Statistical Analysis Plan

Protocol Title:	An Open-label, Phase 2 Study Treating Subjects With First **or Second** Relapse of Multiple Myeloma With Carfilzomib, Pomalidomide, and Dexamethasone (KPd)
Short Protocol Title:	A Study Evaluating Treatment of Multiple Myeloma With Carfilzomib in Combination With Pomalidomide and Dexamethasone
Protocol Number:	20180117
NCT Number:	NCT04191616
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SAP Date:	**Document Version** — **Date** **Original (V1.0)** — 19 December 2019 **Amendment 1 (v2.0)** — 17 March 2021 **Amendment 2 (v3.0)** — 7 September 2022

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	19 December 2019	Original Version
Amendment 1 (v2.0)	17 March 2021	**Changes:** **1.Introduction:** Deleted: Protocol date- 17 September 2019 Added: Protocol date- 13 May 2020 **2.Objectives and endpoints:** **Primary:** Change MRD negative response with MRD negative complete response MRD[-]CR. Change window period ± 2 weeks with ± 4 weeks. **Secondary:** Move overall response as the first endpoint within the secondary endpoints **2.2 Hypotheses and/or Estimation** Change to: The primary hypothesis is that KPd will improve MRD[-]CR rate at 12 months compared with the reference MRD[-]CR rate. This corresponds to evaluating whether the lower bound of the 90% CI of MRD[-]CR rate at 12 months excludes the reference rate of 3%. The secondary hypothesis is that KPd will improve ORR compared with the reference ORR. This corresponds to evaluating whether the lower bound of the 90% CI of ORR excludes the reference rate of 60%. The secondary hypothesis will be assessed only after the primary objective is met. **3.1 Study Design** Added: treating subjects with first or second relapse of multiple myeloma who were

		refractory to prior lenalidomide treatment and may have been exposed to prior daratumumab . Based on available information for this study population, the reference rate for MRD[-]CR was considered to be 3%, while for ORR was considered to be 60%. Added: suspected CR or better Deleted: at least very good partial response. Change window period ± 2 weeks with ± 4 weeks **3.2 Sample Size** Changed to: The sample size was determined based on practical consideration and the intent to optimize the power for testing the primary hypothesis at 1-sided alpha of 0.05. With 85 subjects (safety population), the power for testing the primary hypothesis and secondary hypothesis at 1-sided alpha of 0.05 is expected to be more than 85%. As these estimates are based on data available in the study population, additional scenarios for the experimental arm and power are included in Table 3-1. Updated Table 3-1 **4.2: Subgroups** Added: During maintenance yes vs no **5: Definitions** Added: MRD[-]CR suspected CR

		Change window period ± 2 weeks with ± 4 weeks Added: “Maintaining MRD[-]CR for at least 12 months minus 4 weeks is considered as sustained” in the Sustained MRD[-] CR Rate. Changed 30 days with 30 (+3) days in the “ Treatment-emergent Adverse Event” **6.1.2 MRD Evaluable Analysis Set** Added: At baseline **7.1 Sustained MRD analysis** Changed durable MRD analysis with sustained MRD analysis **9. Statistical Methods of Analysis** Changed 80% CI to 90% CI throughout **9.5 Efficacy Analysis** Deleted: “The data will include the MRD results from bone marrow samples obtained from subjects with a response of VGPR or better obtained no earlier than 8 months and no later than 12 months plus 2 weeks after enrollment” from the table 9-1 Added: MRD[-]CR Suspected CR Change window period ± 2 weeks with ± 4 weeks **9.5.1 Analyses of Primary Efficacy Endpoint(s)** Added: MRD[-]CR Suspected CR

		Change window period ± 2 weeks with ± 4 weeks **9.5.2 Analyses of Exploratory Efficacy Endpoint(s)** Added: "in the MRD Evaluable Analysis Set" "In addition, similar analysis may be done for MRD response at 12 months and 24 months landmarks, if appropriate" in the PFS by depth of MRD response at: $10^{-4,}$ $10^{-5,}$ $10^{-6,}$ Updated: "The **Cox** proportional hazard model will also be fitted with MRD[-] status or MRD[-]CR status as the **time-dependent** covariate to explore the correlation between MRD status and PFS."
Amendment 2 (v3.0)		**Changes:** **List of Abbreviations** Added: Abbreviations of MM and sCR **1. Introduction** Deleted: Protocol date- 13 May 2020 Added: Protocol date- 16 May 2022 **2.1 Objectives and Endpoints/Estimands** Updated: Primary Endpoint was changed from Estimate the rate of minimal residual disease negative complete response (MRD[-]CR) at 12 months landmark to Estimate the overall response rate (ORR) per the changes of protocol amendment 4 Key Secondary Endpoint was changed from Estimate the overall response rate

		(ORR) to Estimate the rate of minimal residual disease negative complete response (MRD[-]CR) at 12 months landmark per the changes of protocol amendment 4 Updated "sustained MRD[-]CR at a sensitivity of 10 5 using NGS based method in the bone marrow at 24 months ± 4 weeks from start of treatment and calculated only within the subjects who reached MRD[-]CR in the time window for **key secondary endpoint** assessment" per the changes of protocol amendment 4 Updated "[redacted] levels in **peripheral blood** at 12 and 24 months (± 4 weeks)" per the protocol Deleted: Removed Estimate ORR at 12 months landmark from secondary endpoint from Secondary Endpoint per the changes of protocol amendment 4 Deleted the typo "response" from "Estimate the frequency of sustained MRD[-]CR" Deleted the typo "Percentage of" from "MRD[-] below the threshold of 10^{-4}, 10^{-5}, and 10^{-6} by NGS-based method at time of suspected CR or better" Removed Evaluate the correlation of PFS in high versus standard risk subject populations from Exploratory Endpoint per the decision of study team **2.2 Hypotheses and/or Estimations** Updated: "The primary hypothesis is that KPd will improve **ORR by** evaluating whether the lower bound of the 90% CI of **ORR** excludes the reference rate of **60**%. The secondary hypothesis is that KPd will

		improve **MRD[-]CR rate at 12 months by** evaluating whether the lower bound of the 90% CI of **MRD[-]CR rate at 12 months** excludes the reference rate of **3**%.“ per the changes of protocol amendment 4 Added: “Both exact binomial 2-sided 90% and 95% CIs will be generated around the point estimate for each of these endpoints.” per the changes of protocol amendment 4 **3.1 Study Design** Added: Added “or other anti-CD38 antibody therapy” per the protocol Updated: Updated “**the reference rate listed in the protocol section 4.2 indicates the ORR was considered to be 60%, while for MRD[-]CR was considered to be 3%.**” per the changes of protocol amendment 4 **3.2 Sample Size** Updated: Updated “The sample size was determined based on **feasibility** and the intent to optimize the power for testing the primary hypothesis at 1-sided alpha of 0.05.” per the protocol Updated “As these estimates are based on **recent data available in the study population (eg, sub-populations within clinical trials CANDOR and A.R.R.O.W.)**” per the changes of protocol amendment 4 Primary Hypothesis and Secondary Hypothesis was changed in Table 3-1 Power for Hypothesized Treatment Effect per the changes of protocol amendment 4

		Added: Added “In late 2021, enrollment was discontinued after 54 subjects were enrolled due to practical consideration.” per the changes of protocol amendment 4 Added “including those based on the actual number of subjects who received at least one dose of carfilzomib (52 subjects)” per the changes of protocol amendment 4 Sample size 52 for Primary Hypothesis and Secondary Hypothesis was added in Table 3-1 Power for Hypothesized Treatment Effect per the changes of protocol amendment 4 **4.2 Subgroups** Added: Added “ORR and PFS will be examined for the below subgroup analysis.” for the clarification Added “When there is not a sufficient number of subjects in the subgroup, i.e., less than 10% of the whole population, the subgroup analysis will not be conducted” for the clarification Additional subgroups added for ORR per the decision of study team • Cytogenetic risk measured by FISH (high risk (t(4;14), t(14;16), deletion 17p), standard risk) • R-ISS (stage I, stage II, stage III) • Prior anti-CD38 exposure (yes, no) • Refractory to prior anti-CD38 treatment (yes, no) • Prior bortezomib exposure (yes, no) • Refractory to prior bortezomib treatment (yes, no) Added subgroup analysis for PFS per the decision of study team • prior carfilzomib exposure (yes, no)

		• number of prior lines of therapy (1, 2) • timing of lenalidomide refractoriness (during maintenance: yes, no) • Cytogenetic risk measured by FISH (high risk (t(4;14), t(14;16), deletion 17p), standard risk) • R-ISS (stage I, stage II, stage III) • Prior anti-CD38 exposure (yes, no) • Refractory to prior anti-CD38 treatment (yes, no) • Prior bortezomib exposure (yes, no) • Refractory to prior bortezomib treatment (yes, no) Deleted: Deleted “Other endpoints may also be examined for these subgroups If appropriate.” per the decision of study team **5. Definition** Baseline Added: Added “of any study treatment” for clarification Cytogenetic Risk group as determined by Fluorescent in Situ Hybridization (FISH) Added definition for clarification Duration of response Updated: Updated “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.” per the DES IMWG version 8

