Statistical Analysis Plan

Protocol Title:	Post-marketing Phase 4 Study to Evaluate Safety, Tolerability, and Efficacy of Kyprolis® (Carfilzomib) in Indian Patients With Relapsed or Refractory Multiple Myeloma: A Prospective, Open label, Non-comparative, Multicenter Study
Short Protocol Title:	Phase 4 Study to Evaluate Safety, Tolerability and Efficacy of Kyprolis (Carfilzomib) in Relapsed or Refractory Multiple Myeloma
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	22 November 2017	
Amendment 1 (v2.0)	3 January 2020	Section 7.1: added section interim analysis. Section 9.6.2: removed 'All AEs, including TEATs, will be included in individual subject listings.' Section 9.6.2: added 'treatment related TEAEs,… will be tabulated'. Section 9.6.3: removed 'the minimums, maximums, last observed values', which is irrelevant or duplicate with lab summaries. Section 9.6.4: removed 'ECOG status scores will also be summarized for each treatment group at baseline and end of study visit.' to be consistent with protocol specification. Section 9.6.7: added 're-started', replaced 'median, and average does per administration' with 'percent of intended dose' to be consistent with protocol language. Section 9.6.9: replaced 'therapies of interest' with 'concomitant medications' to be consistent with protocol language. Section 9.7.1: added section echocardiogram per protocol amendment. Section 10: added section change from protocol-specified analyses per India agency request.
Amendment 2 (v3.0)	22 June 2021	List of Abbreviations: Add NE, RDI and ISS Section 2.1: revised the description of the secondary endpoints.

		Section 3.2: revised the description of the sample size. Section 5: revised the definition of Baseline Section 5: added the definition of Cycle 1 Day 1 (C1D1) Section 5: revised the definition of secondary endpoints including Best overall response, Clinical Benefit Rate (CBR), Duration of response (DOR), Overall Response Rate (ORR), Progression-free survival (PFS), and Time to response (TTR) Section 5: added the definition of Duration of investigational product treatment (/non-investigational product treatment) Section 5: deleted the definition of Enrollment Date Section 5: deleted the definition of First Dose Date Section 5: added the definition of Investigational product and Non-investigational product Section 5: added the definition of Last Subject Last Visit Section 5: added the definition of Relative Dose Intensity (RDI) Section 5: added the definition of Study treatment Section 5: replaced “First Dose Date” with “the first dose date of any study treatment” in the definition of Time (months) since initial diagnosis

		Section 5: revised the definition of Treatment emergent adverse events Section 6.1: added Full Analysis Set Section 6.2: re-organized section numbering Section 8.3: removed “then there is a data error and” from the Imputation rules for partial or missing stop dates Section 8.3: typo corrected in the Imputation for date of initial diagnosis Section 9.1: revised the general considerations Section 9.2: added “completed investigational product and non-investigational products” and “The number and percent of subject enrolled will be tabulated by study site” in Subject Accountability Section 9.2: replaced “study treatment” with “investigational product, non-investigational products” Section 9.4: added “If multiple races have been reported for a subject, the subject will be categorized as other.” Section 9.4: replaced “Bortezomib” with “Bortezomib (Yes, No)” and replaced “Revlimid” with “Revlimid (Yes, No)” Section 9.4: replaced “ISS stage at diagnosis” with “ISS stage at diagnosis (stage I, stage II, stage III, unknown)” Section 9.4: added "As continuous variable" and "As categorical variable..." for Number of prior lines

		Section 9.4: added “derived in RAVE according to” and added additional criteria if albumin is 4 g/dL or greater for Corrected calcium Section 9.4: added “derived in RAVE” for Creatinine clearance Section 9.5: added Table 9-1. Efficacy Endpoint Summary Table Section 9.5.1 & 9.5.2: re-organized section numbering Section 9.6.1: transcribed content to Table 9-4. Safety Endpoint Summary Table Section 9.6.2: updated MedDRA to version 22.0 Section 9.6.2: replaced “withdrawal” with “discontinuation” Section 9.6.2: added “in alphabetical order” in “Subject incidence of all treatment-emergent adverse events (TEAEs)… by system organ class and preferred term in alphabetical order” Section 9.6.2: removed 'and serious' in 'Summaries of treatment-emergent and serious adverse events...and worst grade.' Section 9.6.3: removed Monocytes and Calcium from the selected laboratory endpoints of interest Section 9.6.4: added “Shifts in vital sign value between the baseline and the worst on-study value will be tabulated by treatment group.” Section 9.6.7: replaced 'The number of cycles will be summarized ... intended dose will be summarized by cycle and

