeated 7 more times, [40, 40, 40, 0] ……

Lenalidomide cumulative planned dose:

[25, 25, 25, 25, 25, 25, 25], [25, 25, 25, 25, 25, 25, 25], [25, 25, 25, 25, 25, 25, 25], [0, 0, 0, 0, 0, 0, 0], ……

3. Relative dose intensity is calculated as actual dose intensity / planned dose intensity and expressed as a percent.