		End of Study Added: Added “for evaluation in the study (ie, last subject last visit), including any additional parts in the study (eg, long-term follow-up, additional antibody testing), as applicable.” per the protocol International Staging System (ISS) Stage at Baseline Added definition for clarification Last known to be alive date Updated for clarification: • Date First Taken, Date Last Taken on Concomitant Medications, and Other Protocol Required Therapy CRFs • Date Performed on ECOG Performance Status, Vital Signs, Echocardiogram, Electrocardiogram, Transfusions, Surgery, Procedure, Bone Marrow Biopsy - Multiple Myeloma, Bone Marrow Aspirate - Multiple Myeloma, MRI, PET-CT, CT and X-ray CRFs • Date Collected on Male Reproductive Status, Reproductive Status and Pregnancy Test (Local Lab), Chemistry (Local Lab), Hematology (Local Lab), Coagulation (Local Lab), Immunology (Local Lab) CRFs • Start Date, Stop Date on Investigational Product Administration (Carfilzomib), Non-Investigational Product Administration (Dexamethasone), Investigational Product Administration (Pomalidomide), and Non-Investigational Product Administration (Pomalidomide) CRFs • Start date, Stop date on Anti-Myeloma / Anti-Cancer Therapies CRF • Assessment Date for MRD sample • Date Collected on Pathology FISH CRF • Date of Assessment on Myeloma Response CRF

		• Date of Last Menstrual Period and Breastfeeding Start in Reproductive Status and Pregnancy Test (Local Lab) CRF • COVID-19 Start Date in Confirmed COVID-19 Status CRF • Date Decision Was Made to End Investigational Product on End of Investigational Product Administration (Carfilzomib), Date Decision Was Made to End Non-Investigational Product on End of Non-Investigational Product Administration (Dexamethasone), Investigational Product Administration (Pomalidomide), and End of Non-Investigational Product Administration (Pomalidomide) CRFs, where the Primary Reason for ending treatment is not Death or Lost to follow-up MRD[-]CR Rate at 12 Months Landmark Updated: Updated "no later than 12 months plus 4 weeks after **the start of study treatment**." per the protocol Added: Added "The sensitivity analysis of MRD[-]CR Rate at 12 months landmark will be based on MRD Evaluable Analysis Set." for clarification MRD[-]CR Rate at Any Time During Therapy Added: Added "The sensitivity analysis of MRD[-]CR Rate at any time during therapy will be based on MRD Evaluable Analysis Set." for clarification Overall Survival (OS) Added "OS = (Death date or date of censoring if censored – start **of any study** treatment date + 1) / 30.4" for clarification Progression Free Survival (PFS)

		Changed to: Updated “PFS is defined as the time from the first dose date 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 > 70 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 > 70 days later by disease progression or death; otherwise, at first dose date. Disease progression is based on the IMWG-URC [2016].” per the DES IMWG version 8 Relative Dose Intensity Updated Updated “Day 15” to “Day 28” for clarification Sustained MRD[-]CR Rate at 24 months Updated: Updated “after achieving MRD[-]CR status in the time window of **Key Secondary** endpoint assessment.” per the changes of protocol amendment 4 Revised International Staging System (R-ISS) Stage at Baseline Added definition for clarification Time to Response Added “Time to Response = (response start date – start **of any study** treatment date + 1) / 30.4” for clarification Treatment-emergent Adverse Event Deleted: Removed “investigational product as determined by “Did event start before

		first dose of investigational product" equal to "No" or missing on the Events eCRF" "(+3)" "investigational product" per the decision of study team Changed to: Updated "Treatment-emergent adverse event: Events categorized as Adverse Events (AEs) starting on or after first dose of any study treatment and up to and including 30 days after the last dose of any study treatment excluding events reported after End of Study date." per the decision of study team Primary completion date Deleted definition per the decision of study team **6.4 Modified Safety Analysis Set** Added: A subset of Safety Analysis Set excluding subjects who are impacted by COVID-19 was added per the decision of study team **6.5 Per Protocol Set(s)** Deleted: Deleted "105 Completed 2 Full Cycles of Daratumumab" from major inclusion criteria per the protocol **7.1 Primary Analysis** Updated: Updated "The primary analysis will be triggered **12 months after the last subject enrollment"** per the changes of protocol amendment 4 **7.2 Sustained MRD Analysis** Added: Added "durable" per the protocol

		7.3 Data Review Team Early Stopping Guidelines Changed title from Interim Analysis and Early Stopping Guidelines to Data Review Team Early Stopping Guidelines for clarification **8.3 Handling of Missing and Incomplete Data** Added: Added "No imputation for missing data **of outcomes** will be performed" for clarification Added "The handling of Incomplete dates for the start and stop of adverse event, concomitant medications, **new antimyeloma therapy, death, prior multiple myeloma therapy, and relapse/progression to prior multiple myeloma therapy** are described in Appendix A" per the decision of study team Updated: Updated "Sensitivity analyses **might be needed** to evaluate the robustness of the primary analysis." per the protocol Added: Added "stop" of adverse event described in "Appendix A" for clarification **9.1 General Considerations** Added: Added "The evaluation of whether the key secondary objective was met will follow a fixed-sequence approach using the 90% exact confidence interval: the key secondary objective is met only after the primary objective is met." per the changes of protocol amendment 4 **9.2 Subject Accountability** Added:

		• Number (%) of subjects who discontinued each study treatment (carfilzomib, dexamethasone, pomalidomide) due to COVID-19 control measures" was added the GDE-409220 • Number of subjects enrolled but not dosed was added for clarification Updated: • Number of subjects screened but not **enrolled** (screen failures) was updated to correct the typo **9.3 Important Protocol Deviations** Added: Added Summary of IPD listing including COVID-19 related IPD per the the GDE-409220 **9.4 Demographic and Baseline Characteristics** Updated per the decision of study team: - Race **(If multiple races have been reported for a subject, the subject will be categorized as multiple race)** - Region **(Europe, Non-Europe)** - Age (years) (as continuous variable; as categorical variable: 18 to < 65, 65 to < 75, 75 to < 85, ≥ 85 years; **<65, >=65; 18-<65, 65-<75, >=75**) - Cardiopulmonary history (yes, no) <**by diagnosis category**>, no) - Prior lenalidomide treatment (yes, no) - Refractory to prior lenalidomide treatment (yes, no) - Prior PI treatment (yes, no) - Prior anti-CD38 exposure (yes, no) - Refractory to prior anti-CD38 treatment (yes, no) - Prior bortezomib treatment (yes, no) - Refractory to prior bortezomib treatment (yes, no) - Cytogenetic risk measured by FISH (high risk (t(4;14), t(14;16) ,deletion 17p), standard risk, missing) - Prior tobacco use (yes, no)

		- Albumin (g/dL) (as continuous variables; as categorical variable: <3.5, >=3.5) - Time since last relapse (months) **9.5 Efficacy Analyses** Updated: Updated "The primary analyses will be based on the safety analysis set, **while sensitivity analyses will use different population analysis set listed in table 9-1.**" for the clarification Updated Overall Response Rate (ORR) in Table 9 1. Primary Efficacy Endpoint Summary Table per the changes of protocol amendment 4 Updated MRD[-]CR at a sensitivity of 10^{-5} using next generation sequencing (NGS)-based method in the bone marrow at 12 months ± 4 weeks from start of treatment in Table 9 2. Secondary Efficacy Endpoint Summary Table per the changes of protocol amendment 4 Updated Sensitivity analyses for OS in Table 9 2. Secondary Efficacy Endpoint Summary Table for clarification Deleted: Deleted Overall Response Rate at 12 months landmark in Table 9 2. Secondary Efficacy Endpoint Summary Table per the changes of protocol amendment 4 **9.5.1 Analyses of Primary Efficacy Endpoint(s)/Estimand(s)** Added: Overall Response Rate (ORR) Added "The lower bound of the 90% exact binomial CI is evaluated whether it is larger than the reference ORR. If that happens, then the primary objective is

		met." per the changes of protocol amendment 4 **9.5.2 Analyses of Secondary Efficacy Endpoint(s)** MRD[-] CR at sensitivity of 10-5 using NGS-based method in the bone marrow at 12 months ± 4 weeks from start of treatment. Added: Added "If the primary objective is met, then the lower bound of the 90% exact binomial CI is greater than the reference MRD[-]CR rate. If that happens, the key secondary objective is met." per the changes of protocol amendment 4 MRD[-] response at a sensitivity of 10-5 using NGS based method in the bone marrow at any time during therapy Added: Added "It will be analyzed using the same method as described for the **key secondary** endpoint." per the changes of protocol amendment 4 Deleted: Deleted Overall Response Rate (ORR) by 12 months per the changes of protocol amendment 4 Added: PFS Added "The subcategory of death with the primary reason of COVID-19 infection or COVID-19 pneumonia will be included in the PFS events." per the decision of study team **9.5.3 Analyses of Exploratory Efficacy Endpoint(s)** Added: Added "When there is not a sufficient number of subjects in the subgroup, i.e., less than 10% of the MRD population, the analysis will not be conducted." for clarification

		Deleted: Deleted The correlation PFS in high vs standard risk subject's population per the decision of study team **9.6 Safety Analyses** Added: Added 9.6.9 Exposure to Non-investigational Product for clarification **9.6.2 Adverse Events** Deleted: Removed "All AEs, including TEAEs, will be included in individual subject listings. All on study deaths will be listed." per the decision of study team **9.6.3 Laboratory Test Results** Deleted for clarification: Nucleated RBC Deleted "(+3)" from > 30 days Removed "All available laboratory results will be included in the subject data listings." per the decision of study team **9.6.8 Exposure to Investigational Product** Added: Added "Descriptive statistics will be produced to describe the exposure to investigational product." for clarification Added "If the reason for dose modification is COVID-19 control measures which is recorded in the specified filed (Other) on the CRF, then the number (%) with COVID-19 control measures will also be presented. The summary will include the following:" per the GDE-409220 Updated:

		Changed study treatments to investigational product for clarification Added a new section for clarification **9.6.9 Exposure to Non-investigational Product** **9.7 Other Analyses** Deleted: Deleted “and RVEF” per the decision of study team **10. Changes From Protocol-specified Analyses** Added: Deviations in superseding protocol amendment 3 Analyses for COVID-19 impact Additional subgroup analysis Additional subgroups **Appendices:** Added: Appendix A. Handling of Dates, Incomplete Dates and Missing Dates

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List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AUC	area under the concentration-time curve
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
C_{max}	maximum observed concentration
COA	clinical outcomes assessment
CR	complete response
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CT	computed tomography
D	Dexamethasone
Dara-IV	daratumumab IV
Dara-SC	daratumumab for subcutaneous administration
Dex	Dexamethasone
DLCO	diffusing capacity of the lungs for carbon monoxide
DRT	data review team
ECG	Electrocardiogram
Echo	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
FDA	Food and Drug Administration
FEV	forced expiratory volume
FISH	fluorescence in situ hybridization
HbA1c	hemoglobin A1c
HDL	lactate dehydrogenase
IB	Investigator's Brochure
ICF	informed consent form
IFE	Immunofixation
Ig, IgA, IgD, IgE, IgM	immunoglobulin, immunoglobulin A, immunoglobulin D, immunoglobulin E, immunoglobulin M

IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IMWG-URC	International Myeloma Working Group Uniform Response Criteria
IV	Intravenous
K	Carfilzomib
KPd	carfilzomib in combination with pomalidomide and dexamethasone
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LTFU	long-term follow-up
mAb	monoclonal antibody
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MM	**multiple myeloma**
MRD	minimal residual disease
MRD[-]	minimal residual disease negative
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NDMM	newly diagnosed multiple myeloma
NGS	next-generation sequencing
ORR	overall response rate
OS	overall survival
ORCA	Onyx Response Computer Algorithm
Pd	pomalidomide and dexamethasone
PD	progressive disease
PDn	pharmacodynamics
PET/CT	positron emission tomography/computed tomography
PFS	progression-free survival
PFT	pulmonary function tests
PI	proteasome inhibitor
N/A	Not Applicable
sCR	**stringent complete response**

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study 20180117, Carfilzomib dated **16 May 2022**. The scope of this plan includes the primary analysis and the final analysis that is planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints/Estimands

Objectives	Endpoints
Primary	
• **Estimate the overall response rate (ORR)**	• **overall response defined as the best overall confirmed response of partial response (PR), very good partial response (VGPR), complete response(CR), or stringent complete response(sCR) by Independent Review Committee (IRC) per International Myeloma Working Group Uniform Response Criteria (IMWG-URC)**
Key Secondary	
• **Estimate the rate of minimal residual disease negative complete response (MRD[-]CR) at 12 months landmark**	• **MRD[-]CR at a sensitivity of 10^{-5} using next generation sequencing(NGS)-based method in the bone marrow at 12 months ± 4 weeks from start of treatment**
Secondary	
• Describe the safety and tolerability of carfilzomib combined with dexamethasone and pomalidomide	• subject incidence of treatment-emergent adverse events
• Estimate the frequency of best MRD[-] response in KPd	• MRD[-] response at a sensitivity of 10^{-5} using NGS-based method in the bone marrow at any time during therapy
• Estimate the frequency of sustained MRD[-]CR	• sustained MRD[-]CR at a sensitivity of 10^{-5} using NGS-based method in the bone marrow defined as subjects that maintain MRD[-]CR 12 months or more after achieving MRD[-]CR status, disregarding when the first MRD[-]CR was reached
• Estimate the frequency of sustained MRD[-]CR at landmark 24 months	• sustained MRD[-]CR at a sensitivity of 10^{-5} using NGS-based method in the bone marrow at 24 months ± 4 weeks from start of treatment and calculated only within the subjects who reached MRD[-]CR in the time window **for key secondary endpoint** assessment

• Estimate duration of response, time to response, progression-free survival (PFS), and overall survival (OS)	• duration of response, defined as time from first date of PR or better to date of disease progression or death due to any cause • time to response, defined as time from start of treatment to first date of PR or better • PFS defined as time from start of treatment until progression or death from any cause • OS, defined as time from start of treatment until death from any cause
• Estimate rate of CR or better	• best overall confirmed response of CR or better

Objectives	Endpoints
Exploratory	
• Assess the depth of MRD	• MRD[-] below the threshold of 10^{-4}, 10^{-5}, and 10^{-6} by NGS-based method at time of suspected CR or better
• Evaluate the correlation between MRD status and PFS	• PFS by depth of MRD response at: 10^{-4}, 10^{-5}, and 10^{-6}
• Evaluate pharmacokinetics (PK) and pharmacodynamics (PDn) of carfilzomib when administered in combination with pomalidomide and dexamethasone	• carfilzomib PK parameters (maximum observed concentration [C_{max}], area under the concentration-time curve [AUC], half-life [$t_{1/2}$]) • carfilzomib PDn parameters (inhibition of proteasome activity relative to baseline)
• Assess pharmacogenetics in subjects receiving KPd	• CD138 selection of tumor cells at screening and disease progression
• Analyze exploratory biomarkers	• [redacted] levels in **peripheral blood** at 12 and 24 months (± 4 weeks)

2.2 Hypotheses and/or Estimations

The primary hypothesis is that KPd will improve **ORR by** evaluating whether the lower bound of the 90% CI of **ORR** excludes the reference rate of **60**%. The secondary hypothesis is that KPd will improve **MRD[-]CR rate at 12 months by** evaluating whether the lower bound of the 90% CI of **MRD[-]CR rate at 12 months** excludes the reference rate of **3**%. The secondary hypothesis will be assessed only after the primary objective is met. **Both exact binomial 2-sided 90% and 95% CIs will be generated around the point estimate for each of these endpoints.**

3. Study Overview

3.1 Study Design

The study is an open-label, phase 2 trial treating subjects with first or second relapse of multiple myeloma who were refractory to prior lenalidomide treatment and may have been exposed to prior daratumumab **or other anti-CD38 antibody therapy**. Based on available information for this study population, **the reference rate listed in the protocol section 4.2 indicates the ORR was considered to be 60%, while for MRD[-]CR was considered to be 3%.**

Subjects may receive treatment until progression. Myeloma disease status will be monitored locally for response and progression per International Myeloma Working Group (IMWG) criteria (Kumar et al, 2016) every 28 ± 7 days from cycle 1 day 1 until

confirmed progressive disease (PD), death, lost to follow-up, or withdrawal of full consent (whichever occurs first), regardless of cycle duration, dose delays or treatment discontinuation.

Subjects with a suspected CR or better will have a bone marrow for minimal residual disease (MRD) assessment at 12 and 24 months (± 4 weeks) from start of treatment (unless an MRD assessment was performed within 4 months before planned assessment).

Subjects who end study drug(s) without confirmed PD are required to complete disease response assessments and report new antimyeloma treatment every 28 ± 7 days until first subsequent antimyeloma treatment, death, lost to follow-up, withdrawal of full consent, confirmed PD, or end of study, whichever occurs first. Subjects, who discontinue treatment and either start new antimyeloma treatment or have PD, will enter long-term follow-up every 12 weeks until death or end of study.

3.2 Sample Size

The sample size was determined based on **feasibility** and the intent to optimize the power for testing the primary hypothesis at 1-sided alpha of 0.05. With 85 subjects (safety population), the power for testing the primary hypothesis and secondary hypothesis at 1-sided alpha of 0.05 was expected to be more than 85%. **In late 2021, enrollment was discontinued after 54 subjects were enrolled due to practical consideration.** As these estimates are based on **recent data available for the study population (eg, sub-populations within clinical trials CANDOR and A.R.R.O.W.)**, additional scenarios**, including those based on the actual number of subjects who received at least one dose of carfilzomib (52 subjects),** for the experimental arm and power are included in Table 3-1.

Table 3-1. Power for Hypothesized Treatment Effect

Hypothesis	Sample Size	H0	H1	Power
Primary	85	**ORR ≤ 60%**	**ORR ≥ 75%**	**90.4%**
	85	**ORR ≤ 60%**	**ORR ≥ 80%**	**99.3%**
	52	**ORR ≤ 60%**	**ORR ≥ 75%**	**69.2%**
	52	**ORR ≤ 60%**	**ORR ≥ 80%**	**91.8%**
Secondary	85	**MRD[-]CR rate at 12 months ≤ 3%**	**MRD[-]CR rate at 12 months ≥ 10%**	**86.4%**

	85	**MRD[-]CR rate at 12 months ≤ 3%**	**MRD[-]CR rate at 12 months ≥ 12%**	**95.1%**
	52	**MRD[-]CR rate at 12 months ≤ 3%**	**MRD[-]CR rate at 12 months ≥ 10%**	**60.5%**
	52	**MRD[-]CR rate at 12 months ≤ 3%**	**MRD[-]CR rate at 12 months ≥ 12%**	**76.3%**

ORR = overall response rate; MRD[-]CR = minimal residual disease negative complete response

3.3 Adaptive Design

Adaptive design is not applicable for this study.

4. Covariates and Subgroups

4.1 Planned Covariates

The relationship of covariates to efficacy endpoints will be explored if appropriate.