		overall.' with 'The number of cycles subjects that received Carfilzomib ... and relative dose intensity will be summarized' Section 9.6.7 & 9.6.8: re-organized section numbering Section 9.7.1: replaced "Echocardiogram" with "Echocardiograms" and deleted the list of ECHO parameters of interest Section 9.7.2: added analyses for COVID-19 impact Section 10: updated the changes from protocol-specified analyses
Amendment 3 (v4.0)	**18 February 2023**	**Section 8.3: move imputation rules for incomplete and partial dates for adverse events and concomitant medications, incomplete/missing death dates, the initial diagnosis date to appendix A1-A3** **Section 9.4: add definition of categorical variable for hemoglobin, platelet count, absolute neutrophil count, albumin, corrected calcium; replace the unit (mm3) of absolute neutrophil count with 10^9/L** **Section 9.5.2: remove "and will be summarized using descriptive statistics"** **Section 9.6.2: add summary of "adverse events leading to discontinuation of lenalidomide" by system organ class/preferred term and preferred term** **Section 9.6.2: add summary of "adverse events leading to discontinuation of any study drug" by system organ class/preferred term and preferred term**

		Section 9.6.2: add "in alphabetical order" to illustrate the order when reporting adverse events by events of interest or system organ class **Section 9.6.2: add summary of "Exposure-adjusted incidence rate … by preferred term." and "All TEAEs will be included in individual subject listings."** **Section 9.6.3: add "The summary of post-baseline grade 3 or 4 laboratory toxicities will be included." and "Incidence of potential Hy's Law cases and listing of subjects with ALT/AST > 3x ULN or Total Bilirubin > 2x ULN will be provided."** **Section 9.6.4: remove "Shifts in vital sign ... by treatment group"** **and add "For the summary of changes from baseline by visit, subjects without a baseline and/or post baseline value will be excluded; values from unscheduled assessments will be excluded."** **Section 9.6.5: add "For the summary of changes from baseline by visit, subjects without a baseline and/or post baseline value will be excluded; values from unscheduled assessments will be excluded."** **Section 9.6.6: add "For the summary of changes from baseline by visit, subjects without a baseline and/or post baseline value will be excluded; values from unscheduled assessments will be excluded."** **Section 9.6.9: remove "Descriptive statistics of average daily dose and duration of usage….to other protocol-required therapies by treatment group." and add "The number and proportion of subjects**

		receiving therapies … by preferred term or category...” **Section 9.7.1: add “For the summary of changes from baseline by visit, subjects without a baseline and/or post baseline value will be excluded; values from unscheduled assessments will be excluded.”** **Section 9.7.2.2: add Section 9.7.2.2 to describe the impact of COVID-19 on Adverse Event** **Section 10: updated the changes from Protocol-specified Analyses** **Appendix A: replace "2" with "n/a" in the case where partial stop date (< 1st dose yyyymm) while partial start date(=1st dose date yyyymm)** **Appendix A: add imputation rules for other protocol-required therapy in appendix A1; imputation rules for new antimyeloma therapy start date in appendix A4; imputation rules for prior multiple myeloma therapy and relapse/progression to prior multiple myeloma therapy date in appendix A5**

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List of Abbreviations

Abbreviation	Explanation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BSA	body surface area
CBR	clinical benefit rate
CR	complete response
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eCRF	electronic case report form
IMWG-URC	International Myeloma Working Group-Uniform Response Criteria
ISS	International Staging System
Kd	Kyprolis in combination with dexamethasone
KM	Kaplan-Meier
KRd	Kyprolis in combination with lenalidomide plus dexamethasone
MedDRA	Medical Dictionary for Regulatory Activities
MR	minimal response
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not Evaluable
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PR	partial response
QTc	corrected QT interval
RDI	Relative Dose Intensity
RRMM	relapsed or refractory multiple myeloma
SAP	statistical analysis plan
sCR	stringent complete response
SD	stable disease
SOC	system organ class

TTR	time to response
US FDA	United States Food and Drug Administration
VGPR	very good partial response
WHODRUG	World Health Organization Drug

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 superseding amendment 1 for study 20160372, Carfilzomib (Kyprolis) dated 29 October 2019. The scope of this plan includes the interim analysis, primary analysis and final analysis that are 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/Estimands