4.2 Subgroups

ORR and PFS will be examined for the below subgroup analysis. When there is not a sufficient number of subjects in the subgroup, i.e., less than 10% of the whole population, the subgroup analysis will not be conducted:

- prior carfilzomib exposure (yes, no)
- number of prior lines of therapy (1, 2)
- timing of lenalidomide refractoriness (during maintenance: yes, no)
- **Cytogenetic risk measured by FISH (high risk (t(4;14), t(14;16), deletion 17p), standard risk)**
- **R-ISS (stage I, stage II, stage III)**
- **Prior anti-CD38 exposure (yes, no)**
- **Refractory to prior anti-CD38 treatment (yes, no)**
- **Prior bortezomib exposure (yes, no)**
- **Refractory to prior bortezomib treatment (yes, no)**

5. Definitions

Baseline

The baseline value is defined as the last assessment prior to the first dose **of any study treatment**. Absolute change from baseline will be defined as (post baseline value - baseline value). Relative change from baseline will be defined as (post baseline value – baseline value)/baseline value * 100%.

Complete Response Rate (CRR)

CRR is defined as the proportion of subjects whose best overall response is sCR or CR.

Cytogenetic Risk group as determined by Fluorescent in Situ Hybridization (FISH)

The FISH data will be used to determine the cytogenetic risk group as following:

High risk group: Subjects who have the cytogenetic abnormalities t(4;14) or t(14;16), and/or deletion 17p.

Standard risk group: Subjects who do not have any of the cytogenetic abnormalities t(4;14), t(14;16) and deletion 17p.

Missing: Subjects who cannot be identified as high risk nor standard risk.

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 PFS endpoint. Please see Table 5-1

DOR = [(PD or death date whichever occurs first) or date of censoring if censored - response start date + 1] / 30.4.

End of Study

The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention **for evaluation in the study (ie, last subject last visit), including any additional parts in the study (eg, long-term follow-up, additional antibody testing), as applicable.** The study will end 4 years after the last subjects is enrolled in the study.

International Staging System (ISS) Stage at Baseline

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

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

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

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

Last known to be alive date

Last known alive date is the latest date of the following dates before death date:

- Date First Taken, Date Last Taken on Concomitant Medications**, and Other Protocol Required Therapy** CRF**s**
- Date Performed on ECOG Performance Status, Vital Signs, Echocardiogram, Electrocardiogram, Transfusions, Surgery, Procedure**, Bone Marrow Biopsy - Multiple Myeloma, Bone Marrow Aspirate - Multiple Myeloma, MRI, PET-CT, CT and X-ray** CRFs
- Admission Date, Discharge Date on Hospitalizations, CRF Date of Examination on Physical Measurement CRF
- Date Collected on **Male Reproductive Status,** Reproductive Status and Pregnancy Test (Local Lab), Chemistry (Local Lab), Hematology (Local Lab), Coagulation (Local Lab), **Immunology (Local Lab)** CRFs
- Start Date, Stop Date on Investigational Product Administration **(Carfilzomib), Non-Investigational Product Administration (Dexamethasone), Investigational Product Administration (Pomalidomide), and Non-Investigational Product Administration (Pomalidomide)** CRF**s**
- Date Started and Date Ended or Resulted in Death on Events CRF
- Start date, Stop date on Anti-Myeloma / Anti-Cancer Therapies **CRF**
- Subject Status Date if status is Alive on Survival Status CRF
- Assessment Date on Skeletal Survey and Plasmacytoma Assessment CRF
- **Assessment Date for MRD sample**
- **Date Collected on Pathology FISH CRF**
- **Date of Assessment on Myeloma Response CRF**
- **Date of Last Menstrual Period and Breastfeeding Start in Reproductive Status and Pregnancy Test (Local Lab) CRF**
- **COVID-19 Start Date in Confirmed COVID-19 Status CRF**
- **Date Decision Was Made to End Investigational Product on End of Investigational Product Administration (Carfilzomib), Date Decision Was Made to End Non-Investigational Product on End of Non-Investigational, Product Administration (Dexamethasone), End of Investigational Product Administration (Pomalidomide) and End of Non-Investigational Product Administration (Pomalidomide) CRFs, where the Primary Reason for ending treatment is not Death or Lost to follow-up**

MRD[-]CR

MRD[-]CR is defined as achievement of CR (including sCR) per IMWG-URC and MRD[-] status at a sensitivity of 10^{-5} using next generation sequencing (NGS) based method in the bone marrow at any time.

MRD[-]CR Rate at 12 Months Landmark

MRD[-]CR rate at 12 months landmark is defined as proportion of subjects who reach MRD[-]CR at 12 months landmark assessment among all subjects who received at least 1 dose of carfilzomib. **The sensitivity analysis of MRD[-]CR Rate at 12 months landmark will be based on MRD Evaluable Analysis Set.** The data will include the MRD results from bone marrow samples obtained from subjects with Suspected CR or better obtained no earlier than 8 months and no later than 12 months plus 4 weeks after **the start of any study treatment**.

MRD[-] Rate at Any Time During Therapy

MRD[-] rate at any time during therapy is defined as proportion of subjects who reach MRD[-] at any time during therapy among all subjects who received at least 1 dose of carfilzomib. **The sensitivity analysis of MRD[-]CR Rate at any time during therapy will be based on MRD Evaluable Analysis Set.** The data will include the MRD results from bone marrow samples obtained from the subjects with a response of VGPR or better at any time during therapy.

Number of cycles started for any study drug

It is defined as the total number of treatment cycles in which at least one dose of any study drug is administered.

Number of cycles started for each study drug

It is defined as the total number of treatment cycles in which at least one dose of carfilzomib/pomalidomide/dexamethasone, respectively, is administered.

Number of cycles started for all study drugs

It is defined as the total number of treatment cycles in which at least one dose of carfilzomib, one dose of pomalidomide and one dose of dexamethasone is administered.

Number of doses of carfilzomib administered

It is defined as the total number of non-zero doses of carfilzomib a subject received during the treatment period of the study

Number of doses of pomalidomide administered

It is defined as the total number of non-zero doses of pomalidomide a subject received during the treatment period of the study

Number of doses of dexamethasone administered

It is defined as the total number of non-zero doses of dexamethasone a subject received during the treatment period of the study

Overall Response (OR)

OR is the best overall confirmed response of partial response (PR), very good partial response (VGPR), complete response (CR), or stringent complete response (sCR).

Overall Response Rate (ORR)

Overall Response Rate (ORR) is defined as the proportion of subjects that reach the overall response among all subjects who received at least 1 dose of the carfilzomib.

Overall Survival (OS)

OS is defined as time from start of treatment until death from any cause.

OS = (Death date or date of censoring if censored – start of **any study** treatment date + 1) / 30.4

Subjects still alive will be censored at the date last known to be alive. If the date last known to be alive is after the date that triggers the analysis (ie, the data cutoff date), the subject will be censored at the analysis trigger date.

Progression Free Survival (PFS)

PFS is defined as the time from the first dose date 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 > 70 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 > 70 days later by disease progression or death; otherwise, at first dose date. Disease progression is based on the IMWG-URC [2016].

PFS **time in months**= [(PD or death date, whichever occurs first) or date of censoring if censored– start of treatment date + 1] / 30.4.

Table 5-1. Conventions for Censoring for PFS

Situation	Date of Progression or Censoring	Outcome
No PD or death, no new anticancer treatment	**Last visit; otherwise, first dose date of any study treatment**	**Censored**
No PD or death, new anticancer treatment	**Last visit prior to new treatment; otherwise, first dose date of any study treatment**	**Censored**
PD or death > 70 days after last visit	**Last visit prior to PD or death; otherwise, 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, first dose date of any study treatment[b]**	**Censored**

"Visit" refers to a post-baseline evaluable 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 evaluable disease assessment prior to subsequent anticancer therapy, or (b) the last non-NE, post-baseline assessment followed > 70 days later by disease progression or death; otherwise, first dose date."

[b]PFS will be censored if PD or death > 70 days after last evaluable disease assessment.

Relative Dose Intensity

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

$$\text{Relative Dose Intensity (RDI)} = \frac{\text{Actual dose intensity}}{\text{Planned dose intensity}}$$

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

$$\text{Actual Dose Intensity } (mg/m^2/week) = \frac{\text{Actual cumulative dose } (mg/\ m^2)}{\text{Number of weeks of actual treatment}}$$

Actual cumulative dose in (mg/m^2) is the sum of received doses (mg) divided by baseline body surface area (BSA) (m^2) of the patient. Each subject's first dose of carfilzomib will be calculated based upon baseline BSA using the Mosteller formula. The dose for each subject should not be revised unless the subject experiences a change in body weight of > 20% in which case the BSA and dose should be recalculated. The recalculated BSA becomes the new baseline and is used in dose calculation. BSA will be capped at 2.2 for carfilzomib. Number of weeks of actual treatment will be calculated as (Last Dose Date of carfilzomib – First Dose Date of carfilzomib + i) / 7. When the last cycle is among cycles 1 to 12, i = 7 if the last infusion is given on day 1 or 8 within the last cycle, i = 14 if the last infusion is given on day 15. When the last cycle is among cycles 13+, i = 14 if the last infusion is given on day 1 or day 15 within the last cycle.

Planned dose intensity is defined as the planned amount of carfilzomib in mg/m^2 delivered to a subject per week of treatment.

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

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. When c is less than or equal to 12, j =1 if the last carfilzomib infusion is given on day 1 within the last cycle, j=2 if the last infusion is given on day 8 , j=4 if the last infusion is given on day 15. When c is greater than or equal to 13, j=2 if the last infusion is given on day 1 within the last cycle, j=4 if the last infusion is given on day 15. The planned cumulative dose of carfilzomib is the summation of planned carfilzomib dose (mg/m^2) per week as: [20, 56, 56, 0] in cycle 1, [56, 56, 56, 0] in cycle 2 to 12 and [56, 0, 56, 0] in cycle 13 onwards, across the planned number of treatment weeks.

For dexamethasone: Actual dose intensity is the actual amount of drug in mg delivered to a subject per week of treatment.

$$\text{Actual Dose Intensity (mg/week)} = \frac{\text{Actual cumulative dose (mg)}}{\text{Number of weeks of actual treatment}}$$

The cumulative dose in mg is the summation of total quantity administered (mg) over the study. Number of weeks of actual treatment will be calculated as (Last Dose Date of dexamethasone – First Dose Date of dexamethasone + i)/7. When the last cycle is among cycle 1 to 12, i=7 if the last dexamethasone dose is given on day 1, 8, 15, or 22. When the last cycle is among cycle 13+, i = 14 if the last dexamethasone dose is given on day 1 or day 15 within the last cycle. Planned dose intensity (mg/week) is defined as the planned amount of dexamethasone in mg delivered to a subject per week of treatment.

$$\text{Planned Dose Intensity (mg/week)} = \frac{\text{Planned cumulative dose (mg)}}{\text{Number of protocol specified treatment weeks}}$$

It will be calculated as the planned cumulative dose of dexamethasone in mg divided by the planned number of weeks for the treatment per protocol based on the corresponding cycle and day of the last dexamethasone dose. 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 dexamethasone dose is given. When c is less than or equal to 12, j =1 if the last dexamethasone dose is given on day 1 within the last cycle, j=2 if the last dose is given on day 8, j=3 if the last dose is given on day 15, j=4 if the last dose is given on 22. When c is greater than or equal to 13, j=2 if the last dose is given on day 1, j=4 if the last dose is given on day 15. The planned cumulative dose of dexamethasone is the summation of planned dexamethasone dose (mg) per week as: [40, 40, 40, 40] in cycle 1 to12 (20 mg for subjects >75 years of age) and [20, 0, 20, 0] in cycle 13 onwards (10mg for subjects > 75 years age), across the planned number of treatment weeks.

For pomalidomide: Actual dose intensity is the actual amount of drug in mg delivered to a subject per week of treatment.

$$\text{Actual Dose Intensity (mg/week)} = \frac{\text{Actual cumulative dose (mg)}}{\text{Number of weeks of actual treatment}}$$

The cumulative dose in mg is the summation of total quantity administered (mg) over the study. Number of weeks of actual treatment will be calculated as (Last Dose Date of

pomalidomide – First Dose Date of pomalidomide + i)/7, where the value of i depends on the day of the cycle on which the last pomalidomide is taken, which is shown in the table below.

The last pomalidomide dose day in the cycle	Value of i
Day 1 or Day 8	7
Day 2 or Day 9	6
Day 3 or Day 10	5
Day 4 or Day 11	4
Day 5 or Day 12	3
Day 6 or Day 13	2
Day 7 or Day 14	1
Day 15 to Day 28	14 – (Day # - 15)

Planned dose intensity (mg/week) is defined as the planned amount of pomalidomide in mg delivered to a subject per week of treatment.

$$\text{Planned Dose Intensity (mg/week)} = \frac{\text{Planned cumulative dose (mg)}}{\text{Number of protocol specified treatment weeks}}$$

It will be calculated as the planned cumulative dose of pomalidomide in mg divided by the planned number of weeks for the treatment per protocol based on the corresponding cycle and day of the last pomalidomide 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 pomalidomide dose is taken and j =1 if the last pomalidomide dose is taken on day 1 to 7 within the last cycle, j=2 if the last dose is given on day 8 to 14, j=4 if the last dose is given on day 15 to 21. The planned cumulative dose of pomalidomide is the summation of planned pomalidomide dose (mg) per week ([7*4, 7*4, 7*4, 0]) across the planned treatment weeks.

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

R-ISS stage at baseline will be calculated using ISS, risk group by FISH, and LDH, based on the criteria published by the International Myeloma Working Group (Palumbo, 2015):

Stage I: ISS stage I and standard risk group by FISH and normal LDH

Stage II: Not R-ISS stage I or III

Stage III: ISS stage III and {either high-risk group by FISH or high LDH}

Sustained MRD[-]CR Rate

Sustained MRD[-]CR rate is defined as the proportion of subjects that maintain MRD[-]CR for 12 months +/- 4 weeks or more, ie, maintaining MRD[-]CR for at least 12 months minus 4 weeks is considered as sustained, after achieving MRD[-]CR status among the subjects who reach the MRD[-]CR status, disregarding when the first MRD[-]CR was reached.

Sustained MRD[-]CR Rate at 24 months

Sustained MRD[-]CR rate at 24 months is defined as the proportion of subjects that maintain MRD[-]CR for 12 months +/- 4 weeks or more, ie, maintaining MRD[-]CR for at least 12 months minus 4 weeks is considered as sustained, after achieving MRD[-]CR status in the time window of **Key Secondary** endpoint assessment.

Time to Response

Time from start of treatment to first date of confirmed PR or better.

Time to Response = (response start date – start of **any study** treatment date + 1) / 30.4

Time (month) since initial diagnosis

Time since initial diagnosis is defined as:

(Date of informed consent signed - date of first diagnosis of MM + 1) / 30.4

Treatment-emergent Adverse Event

Treatment-emergent adverse event: Events categorized as Adverse Events (AEs) starting on or after first dose of **any study treatment** and up to and including 30 days after the last dose of any study treatments excluding events reported after End of Study date.

Treatment Duration (weeks) for each study drug

Treatment duration (weeks) for carfilzomib, dexamethasone and pomalidomide defined as: (Date of last dose – Date of first dose + 1)/7.

6. Analysis Sets

6.1 Full Analysis Set

Not Applicable

6.1.1 Primary Analysis Set

Not Applicable

6.2 Safety Analysis Set

The Safety Analysis Set includes all enrolled subjects who received at least 1 dose of carfilzomib. The analysis of efficacy and safety analyses will be based on the Safety Analysis Set.

6.3 MRD Evaluable Analysis Set

The MRD Evaluable Analysis Set includes all enrolled subjects with measurable MRD status at baseline and at least 1 measurable MRD status postbaseline (subjects who don't have measurable MRD status due to technical issues will be excluded), who received at least 1 dose of carfilzomib. The MRD sensitivity analysis will be based on MRD Evaluable Analysis Set.

6.4 Modified Safety Analysis Set

The modified safety analysis set (mSAS) will be used in the sensitivity analysis for primary endpoint and key secondary endpoints, and other efficacy endpoints including PFS, OS, and CR in order to adjust for the COVID-19 impact on the Safety Analysis Set population. The mSAS is a subset of Safety Analysis Set excluding subjects who are impacted by COVID-19.

The COVID-19 impact refers to:

(1) any COVID-19 adverse events which are identified using the COVID-19 Standardized MedDRA Query (SMQ) narrow search strategy, and COVID-19 events collected on the Confirmed COVID-19 Status CRF;

(2) the reason for Investigational Product (IP)/Non-IP Dose Change/Withheld/Dose Delay is COVID-19 control measures recorded on the CRFs for IP Administration and Non-IP Administration;

(3) the reason for ending IP/Non-IP is COVID-19 control measures recorded on CRFs for End of IP Administration and End of Non-IP Administration;

(4) important protocol deviations (IPDs) related to COVID-19 control measures;

(5) COVID-19 related protocol deviation: 940 series, 950 series and 960 series of protocol deviation codes in the study IPD list.

6.5 Per Protocol Set(s)

The per protocol analysis set is a subset of the safety analysis set which includes subjects who do not have important protocol deviations that might affect the interpretation of the analyses of the efficacy endpoints. Subjects with the following protocol deviations will be excluded from the per protocol set:

Major inclusion criteria not met:

- 103 – First or Second Relapse
- 104 – Refractory to Lenalidomide
- 106 – Measurable Disease
- 107 – Prior Therapy Response
- 108 – Prior Carfilzomib Response
- 109 – ECOG

Major exclusion criteria met:

- 201 – Primary Refractory
- 202 – Waldenström macroglobulinemia
- 203 – Multiple myeloma of IgM subtype
- 204 – POEMS syndrome
- 205 – Plasma cell leukemia
- 206 – Primary amyloidosis
- 207 – Amyloidosis associated with myeloma
- 208 – Myelodysplastic syndrome
- 209 – Toxicity with lenalidomide therapy
- 210 – Prior treatment with pomalidomide
- 211 – History of other malignancy within past 3 years
- 212 – Active hepatitis B virus infection
- 213 – HIV or hepatitis C infection
- 214 – Graft vs host disease
- 215 – Cirrhosis
- 216 – Uncontrolled hypertension
- 217 – Impaired cardiac function within 4 months
- 218 – Intolerance to hydration

Major treatment non-compliance

- 501 – Incorrect carfilzomib dose (over dose)
- 502 – Incorrect carfilzomib dose (under dose)
- 503 – Carfilzomib dose not adjusted per protocol
- 504 – Carfilzomib not reduced for 1 cycle before re-escalation
- 505 – Carfilzomib insufficient infusion time
- 506 – Carfilzomib dose off schedule
- 507 – Pomalidomide not administered per protocol
- 508 – Pomalidomide not withheld per protocol
- 509 – Dexamethasone not administered per protocol
- 510 – Compromised IP

6.6 Health-related Quality-of-Life or Health Economics Analyses Set(s)

Not Applicable

6.7 Pharmacokinetic/Pharmacodynamic Analyses Set(s)

The PK/PDn Analysis Set will include a subset of up to 20 evaluable subjects in Safety Analysis Set, who have consented to participate in the optional PK/PDn substudy. Evaluable subjects are defined as those subjects receiving at least 1 dose of carfilzomib and 1 post-dose PK and/or PDn sample collected, as defined by the Schedule of Assessments. These subjects will be evaluated for pharmacokinetics and pharmacodynamics unless significant protocol deviations affect data analysis or if key dosing, dosing interruption, or sampling information is missing.