Objectives	Endpoints
Primary	
• To characterize safety associated with the use of Kyprolis under the locally approved label	• The subject incidence, severity, and outcome of treatment-emergent adverse events using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03 including clinically significant laboratory parameter changes over time
Secondary	
• To characterize efficacy of Kyprolis when administered under the locally approved label	Progression free survival (PFS), overall response rate (ORR), clinical benefit rate (CBR), time to response (TTR), and duration of response (DOR) will be evaluated by the investigator as per local standard procedure using International Myeloma Working Group-Uniform Response Criteria (IMWG-URC). • PFS is defined as the time from the first dose of any study treatment until the first documentation of disease progression or death due to any cause, whichever occurs first in the absence of subsequent anticancer therapy and if not > 120 days from the last non-NE, post-baseline disease assessment. • ORR is defined as the proportion of subjects with a best overall response of either stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) • CBR is defined as the proportion of subjects with a best overall response of

	either sCR, CR, VGPR, PR, and minimal response (MR) • TTR is calculated only for subjects who achieve a best overall response of PR or better and is defined as the time from first dose of study treatment to the earliest date a response of PR or better is first achieved and subsequently confirmed • DOR is defined as the time from first evidence of PR or better per IMWG-URC to the earliest of disease progression or death due to any cause for subjects with a best response of PR or better. DOR will be censored as per the primary PFS endpoint.

2.2 Hypotheses and/or Estimations

This phase 4 study is descriptive in nature. There is no hypothesis to be tested. The study will provide descriptive data on the safety profile associated with the use of Kyprolis under the locally approved label as well as its efficacy in terms of PFS, ORR, CBR, TTR, and DOR.

3. Study Overview

3.1 Study Design

This open-label, multicenter, non-comparative phase 4 study of Kyprolis is part of Amgen's post-marketing requirement to the Indian Regulatory Authority. The study population consists of approximately 100 subjects with RRMM and for whom Kyprolis is indicated in accordance with the approved prescribing information in India.

The assignment of subjects to protocol treatment will be decided by the investigator based on clinical evaluation and before the decision to include the subject in this study.

A subject will be considered on study treatment while receiving Kyprolis. If Kyprolis is discontinued, lenalidomide and/or dexamethasone may be continued outside of the study. No crossover between the treatments will be allowed.

Safety assessments include the collection of adverse events and serious adverse events until the last follow-up visit. All subjects will be evaluated by the investigator for multiple myeloma disease response based on local standard procedures. Following disease progression or discontinuation of study treatment, all subjects will have one final assessment that occurs 30 days (+3 days) after the last dose of Kyprolis.

3.2 Sample Size

Approximately 100 subjects with previously treated RRMM will be enrolled as directed by the India Regulatory Authority. A total of 100 subjects is considered to be large enough to rule out an adverse event incidence rate greater than 3.6% if none is observed, with 95% confidence.

3.3 Adaptive Design

Not applicable.

4. Covariates and Subgroups

4.1 Planned Covariates

Not applicable.

4.2 Subgroups

Not applicable.

5. Definitions

Baseline

Unless otherwise specified, the baseline value is defined as the last assessment prior to the administration of the first dose of any study treatment. If a subject doesn't receive any study treatment, the latest value prior to or on enrollment date will be used.

Best overall response

Best overall response will be assessed by investigator according to International Myeloma Working Group Uniform Response Criteria (IMWG-URC). Best overall response for a subject is the best observed post baseline confirmed disease response prior to subsequent anticancer therapy.

Clinical Benefit Rate (CBR)

CBR is defined as the proportion of subjects with a best overall response of either sCR, CR, VGPR, PR, and MR.

Cycle 1 Day 1 (C1D1)

The date of the first dose of investigational product is defined as cycle 1 day 1.

Duration of investigational product treatment (non-investigational product treatment)

Duration of investigational product treatment (non-investigational product treatment) is calculated as the time from the first dose date of investigational product (non-investigational product treatment) to the last dose date of investigational product (non-investigational product treatment).

Duration (weeks) = (last dose date of the drug – first dose date of the drug + 1) / 7

Duration of response (DOR)

DOR is defined as the time from first evidence of PR or better per IMWG-URC to the earliest of disease progression or death due to any cause for subjects with a best response of PR or better. DOR will be censored as per the primary PFS endpoint. The determination of progression disease and censoring date will also follow conventions as in Table 5-1.

DOR (months) = (PD / death – response start date + 1) / 30.4

Investigational product

Investigational product for this study refers to Kyprolis® (carfilzomib).

Last Subject Last Visit

The date when the last subject is assessed or receives an intervention for evaluation in the study.

Non-investigational product

Non-investigational products for this study refer to dexamethasone and lenalidomide.

Overall Response Rate (ORR)

ORR is defined as the proportion of subjects with a best overall response of either stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR).

Progression-free survival (PFS)

PFS is defined as the time from the first dose of any study treatment until the first documentation of disease progression or death due to any cause, whichever occurs first in the absence of subsequent anticancer therapy and if not > 120 days from the last non-NE, post-baseline disease assessment. PFS will be censored at the last non-NE, post-baseline disease assessment or the earlier of the following, where applicable: (a) the last non-NE, post-baseline disease assessment prior to subsequent anticancer therapy, or (b) the last non-NE, post-baseline assessment followed > 120 days later by disease progression or death; otherwise, at first dose date. Disease progression is defined by the IMWG-URC [2016] as assessed by investigator assessment.

PFS time in months: (date of disease progression, death or censoring - first dose date of any study treatment +1)/30.4

The censoring rules for the primary analysis of PFS are described in Table 5-1.

Table 5-1. Conventions for Censoring for PD dates

Situation	Date of Progression or Censoring	Outcome
No PD or death, no new anticancer treatment	Last visit; otherwise, the first dose date of any study treatment	Censored

No PD or death, new anticancer treatment	Last visit prior to new treatment; otherwise, the first dose date of any study treatment	Censored
PD or death > 120 days after last visit	Last visit prior to PD or death; otherwise, the first dose date of any study treatment[a]	Censored
PD or death, no prior new anticancer therapy	Earlier of PD or death[b]	Event
No PD, new anticancer treatment, death	Last visit prior to new treatment; otherwise, the first dose date of any study treatment[b]	Censored

"Visit" refers to a post-baseline non-NE, disease assessment.

[a]If new anticancer therapy starts prior to PD or death, PFS will be censored at the earliest of the following: (a) the last non-NE, post-baseline disease assessment prior to subsequent anticancer therapy, or (b) the last non-NE, post-baseline assessment followed > 120 days later by disease progression or death; otherwise, first dose date.

[b]PFS will be censored if PD or death > 120 days after last non-NE, disease assessment.

Relative Dose Intensity (RDI)

RDI reflects whether the dose intensity of a therapy was implemented as planned. It will be calculated as the ratio of actual dose intensity relative to planned dose intensity.

$$\text{Relative Dose Intensity (\%)} = 100 \times \frac{\text{Actual Dose Intensity}}{\text{Planned Dose Intensity}}$$

Carfilzomib: Actual dose intensity is defined as the actual amount of drug in mg/m^2 delivered to a subject per week of treatment.

$$\text{Actual Dose Intensity } (mg/m^2/\text{week}) = \frac{\text{Cumulative Dose of Carfilzomib } (mg/m^2)}{\text{Number of Weeks of Actual Treatment}}$$

Cumulative dose of Carfilzomib in mg/m^2 will be calculated as the summation of dose received (mg) divided by BSA (m^2). The baseline BSA will be used in the calculation unless the subject experiences a > 20% change in body weight per dosing instruction specified in protocol. When BSA is recalculated, the new BSA will be used in

the calculation thereafter. Number of weeks of actual treatment will be calculated as (last dose date of Carfilzomib – first dose date of Carfilzomib + i)/7, where i is specified as follows:

Arm	Cycle of last carfilzomib infusion (c)	Last infusion day	i
KRd	Cycle 1-12	Day 1, 8	7
		Day 2, 9	6
		Day 15	14
		Day 16	13
	Cycle 13-18	Day 1, 15	14
		Day 2, 16	13
Kd	All cycles	Day 1, 8	7
		Day 2, 9	6
		Day 15	14
		Day 16	13

Planned dose intensity is defined as the planned amount of carfilzomib in mg/m^2 delivered to a subject per week of treatment. It will be calculated as the planned cumulative dose of carfilzomib in mg/m^2 divided by the planned number of weeks for the treatment per protocol based on the corresponding cycle and day of the last carfilzomib infusion. Per protocol, one cycle is 28 days (4 weeks); so, the planned number of treatment weeks will be calculated as 4 x (c-1) + j, where c is the cycle in which the last carfilzomib infusion is given and j is specified in Table 5-2. The planned cumulative dose of carfilzomib is the summation of planned carfilzomib dose per week as specified in Table 5-3.

Table 5-2. Planned number of treatment weeks calculation

Arm	Cycle of last carfilzomib infusion (c)	Last infusion day	j
KRd	1 to 12	Day 1, 2	1

		Day 8, 9	2
		Day 15, 16	4
	13 to 18	Day 1, 2	2
		Day 15, 16	4
Kd	All cycles	Day 1, 2	1
		Day 8, 9	2
		Day 15, 16	4

Table 5-3. Planned Carfilzomib Dose per Week

Arm	Cycle	Week	Protocol Specified Dose for Treatment Week (mg/m^2)
KRd	1	1st	20+20
	2 or later	1st	27+27
	1 to 12	2nd	27+27
	13 to 18	2nd	0
	All cycles	3rd	27+27
	All cycles	4th	0
Kd	1	1st	20+20
	2 or later	1st	56+56
	All cycles	2nd, 3rd	56+56
	All cycles	4th	0

Study treatment

Study treatment is defined as any investigational product(s) or non-investigational product(s) intended to be administered to a study subject according to the study protocol.