6.8 Interim Analyses Set(s)

There are no formal interim analyses planned for this study.

6.9 Study-specific Analysis Sets

Not Applicable

7. Planned Analyses

7.1 Primary Analysis

The primary analysis will be triggered **12 months after the last subject enrollment**. The primary analysis will be based on a clean database lock.

7.2 Sustained MRD Analysis

A sustained **durable** MRD analysis is planned after all subjects have had the opportunity to complete their 24 months landmark MRD assessments. The analysis will be based on a clean database lock.

7.3 Data Review Team Early Stopping Guidelines

A data review team (DRT) is a group internal to Amgen, but external to the carfilzomib product team(s). The DRT is composed of members that are external to the study team and include a clinician, a safety physician, and a biostatistician. The DRT will review accumulating safety data from the ongoing clinical trial to ensure no avoidable that there is no increased risk for harm to subjects. Membership, procedures, and meeting timing will be described in detail in the study DRT charter.

7.4 Final Analysis

The final analysis is planned after all subjects have had the opportunity to complete their end of study visit. The analysis will be based on a clean database lock.

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

No imputation for missing data **of outcomes** will be performed; Sensitivity analyses **might be needed** to evaluate the robustness of the primary analysis. The handling of Incomplete dates for the start and **stop** of adverse event, concomitant medications, **new antimyeloma therapy, death, prior multiple myeloma therapy, and relapse/progression to prior multiple myeloma therapy** 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

Pharmacokinetic (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 pharmacokinetic evaluation practice.

8.6 Distributional Characteristics

Not Applicable

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

The analyses of efficacy and safety will be based on the safety analysis set. In principle, 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, KM proportions at select time points, KM quartiles (when estimable), the number of subjects with events, the number of subjects censored, and censoring reasons.

Duration of follow-up for time to event endpoints will be estimated using the reverse Kaplan Meier method (Schemper and Smith, 1996). Point estimates for efficacy endpoints will be accompanied by 2-sided 90% and 95% CIs including estimates of KM quartiles (Klein and Moeschberger, 1997), KM proportions (Kalbfleisch and Prentice, 1980), and binomial proportions (Clopper and Pearson, 1934).

The evaluation of whether the key secondary objective was met will follow a fixed-sequence approach using the 90% exact confidence interval: the key secondary objective is met only after the primary objective is met.

9.2 Subject Accountability

The following subject disposition information will be summarized descriptively:

- Number of screened subjects
- Number of subjects screened but not **enrolled** (screen failures)
- **Number of subjects enrolled but not dosed**
- Number of treated subjects (Safety population)
- Number (%) of subjects who discontinued treatment and the primary reason for discontinuation. The percentage is calculated with respect to Safety population.

- Number (%) of subjects who discontinued study and the primary reason for discontinuation. The percentage is calculated with respect to safety population.
- Number (%) of subjects who entered long-term follow-up before disease progression. The percentage is calculated with respect to safety population.
- Number (%) of subjects who entered long-term follow-up for survival. The percentage is calculated with respect to safety population.
- **Number (%) of subjects who discontinued each study treatment (carfilzomib, dexamethasone, pomalidomide) or end of study due to COVID-19 control measures**

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. **The following information of IPD and protocol deviations will be summarized, where applicable, with respect to the following:**

- **Number (%) of subjects with IPDs and total number of IPDs will be summarized by category and sub-category by treatment arm in Safety Analysis Set**
- **Number (%) of subjects with IPDs related to COVID-19 control measures will be summarized by treatment arm in Safety Analysis Set**
- **Number (%) of subjects with IPDs related to COVID-19 control measures by protocol deviation category (940 series, 950 series and 960 series of protocol deviations codes) and by treatment arm in Safety Analysis Set**
- **Subject listing of IPD in Safety Analysis Set, including IPDs related to COVID-19 control measures with the descriptions.**
- **Subject listing of IPDs related to COVID-19 control measures based on protocol deviations category (940 series, 950 series and 960 series of protocol deviations codes) in Safety Analysis Set**

In addition to the summary of IPD, subject listing of inclusion/exclusion deviations will also be generated.

9.4 Demographic and Baseline Characteristics

The following demographic, baseline characteristics and baseline disease characteristics will be summarized for the Safety Analysis Set. These includes but not limited to the following,

- **Baseline demographic and Baseline characteristics**
  - Age (years) (as continuous variable; as categorical variable: 18 to < 65, 65 to < 75, 75 to < 85, ≥ 85 years**; <65, >=65; 18-<65, 65-<75, >=75**)
  - Sex (Male, Female)
  - Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
  - Race **(If multiple races have been reported for a subject, the subject will be categorized as multiple race)**
  - Region **(Europe, Non-Europe)**
  - Weight (kg)
  - Height (cm)
  - Body mass index
  - Body Surface Area (m^2) (as continuous variable; as categorical variable: ≤ 2.2, > 2.2 m^2)
  - ECOG performance status (0, 1, 2)
  - 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)
  - Corrected calcium (mg/dL) (as continuous variable; as categorical variable: ≤ 11.5, > 11.5 mg/dL)
  - Creatinine clearance (CrCl, mL/min) (as continuous variable; as categorical variable: < 30, 30 - < 50, 50 - < 80, ≥ 80 mL/min)

    Measured or calculated accordingly to the Cockcroft-Gault formula:

    $$CrCl\ (mL/min) = \frac{(140 - Age(years)) \times Weight(kg)}{72 \times Serum\ Creatinine(mg/dL)} \times (0.85 female)$$

  - Baseline LVEF (%)
  - Hypertension history (yes, no)
  - Cardiopulmonary history (yes **<by diagnosis category>**, no)
- **Baseline Disease characteristics**
  - ISS stage at baseline (stage I, II, III)
  - Revised ISS stage at baseline (stage I, II, III)

- **Prior lenalidomide treatment (yes, no)**
- **Refractory to prior lenalidomide treatment (yes, no)**
- **Prior PI treatment (yes, no)**
- **Prior anti-CD38 exposure (yes, no)**
- **Refractory to prior anti-CD38 treatment (yes, no)**
- **Prior bortezomib treatment (yes, no)**
- **Refractory to prior bortezomib treatment (yes, no)**
- Time (month) since initial diagnosis
- Type of measurable disease (both SPEP and UPEP, SPEP only, UPEP only, Free light chain and abnormal Kappa/Lambda ratio (SFLC) only)
- Plasma cell involvement in bone marrow (%)
- MM subtype and immunoglobulin heavy chain and Light chain types (IgG, IgA, IgD, IgE, IgM, None; Kappa, Lambda, Not detectable within each subtype)
- Baseline beta2 microglobulin (mg/L) (as continuous variable; as categorical variable: < 3.5, 3.5 - < 5.5, ≥ 5.5 mg/L)
- Presence of plasmacytoma (yes, no)
- Prior Transplant (yes (Autologous, Allogeneic), no)
- **Prior tobacco use (yes, no)**
- Number of prior lines of therapy
- **Cytogenetic risk measured by FISH (high risk (t(4;14), t(14;16), deletion 17p), standard risk, missing)**
- Refractory to the last prior line of therapy
- **Albumin (g/dL) (as continuous variables; as categorical variable: <3.5, >=3.5)**
- Timing of refractoriness to Lenalidomide (during maintenance: yes vs no)
- **Time since last relapse (months)**

9.5 Efficacy Analyses

The primary analyses will be based on the safety analysis set, **while sensitivity analyses will use different population analysis set listed in Table 9-1.**

Table 9-1. Primary Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
Overall Response Rate (ORR)	**Safety Analysis Set:** • Based on Independent Review Committee	**Investigator Assessment** • Same as per primary analysis method

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
	• rate will be calculated along with the associated 90% and 95% exact binomial CIs that will be estimated using the Clopper-Pearson method.	based on Investigator assessment **Internal computational assessment:** • Same as per primary analysis method based on ORCA assessment. **Per protocol population** • **Same as per primary analysis method based on per protocol population** **Modified safety population** • **Same as per primary analysis method based on modified safety population.**

Table 9-2. Secondary Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
MRD[-]CR at a sensitivity of 10^{-5} using next generation sequencing (NGS)-based method in the bone marrow at 12 months ± 4 weeks from start of treatment.	**Safety Analysis Set:** • **Based on Independent Review Committee** • The rate will be calculated along with the associated 90% and 95% exact binomial CIs that will be estimated using the Clopper-Pearson method.	**Investigator Assessment** • Same as per primary analysis method based on Investigator assessment **Internal computational assessment:** • Same as per primary analysis method based on ORCA assessment. **MRD-evaluable analysis Set:** • Same method as for primary analysis will be performed. **Per protocol population** • **Same as per primary analysis method based on per protocol population**