Time (months) since initial diagnosis

Time since initial diagnosis is defined as the time (months) from first diagnosis of multiple myeloma to the first dose date of any study treatment or to enrollment date for subjects who did not receive Kyprolis.

Time to response (TTR)

TTR is calculated only for subjects who achieve a best overall response of PR or better and is defined as the time from first dose of study treatment to the earliest date a response of PR or better is first achieved and subsequently confirmed.

TTR (months) = (Response start date - first dose date of study treatment + 1) / 30.4

Treatment emergent adverse events

Treatment emergent adverse events (TEAEs) are defined as Adverse Events that start on or after first dose of any study treatment and up to the End of Study date.

6. Analysis Sets

6.1 Full Analysis Set

The Full Analysis Set will include all enrolled subjects. All subjects will be analyzed according to the treatment arm to which they are enrolled. Full Analysis Set will be used for the medical history, demographic and baseline characteristics analyses.

6.2 Safety Analysis Set

This analysis set includes all enrolled subjects who have received at least one dose of the investigational product. This analysis set will be used for both safety and efficacy endpoints.

7. Planned Analyses

7.1 Interim Analysis

The interim analysis will be performed to support interim report submitted to India agency. The data cutoff date will be determined to submit this report within two years since approval from Central Drugs Standard Control Organization.

All subjects enrolled before data cutoff date will be included. All data by data cutoff date will be used. The analysis scope is specified in section 10.

7.2 Primary Analysis

The primary analysis will occur when the last subject enrolled has had the opportunity to receive the study treatment for at least 9 months.

7.3 Final Analysis

The final analysis will occur when last subject completes the last assessment in the study (last subject last visit) or a study duration up to 3 years, whichever occurs earlier.

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

Rules for handing missing data related to endpoints are described in the endpoint definitions (Section 5) or the description of analyses (Section 9).

The handing of incomplete and partial dates for adverse events and concomitant medications are described in Appendix A.

8.4 Detection of Bias

If applicable, the methods to detect bias are described in the analyses of particular endpoints.

8.5 Outliers

Not Applicable

8.6 Distributional Characteristics

If applicable, the distributional characteristics will be explored for particular endpoints

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, the summaries of medical history, demographic and baseline characteristics will be based on the Full Analysis Set. The summaries of safety and efficacy data will be based on the Safety Analysis Set. All data will be analyzed by treatment groups, including Kyprolis in combination with dexamethasone (Kd) and Kyprolis in combination with lenalidomide and dexamethasone (KRd).

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, received study treatment, completed investigational product, and completed non-investigational products will be summarized by treatment group. The number and percent of subjects who discontinued investigational product, non-investigational products and study will also be tabulated by treatment group, 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. The number and percent of subjects enrolled will be tabulated by study site.

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 by treatment group. If multiple races have been reported for a subject, the subject will be categorized as other.

Baseline demographics and characteristics includes following variables:

- Age
  - As continuous variable
  - As categorical variable: <75, ≥ 75 years and <65, ≥ 65 years
- Sex (Male, Female)
- Race (Asian, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Weight (kg)
- Body surface area (m^2)
- Body mass index
- ECOG performance scale (0, 1, 2)
- Number of prior lines
  - As continuous variable
  - As categorical variable: 1, 2, 3, > 3
- Prior Bortezomib (Yes, No)
- Prior Revlimid (Yes, No)

Baseline organ function and comorbid conditions:

- Time since initial diagnosis (months)
- ISS stage at diagnosis (stage I, stage II, stage III, unknown)
- Left ventricular ejection fraction (%)
- Hepatic function (ALT, AST, Total and direct bilirubin)
- Hemoglobin (g/L) **(as continuous variable; as categorical variable: <105, >=105 (g/L))**
- Absolute Neutrophil Count (**10^9/L**) **(as continuous variable; as categorical variable: <1.5, >=1.5 (10^9/L))**
- Platelet count (10^9/L) **(as continuous variable as categorical variable: <150, >=150 (10^9/L))**

- **Albumin (g/dL) (as continuous variable; as categorical variable: <3.5, >=3.5 (g/dL))**
- Corrected calcium (mg/dL**; as categorical variable: <=11.5, >11.5 mg/dL**): as derived in RAVE according to [serum calcium (mg/dL) + 0.8×(4 - serum albumin (g/dL))] when albumin is less than 4 g/dL. If albumin is 4 g/dL or greater, corrected calcium is equal to calcium.
- Creatinine clearance (CrCl, mL/min; as categorical variable:15 - < 30, 30-<50, 50-<80, >=80 mL/min): as derived in RAVE according to the Cockcroft-Gault formula:

$$\text{CrCl}\,(\text{mL/min}) = \frac{(140\text{-Age})\times\text{Weight(kg)}}{72\times S_{Cr}(\text{mg/dL})}\times(0.85\text{female})$$

9.5 Efficacy Analyses

The analysis of efficacy endpoints will be based on Safety Analysis Set and will be analyzed by treatment groups.