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
		Modified safety population • **Same as per primary analysis method based on modified safety population.**
MRD response at a sensitivity of 10^{-5} using next generation sequencing (NGS)-based method in the bone marrow at any time during therapy	**Safety Analysis Set:** • **Based on Independent Review Committee** • The rate will be calculated along with the associated 90% and 95% exact binomial CIs that will be estimated using the Clopper-Pearson method.	**Investigator Assessment** • Same as per primary analysis method based on Investigator assessment **Internal computational assessment:** • Same as per primary analysis method based on ORCA assessment. **MRD-evaluable analysis Set:** • Same method as for primary analysis will be performed.
Sustained MRD[-]**CR**	**Safety Analysis Set:** • **Based on Independent Review Committee** • The rate will be calculated along with the associated 90% and 95% exact binomial CIs that will be estimated using the Clopper-Pearson method.	**Investigator Assessment** • Same as per primary analysis method based on Investigator assessment **Internal computational assessment:** • Same as per primary analysis method based on ORCA assessment. **MRD-evaluable analysis Set:** • Same method as for primary analysis will be performed.
Sustained MRD[-]**CR** response at 24 months ± **4** weeks	**Safety Analysis Set:** • **Based on Independent Review Committee** • The rate will be calculated along with the associated 90% and 95% exact binomial CIs that will be estimated using the Clopper-Pearson method.	**Investigator Assessment** • Same as per primary analysis method based on Investigator assessment **Internal computational assessment:** • Same as per primary analysis method

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
		based on ORCA assessment. **MRD-evaluable analysis Set:** • Same method as for primary analysis will be performed.
Duration of Response	**Safety Analysis Set:** • **Based on Independent Review Committee** • The distribution of DOR including the median will be characterized using the Kaplan-Meier method.	**Investigator Assessment** • Same as per primary analysis method based on Investigator assessment **Internal computational assessment:** • Same as per primary analysis method based on ORCA assessment.
Time to Response	**Safety Analysis Set:** • **Based on Independent Review Committee** • Non-missing sample size (n), mean, standard deviation, median, minimum, and maximum.	**Investigator Assessment** • Same as per primary analysis method based on Investigator assessment **Internal computational assessment:** • Same as per primary analysis method based on ORCA assessment.
Progression Free survival (PFS)	**Safety Analysis Set:** • **Based on Independent Review Committee** • The 90% and 95% CIs for PFS rate will be reported using the methods by Kalbfleisch and Prentice (1980) with log-log transformation. • The distribution of PFS, including median, will also be estimated using the Kaplan-Meier method. • The 90% and 95% CIs for the median and other percentiles of PFS will be constructed using the method of Klein and	**Investigator Assessment** • Same as per primary analysis method based on Investigator assessment **Internal computational assessment:** • Same as per primary analysis method based on ORCA assessment. **Per protocol population** • **Same as per primary analysis method based on per protocol population** **Modified safety population**

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
	Moeschberger (1997) with log-log transformation.	• **Same as per primary analysis method based on modified safety population.**
Overall Survival	Same method described for PFS.	**Per protocol population** • **Same as per primary analysis method described for PFS based on per protocol population** **Modified safety population** • **Same as per primary analysis method described for PFS based on modified safety population.**
Complete Response rate or better rate	Same methods as described for ORR.	**Investigator Assessment** • Same as per primary analysis method described for ORR based on Investigator assessment **Internal computational assessment:** • Same as per primary analysis method described for ORR based on ORCA assessment. **Per protocol population** • **Same as per primary analysis method described for ORR based on per protocol population** **Modified safety population** • **Same as per primary analysis method described for ORR based on modified safety population.**

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

The primary analyses will be based on the safety analysis set, while the MRD sensitivity analyses will be performed on the MRD-evaluable analysis set.

Overall Response Rate (ORR)

It will be calculated along with the associated 90% and 95% exact binomial CIs that will be estimated using the Clopper-Pearson method. **The lower bound of the 90% exact binomial CI is evaluated whether it is larger than the reference ORR. If that happens, then the primary objective is met.**

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

Key Secondary Efficacy Endpoint:

MRD[-]CR at sensitivity of 10^{-5} using NGS-based method in the bone marrow at 12 months ± 4 weeks from start of treatment.

The rate will be calculated along with the associated 90% and 95% exact binomial CIs that will be estimated using the Clopper-Pearson method. **If the primary objective is met, then the lower bound of the 90% exact binomial CI is greater than the reference MRD[-]CR rate. If that happens, the key secondary objective is met.**

Secondary Efficacy Endpoint:

MRD[-] response at a sensitivity of 10^{-5} using NGS based method in the bone marrow at any time during therapy

It will be analyzed using the same method as described for the **key secondary** endpoint.

Sustained MRD[-]CR

It will be calculated along with the associated 90% and 95% exact binomial CIs that will be estimated using the Clopper-Pearson method.

Sustained MRD[-]CR at 24 months ± 4 weeks

It will be calculated along with the associated 90% and 95% exact binomial CIs that will be estimated using the Clopper-Pearson method.

Duration of Response (DOR)

The distribution of DOR including the median will be characterized using the Kaplan-Meier method based on the subjects who achieve best overall response of sCR, CR, VGPR or PR.

Time to Response

Time to response will be summarized with the non-missing sample size (n), mean, standard deviation, median, minimum, and maximum for responders, ie, subjects who achieve best overall response of sCR, CR, VGPR, or PR.

Progression Free Survival (PFS)

The distribution of PFS, including median, will be estimated using the Kaplan-Meier method. PFS rate at selected time points (12 months and 24 months) will be reported. The 90% and 95% CIs for the median and other percentiles of PFS will be constructed using the method of Klein and Moeschberger (1997) with log-log transformation. The 90% and 95% CIs for PFS rates will be estimated using the methods by Kalbfleisch and Prentice (1980) with log-log transformation. **The subcategory of death with the primary reason of COVID-19 infection or COVID-19 pneumonia will be included in the PFS events.**

Overall Survival (OS)

OS will be analyzed using the same method as described for the PFS endpoints.

Complete Response or better rate (CRR)

The CR will be analyzed using the same methods as described for ORR.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

Assess the depth of MRD

Percentage of the MRD[-] below the threshold of 10^{-4}, 10^{-5} and 10^{-6} by NGS-based method at time of suspected CR or better will be summarized.

PFS by depth of MRD response at: 10^{-4}, 10^{-5} and 10^{-6}

The correlation between MRD status and PFS will be explored in the MRD Evaluable Analysis Set. In the MRD Evaluable Analysis Set, subjects will be categorized into following subgroups: subjects who achieve MRD[-] any time during study and subjects who don't achieve MRD[-] any time during study, subjects who achieve MRD[-]CR any time during study and subjects who don't reach MRD[-]CR any time during study. Within each subgroup the distribution of PFS including the median and corresponding 95% CI will be summarized descriptively using the Kaplan-Meier method. Three different thresholds (10^{-4}, 10^{-5} and 10^{-6}) will be explored to define MRD status. The Cox proportional hazard model will also be fitted with MRD[-] status or MRD[-]CR status as

the time-dependent covariate to explore the correlation between MRD status and PFS. In addition, similar analysis may be done for MRD response at 12 months and 24 months landmarks. **When there is not a sufficient number of subjects in the subgroup, i.e., less than 10% of the MRD population, the analysis will not be conducted.**

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

Not applicable.

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term.

Subject incidence of all treatment-emergent adverse events, serious adverse events, grade 3 and above adverse events, **Treatment-emergent treatment-related** adverse events, **Treatment-emergent treatment-related** serious adverse events, adverse events leading to withdrawal of investigational product or other protocol-required therapies, and fatal adverse events will be tabulated by system organ class and preferred term in alphabetical order.

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

In addition, summaries of treatment-emergent adverse events, serious adverse events, grade 3 or higher adverse events, **Treatment-emergent treatment-related** adverse events, **Treatment-emergent treatment-related** serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and fatal adverse event of the subjects by preferred term will be provided in descending order of frequency.

Summaries of treatment-emergent adverse events, **Treatment-emergent treatment-related** adverse events, **Treatment-emergent treatment-related** serious adverse events and serious adverse events will be tabulated by system organ class, preferred term, and grade. Fatal adverse events by system organ class and preferred term will also be provided in descending order of frequency

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.

9.6.3 Laboratory Test Results

The laboratory test results and their change from baseline will be summarized by cycle.

Actual value and change from baseline of hematology, chemistry, and other laboratory values will be summarized by cycle. For the summary of changes from baseline values, subjects without baseline and/or post baseline values will be excluded. Laboratory assessments collected > 30 days after the last dose will not be included in the summaries.

Selected laboratory test results will be assigned toxicity grades using CTCAE 5. Shift tables assessing the toxicity grade at baseline versus worst toxicity on study and to the last value recorded on study will be presented for selected laboratory test results. A listing of all grade 3 or higher laboratory values will be provided.

The laboratory analytes in the study are given below.

Local Laboratory: Chemistry	**Local Laboratory: Hematology**	**Local Laboratory: Disease Assessments**	**Other Labs**
Sodium	ANC	FISH (bone marrow aspirate)	**Central Laboratory:**
Potassium	RBC	SPEP	PK (optional)
Chloride	Hemoglobin	**SIFE**	PDn (optional)
Bicarbonate/CO_2	Hematocrit	UPEP	PG (optional)
Total protein	MCV	**UIFE**	Biomarker samples (optional)
Albumin	MCH	SFLC	MRD assessment by NGS (bone marrow aspirate)
Calcium	MCHC	**Local Laboratory: Urinalysis:**	**Local Laboratory:**
Adjusted/corrected calcium	RDW	• Specific Gravity	Serum or urine Pregnancy
Glucose	Platelets	• pH	Quantitative immunoglobulins (serum):
BUN or Urea	WBC	• Blood	• IgA, IgD, IgE, IgG, IgM
Creatinine	Differential	• Glucose	beta2-microglobulin (serum)
Uric acid	*(including manual)	• Ketones	NT-proBNP **(**or if unavailable, BNP)
Total bilirubin	• Plasma Cells	• Protein	HBV serology
Direct bilirubin	• Bands/stabs	• Bilirubin	Hepatitis B DNA
ALP	• Eosinophils	• WBC	
LDH	• Basophils	• RBC	
AST (SGOT)	• Lymphocytes	• Bacteria	
ALT (SGPT)	• Monocytes	• Casts	
Phosphorus	• Segmented Neutrophils	• Crystals	
Amylase	**Local Laboratory: Coagulation**		
Lipase	PT/INR		
HbA1c	APTT		
Fasting glucose (screening)			
Fasting lipid panel:			
• Cholesterol			
• HDL			
• LDL			
• Triglycerides			

9.6.4 Vital Signs

The vital sign results including systolic/ diastolic blood pressure, heart rate, temperature, and if available, respiratory rate and oxygen saturation and their change from baseline will be summarized by cycle. 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. Vital sign results taken > 30 days after the last administration of protocol therapy will be excluded from all vital sign summaries.

9.6.5 Physical Measurements

The physical measurements weight, BSA and their change from baseline will be summarized by cycle. Body surface area (BSA) should be calculated using the Mosteller Formula (Mosteller, 1987):

BSA (m^2) = ([height (cm) × weight (kg)] / 3600) ^{½}.

9.6.6 Electrocardiogram

The ECG measurements from this clinical study are performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials.

9.6.7 Antibody Formation

Not Applicable

9.6.8 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product. The extent of exposure to **investigational products** (carfilzomib and pomalidomide) will be evaluated with respect to treatment duration, number of cycles started, total dose received, average dose received, number of doses administered, and dose intensity. The reasons for dose modification or discontinuation from any study treatment will be summarized. **If the reason for dose modification is COVID-19 control measures which is recorded in the specified filed (Other) on the CRF, then the number (%) with COVID-19 control measures will also be presented. The summary will include the following:**

- Number (%) of subjects with doses missed, dose delays, dose reductions, and dose interruptions for carfilzomib will be summarized.
  - Number of doses missed, delayed, reduced, and interrupted per subject
  - Primary reasons for dose missed, delays, reductions, and interruptions.
- Number (%) of subjects with doses missed, dose delays, dose reductions, and dose interruptions for pomalidomide.
  - Number of doses missed, delayed, reduced, and interrupted per subject
  - Primary reasons for dose missed, delays, reductions, and interruptions.

Some variables of interest ie, treatment duration, number of cycles started, total dose received, number of doses administered, and dose intensity are defined in the section 5.

- Number (%) of subjects dosed by cycle for any study drug, each study drug and all study drugs

9.6.9 Exposure to Non-investigational Product

Descriptive statistics will be produced to describe the exposure to non-investigational product. The extent of exposure to non-investigational product (dexamethasone) will be evaluated with respect to treatment duration, number of cycles started, total dose received, average dose received, number of doses administered, and dose intensity. The reasons for dose modification or discontinuation from any study treatment will be summarized. If the reason for dose modification is COVID-19 control measures which is recorded in the specified field (Other) on the CRF, then the number (%) with COVID-19 control measures will also be presented. The summary will include the following:

- **Number (%) of subjects with doses missed, dose delays, dose reductions, and dose interruptions for dexamethasone.**
  - **Number of doses missed, delayed, reduced, and interrupted per subject**
  - **Primary reasons for dose missed, delays, reductions, and interruptions.**

Some variables of interest ie, treatment duration, number of cycles started, total dose received, number of doses administered, and dose intensity are defined in the section 5.

9.6.10 Exposure to Other Protocol-required Therapy

Not applicable.

9.6.11 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized by preferred term for each treatment group as coded by the World Health Organization Drug dictionary.

9.7 Other Analyses

Echocardiogram, including LVEF will be summarized by actual values and changes from baseline values by visit using descriptive statistics.

Pulmonary Function Tests, including spirometry and DLCO, will be summarized by actual values and changes from baseline values by visit using descriptive statistics.

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

Carfilzomib PK parameters (maximum observed concentration [C_{max}], area under the concentration-time curve [AUC], and if feasible, terminal half-life [$t_{1/2}$]) will be estimated from plasma concentration-time profiles obtained from subjects enrolled in the optional PK/PDn substudy. Additional analyses may be performed to evaluate relationships between carfilzomib PK and selected safety or efficacy endpoints.

For carfilzomib PDn parameters, proteasome activity for the chymotrypsin-like, trypsin-like and caspase-like activities from whole blood will be reported for the scheduled timepoints to determine if carfilzomib treatment produces a pharmacodynamic reduction in proteasome activity relative to baseline activity levels.

PK/PDn analyses will be provided by the Department of Clinical Pharmacology, Modeling & Simulation (CPMS) (PK analyses) and Clinical Biomarkers and Diagnostics (CBD) (PDn analyses). Details regarding the analyses will be provided in a separate population modeling analysis plan by CPMS and CBD.

9.7.2 Analyses of Clinical Outcome Assessments

Not Applicable

9.7.3 Analyses of Health Economic Endpoints

Not Applicable

9.7.4 Analyses of Biomarker Endpoints

Not Applicable

10. Changes From Protocol-specified Analyses

The Per Protocol Set(s) is added in section 6.3 and it includes subjects who do not have important protocol deviations that might affect the interpretation of the analyses of the efficacy endpoints.

Per the protocol amendment 4 (section 10.2.4), incomplete dates for the start of adverse event, concomitant medications, and death will be imputed and the detailed rules will be specified in the statistical analysis plan.

Addition to the start dates, stop of adverse event, concomitant medications, new antimyeloma therapy, death, prior multiple myeloma therapy, and relapse/progression to prior multiple myeloma therapy will be imputed by the algorithms (section 8.3).

Impact analyses of COVID-19 on the overall trail conduct and assessment of safety and efficacy parameters are added in the statistical analysis plan.

SAP contains some changes in subgroups (section 4.2) from Protocol.

- **Added below subgroups for primary endpoint:**
  - **Cytogenetic risk measured by FISH (high risk (t(4;14), t(14;16), deletion 17p), standard risk)**
  - **R-ISS (stage I, stage II, stage III)**
  - **Prior anti-CD38 exposure (yes, no)**
  - **Refractory to prior anti-CD38 treatment (yes, no)**
  - **Prior bortezomib exposure (yes, no)**
  - **Refractory to prior bortezomib treatment (yes, no)**
- **Added below subgroups for PFS:**
  - **prior carfilzomib exposure (yes, no)**
  - **number of prior lines of therapy (1, 2)**
  - **timing of lenalidomide refractoriness (during maintenance: yes, no)**
  - **Cytogenetic risk measured by FISH (high risk (t(4;14), t(14;16), deletion 17p), standard risk)**
  - **R-ISS (stage I, stage II, stage III)**
  - **Prior anti-CD38 exposure (yes, no)**
  - **Refractory to prior anti-CD38 treatment (yes, no)**
  - **Prior bortezomib exposure (yes, no)**
  - **Refractory to prior bortezomib treatment (yes, no)**

11. Literature Citations / References

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12. Prioritization of Analyses

Not Applicable

13. Appendices

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

A1. Imputation Rules for Adverse Events and Concomitant Medications (other than the new anti-myeloma therapy) dates

Imputation Rules for Partial or Missing Start Dates

The reference date for the following rules is the date of first dose.

Start Date		Stop Date						
		Complete: yyyymmdd		Partial: yyyymm		Partial: yyyy		Missing
		< 1st dose	≥ 1st dose	< 1st dose yyyymm	≥ 1st dose yyyymm	< 1st dose yyyy	≥ 1st dose yyyy	
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 of the month; 3=Impute January 1 of the year; 4=Impute January 1 of the stop year
Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month or first day of year if month is also missing.

Imputation Rules for Partial or Missing Stop Dates

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.**
- **If the imputed stop date is before the start date, set stop date to missing.**

- **If the imputed stop date is after the death date, impute as death date.**

A2. Imputation Rules for New Antimyeloma Therapy Start Date

If the start day of new antimyeloma 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 antimyeloma 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.

A3. Imputation Rules for Partial or Missing Death Dates

If death year and month are available but day is missing:

- **If yyyymm for the date last known to be alive equals yyyymm for death date, set death date to the day after the date last known to be alive.**
- **If yyyymm for the date last known to be alive is less than the yyyymm for death date, set death date to the first day of the death month.**
- **If yyyymm for the date last known to be alive is greater than yyyymm for death date, assume death date is in error, do not impute and censor the subject survival time.**

If month and day are missing and year of death is known:

- **If yyyy for the date last known to be alive equals yyyy for death date, set death date to the day after last known to be alive date.**
- **If yyyy for the date last known to be alive is less than yyyy for death date, set death date to the first day of the death year.**
- **If yyyy for the date last known to be alive is greater than yyyy for death date, assume death date is in error, do not impute and censor the subject survival time.**

If a death date is totally missing:

Do not impute and censor the subject survival time.

A4. Imputation Rules for Dates of Prior Multiple Myeloma Therapy and Relapse/progression to Prior Multiple Myeloma Therapy:

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.