Table 9-1. Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method	Sensitivity Analysis
Progression-Free Survival	• Will be summarized by Kaplan-Meier method to estimate median and quartiles and associated 95% confidence intervals	Not applicable.
Overall Response Rate Clinical Benefit Rate	• Point estimate of ORR/CBR and 95% confidence interval (Clopper-Person method) will be summarized	Not applicable.
Time to Response	• Descriptive summary statistics will be provided	Not applicable.
Duration of Response	• Will be summarized by Kaplan-Meier method to estimate median and quartiles and associated 95% confidence intervals	Not applicable.

9.5.1 Analyses of Primary Efficacy Endpoint(s)/Estimand(s)

Not applicable.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

Safety Analysis set will be used to perform efficacy analyses, which will include following endpoints: PFS, ORR, CBR, TTR, and DOR. All response subcategories used in aforementioned endpoints are determined by investigator according to International Myeloma Working Group Uniform Response Criteria (IMWG-URC) per standard procedure.

PFS will be summarized descriptively using the KM method. 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).

The point estimates of ORR and CBR will be summarized along with exact binomial 95% confidence intervals (Clopper-Person method).

TTR and DOR will also be calculated only for the subjects with confirmed responses. Time to response will be summarized by the non-missing sample size (n), mean, standard deviation, median, minimum, and maximum for responders by treatment group. Kaplan-Meier curves will be used to estimate the distribution of DOR and median and other quartiles in addition to the corresponding two-sided 95% confidence intervals.

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

The analysis of safety endpoint will be based on Safety Analysis Set and will be analyzed by treatment groups.

Table 9-4. Safety Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method (Safety Analysis Set is used)	Sensitivity Analysis
Adverse Event	The subject incidence, severity, and outcome of treatment emergent adverse events will be summarized using NCI CTCAE v. 4.03 including clinical significant laboratory parameter changes over time.	Not applicable.

	Each reported adverse event term will be mapped to a Preferred Term and a System Organ Class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events will be summarized based on the number (%) of subjects experiencing events by MedDRA SOC and preferred term. The denominator for the percentage will be based on the number of subjects in the Safety population. A subject reporting the same treatment-emergent adverse event more than once will be counted only once when calculating 1) within a given SOC, and 2) within a given SOC and preferred term combination. For such cases, the maximum NCI; US - CTCAE 4.03 toxicity grade and strongest causal relationship to study treatment for the event will be used in the incidence calculations. Treatment-emergent adverse events will also be summarized by severity, and seriousness, and by relationship to study treatment.	

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term.

The subject incidence of adverse events will be summarized for all treatment-emergent adverse events, grade 3 or higher TEAE, serious adverse events, adverse events leading to discontinuation of investigational product, and fatal adverse events, and adverse events of interest (EOI). In the event that a subject experiences repeated episodes of the same AE, the subject will be counted once within each system organ class and similarly counted once within each preferred term and the event with the highest severity grade and/or strongest causal relationship to each treatment will be used for purposes of incidence tabulations.

Subject incidence of all treatment-emergent adverse events (TEAEs), treatment related TEAEs, grade 3 or higher TEAEs, serious TEAEs, adverse events leading to discontinuation of investigational product**, adverse events leading to discontinuation of lenalidomide, adverse events leading to discontinuation of any study drug,** and fatal adverse events will be tabulated by system organ class **in alphabetical order** and preferred term in **descending order of frequency**.

In addition, summaries of treatment-emergent AEs, grade 3 or higher TEAEs, serious adverse events, adverse events leading to discontinuation of investigational product, **adverse events leading to discontinuation of lenalidomide, adverse events leading to discontinuation of any study drug,** and fatal adverse events by preferred term in any treatment arm will be provided in descending order of frequency.

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

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

Exposure-adjusted incidence rate will be summarized for all treatment-emergent adverse events, grade 3 or higher TEAEs, serious TEAEs, fatal TEAEs by system organ class and preferred term. Exposure-adjusted incidence rate will also be summarized for adverse events of interest and grade 3 or higher adverse events of interest by preferred term.

All TEAEs will be included in individual subject listings.

All on study deaths will be listed.

9.6.3 Laboratory Test Results

For hematology, chemistry, and other laboratory values, the baseline values and changes from baseline by visit will be summarized descriptively by treatment group.

For the summary of changes from baseline by visit, subjects without a baseline and/or post baseline value will be excluded; values from unscheduled assessments will be excluded. Subjects with missing data for a scheduled assessment time point will be excluded from the summary for that time point. Laboratory results from samples taken > 30 days after the last administration of protocol therapy will be excluded from the laboratory summaries.

Laboratory test results will be graded using the NCI CTCAE (Version 4.03). Shifts in laboratory toxicity grades to outside the normal range will be evaluated for selected laboratory parameters below by assessing the maximum increase and/or decrease observed during the course of study treatment relative to the baseline toxicity grade**. The summary of post-baseline grade 3 or 4 laboratory toxicities will be included. Incidence of potential Hy's Law cases and listing of subjects with ALT/AST > 3x ULN or Total Bilirubin > 2x ULN will be provided.** The selected laboratory endpoints of interest are:

Hematology	**Serum Chemistry**	
Hemoglobin	Albumin	Glucose
Platelet count	ALP	Magnesium
WBC count with differential:	ALT (SGPT)	Phosphorus
Lymphocytes	AST (SGOT)	Potassium
Neutrophils	Corrected Calcium	Total bilirubin
	Creatinine	Uric acid

9.6.4 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 by treatment group. **. For the summary of changes from baseline by visit, subjects without a baseline and/or post baseline value will be excluded; values from unscheduled assessments will be excluded.**

9.6.5 Physical Measurements

The analyses of physical measurements **(height (cm), weight (kg), BSA (m^2))** will include summary statistics at scheduled time points by treatment group. Changes will be calculated relative to the baseline visit. **For the summary of changes from baseline by visit, subjects without a baseline and/or post baseline value will be excluded; values from unscheduled assessments will be excluded.**

9.6.6 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. Summaries over time and/or

changes from baseline over time will be provided for all ECG parameters. **For the summary of changes from baseline by visit, subjects without a baseline and/or post baseline value will be excluded; values from unscheduled assessments will be excluded.**

9.6.7 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to Kyprolis. The number of cycles that subjects received Carfilzomib and number of subjects who received Carfilzomib in each cycle will be summarized. In addition, the duration of therapy, the cumulative dose, the number of Carfilzomib administrations, the average dose per administration, and relative dose intensity will be summarized. The number and percent of subjects with dose modifications (e.g., dose changes and dose interruptions) and reason for modification will be summarized.

9.6.8 Exposure to Non-investigational Product

Descriptive statistics will be produced to describe the exposure to non-Amgen non investigational products (dexamethasone and/or lenalidomide). The cumulative dose, number of cycles, duration of usage, number and percentage of subjects with dose modifications, reasons for modification will be summarized using descriptive statistics.

9.6.9 Exposure to Other Protocol-required Therapy

The number and proportion of subjects receiving therapies of interest will be summarized by preferred term or category as coded by the World Health Organization Drug (WHO DRUG) dictionary by treatment group.

9.6.10 Exposure to Concomitant Medication

The number and proportion of subjects receiving concomitant medications will be summarized by preferred term or category as coded by the World Health Organization Drug (WHO DRUG) dictionary by treatment group.

9.7 Other Analyses

9.7.1 Echocardiogram

Echocardiograms (ECHO) are to be repeated every 6 months (± 2 weeks) from cycle 1 day 1, until end of study, or if clinically indicated. Results of LVEF% will be summarized at each scheduled visit using descriptive statistics and by treatment group. **For the summary of changes from baseline by visit, subjects without a baseline and/or post baseline value will be excluded; values from unscheduled assessments will be excluded.**

9.7.2 Analyses for COVID-19 Impact

9.7.2.1 Impact of COVID-19 on Trial Conduct

Additional summary of disposition impacted by COVID-19 will be summarized. Listing of protocol deviations related to COVID-19 control measures will be provided. Subject incidence of protocol deviation related to COVID-19 will be summarized. Missed investigational product due to COVID-19 will also be summarized.

9.7.2.2 Impact of COVID-19 on Adverse Event

Treatment-emergent serious adverse events occurring on or after the COVID-19 infection will be summarized. Summaries of treatment-emergent AEs, grade 3 or higher TEAEs, serious adverse events, and fatal adverse events identified by COVID-19 standard MedDRA query (SMQ) narrow scope will be provided.

10. Changes From Protocol-specified Analyses

Per India regulatory authority request, an interim report of the study should be submitted within two years of approval from Central Drugs Standard Control Organization. The analysis scope of this report includes subject accountability (section 9.2), Important Protocol Deviations (section 9.3), demographic (section 9.4), adverse events (section 9.6.2), lab test results (section 9.6.3), electrocardiogram (section 9.6.6), exposure to investigational product (section 9.6.7), and echocardiogram results (section 9.7.1).

The snapshot for this analysis will be “as-is”.

Per superseding protocol amendment 1 (section 4.1), PFS is defined as the time from first dose of study treatment until the earliest date of disease progression or death due to any cause. DOR is defined as the time from initial response (sCR, CR, VGPR, or PR) to date of disease progression.

The definition of PFS and DOR in section 2.1 is modified. PFS is defined as the time from the first dose of study treatment until the first documentation of disease progression or death due to any cause, whichever occurs first in the absence of subsequent anticancer therapy and if not > 120 days from the last non-NE, post-baseline disease assessment. DOR is defined as the time from first evidence of PR or better per IMWG-URC to the earliest of disease progression or death due to any cause for subjects with a best response of PR or better. DOR will be censored as per the primary PFS endpoint.

The Full Analysis Set is added in section 6.1 and this analysis set will be used for the medical history, demographic and baseline characteristics analyses.

Per superseding protocol amendment 1 (section 10.3.2.3.7), the number of cycles will be summarized with an additional breakdown of the number of cycles completed, discontinued, and re-started. In addition, the duration of therapy, the cumulative dose, and the percent of intended dose will be summarized by cycle and overall.

Instead of summarizing the number of cycles completed, discontinued, and re-started, summary of number of cycles that subjects received Carfilzomib as well as number of subjects who received Carfilzomib in each cycle will be tabulated. In addition, the percent of intended dose will not be summarized by cycle and overall. Alternatively, relative dose intensity will be summarized (section 9.6.7).

Per superseding protocol amendment 1 (section 10.3.2.3.1), treatment-emergent adverse events are defined as adverse events that start on or after the first day of study treatment and within 30 days of the last day of study treatment.

The definition of treatment-emergent adverse events is modified as adverse events that start on or after first dose of any study treatment and up to the End of Study date.

Impact analyses of COVID-19 on the overall trail conduct **and COVID-19 on adverse event** are added in the statistical analysis plan (section 9.7.2).

Per the superseding protocol amendment 1 (section 10.3.2.3.4), shifts in vital sign value between the baseline and the worst on-study value will be tabulated by treatment group.

Since the worst on-study value for vital sign is not applicable to this study, shifts in vital sign value between the baseline and the worst on-study value will not be summarized.

Per the superseding protocol amendment 1 (section 10.3.2.3.8), descriptive statistics of average daily dose and duration of usage will be produced to describe the exposure to other protocol-required therapies by treatment group.

Instead of summarizing average daily dose and duration of usage, summary of exposure of other protocol-required therapy by the number and proportion of subjects receiving therapies of interest will be provided.

These changes will also be documented in the Clinical Study Report.

11. Literature Citations / References

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12. Appendices

Appendix A. Handling of Dates, Incomplete Dates and Missing Dates

A1. Incomplete and partial dates for adverse events, concomitant medications, other protocol-required therapy will be imputed by following algorithm:

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	n/a	1	n/a	1	1
	≠ 1st dose *yyyymm*		2	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 day of the month

3 = Impute January 1 of the year

4 = Impute January 1 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:

- **For partial stop date mmyyyy, impute the last day of the month.**
- **For partial stop date yyyy, impute December 31 of the year.**
- **For completely missing stop date, do not impute.**

- **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.**
- **If the stop date imputation leads to a stop date that is before the start date, do not impute the stop date. (i.e., set the stop date as missing).**

A2. Incomplete/missing death dates will be imputed by following algorithm:

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.**

A3. The initial diagnosis date will be imputed by following algorithm:

- **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.**

A4. The anti-cancer therapy date will be imputed by following algorithm:

If the start day of new anti-cancer therapy is missing and month and year are not the same as last dosing date of study treatment, it will be assumed to be the first day of the month. If the start day of new anti-cancer therapy is missing and month and year are same as last dosing date of study treatment, the start date will be assumed as last dosing date of study treatment. In other situations, do not impute.

A5. The prior multiple myeloma therapy and relapse/progression to prior multiple myeloma therapy date will be imputed by following algorithm:

If the day of prior multiple myeloma therapy or relapse/progression to prior multiple myeloma therapy is missing but month and year are available, then impute the date to 15th of the month. If month or year is missing or the date is completely missing, do not impute.