Title Page

Protocol Title:		A Randomized, Open-label, Phase 3 Study Comparing Once-weekly vs Twice-weekly Carfilzomib in Combination With Lenalidomide and Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma (A.R.R.O.W.2)
Short Protocol Title:		A Study Comparing Once-weekly vs Twice-weekly Carfilzomib in Combination with Lenalidomide and Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma
Protocol Number:		20180015
Investigational Product:		Carfilzomib
Trade Name:		Kyprolis®
Sponsor	**Name of Sponsor:**	Amgen Inc.
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EudraCT Number:		2018-000665-36
NCT Number:		03859427
Protocol Date:		**Document Version** / **Date** Original / 04 October 2018 Amendment 1 / 10 October 2019 Amendment 2 / 24 August 2020 Amendment 3 / 12 August 2021 **Superseding Amendment 3** / **02 September 2021**
Version/Date:		**Data Element Standards Version** 6.1

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures. The format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (ICH E6).

Confidentiality Notice

Investigator's Agreement:

I have read the attached protocol entitled A Randomized, Open-label, Phase 3 Study Comparing Once-weekly vs Twice-weekly Carfilzomib in Combination With Lenalidomide and Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma (A.R.R.O.W.2) , dated **02 September 2021**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse [or legal partner] and dependent children) and my sub-investigators (including, if applicable, their spouses [or legal partners] and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

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[redacted]

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1. Protocol Synopsis

Protocol Title: A Randomized, Open-label, Phase 3 Study Comparing Once-weekly vs Twice-weekly Carfilzomib in Combination With Lenalidomide and Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma (A.R.R.O.W.2)

Short Protocol Title: A Study Comparing Once-weekly vs Twice-weekly Carfilzomib in Combination with Lenalidomide and Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma

Study Phase: 3

Indication: relapsed or refractory multiple myeloma (RRMM)

Rationale

The ASPIRE study demonstrated the superiority of the combination of carfilzomib (Kyprolis®) with lenalidomide and dexamethasone (KRd; 27 mg/m^2 twice-weekly) over lenalidomide with dexamethasone (Rd). Superiority of the KRd regimen was demonstrated in terms of median progression-free survival (PFS) (26.3 vs 17.6 months, hazard ratio [HR] = 0.69), overall response rate (ORR) (87.1% vs 66.7%, odds ratio [OR] = 3.47) (Stewart et al, 2015), health-related quality-of-life (Stewart et al, 2016), as well as overall survival (OS) (median OS: 48.3 vs 40.4 months, HR = 0.79 [Siegel et al, 2018]).

Safety results from the final analysis were consistent with the known safety profile of carfilzomib, with no new safety signals observed after extended follow-up.

Despite the favorable benefit-risk profile of the KRd regimen, as demonstrated in the ASPIRE study, compliance with the currently available twice-weekly KRd dosing schedule may be less than optimal because of the convenience-related attributes of this regimen.

The purpose of this study is to:

- Compare efficacy of a once-weekly combination of KRd (56 mg/m^2) with the on-label twice-weekly combination of KRd (27 mg/m^2)
- Compare PFS, patient-reported convenience and other patient-reported outcomes, OS, and minimal residual disease (MRD) rate between the 2 regimens
- Describe the safety profile of once-weekly KRd 56 mg/m^2 and twice-weekly KRd 27 mg/m^2 in subjects with RRMM with 1 to 3 prior lines of therapy.

Objectives/Endpoints

Objectives	Endpoints
Primary	
• compare efficacy of 56 mg/m^2 carfilzomib administered once-weekly in combination with lenalidomide and dexamethasone (KRd 56 mg/m^2) to 27 mg/m^2 carfilzomib administered twice-weekly in combination with lenalidomide and dexamethasone (KRd 27 mg/m^2) in subjects with relapsed or refractory multiple myeloma (RRMM) with 1 to 3 prior lines of therapy	• overall response, defined as the best overall response of stringent complete response [sCR], complete response [CR], very good partial response [VGPR], and partial response [PR] per International Myeloma Working Group Uniform Response Criteria [IMWG-URC] over the duration of the study
Key Secondary	
• compare progression-free survival (PFS) between treatment arms	• PFS over the duration of the study
• compare patient-reported convenience with carfilzomib-dosing schedule between treatment arms	• convenience as measured by the Patient-reported Convenience With Carfilzomib-dosing Schedule Question after cycle 4 of treatment
Secondary	
• describe safety and tolerability in treatment arms	• incidence of treatment-emergent adverse events
• compare additional efficacy parameters between treatment arms	• time to response (TTR) • duration of response (DOR) • time to progression (TTP)
• compare overall survival (OS) between treatment arms	• OS over the duration of the study
• compare rate of minimal residual disease negative (MRD[-]) in bone marrow aspirates between treatment arms	• MRD[-]CR, defined as achievement of CR or better by Independent Review Committee (IRC) per IMWG-URC and achievement of MRD negativity as assessed by next-generation sequencing method at a 10^{-5} threshold over the duration of the study • MRD[-] status at 12 months, defined as achievement of MRD negativity at 12 months (± 4 weeks) from randomization, as assessed by next-generation sequencing method at a 10^{-5} threshold

Objectives	Endpoints
Secondary (continued)	
• compare patient-reported physical functioning and role functioning between treatment arms	• physical functioning and role functioning over time as measured by the Physical Functioning and Role Functioning scales of the European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30) over the duration of the study
• compare patient-reported treatment satisfaction between treatment arms	• treatment satisfaction as measured by the Satisfaction With Therapy (SWT) scale of the Cancer Therapy Satisfaction Questionnaire (CTSQ) after cycle 4 of treatment

Hypotheses

Once-weekly KRd 56 mg/m^2 is non-inferior in terms of efficacy when compared with twice-weekly KRd 27 mg/m^2.

Overall Design

This is a phase 3, multicenter, open-label, randomized study in subjects with RRMM who have received 1 to 3 prior therapies. The study will consist of a screening period of up to 28 days, a treatment duration of up to 12 cycles of 28 days, and a 30-day safety follow-up period.

Subjects will receive the study drug(s) determined by randomization for a maximum of 12 cycles. No crossover between the treatment arms is allowed. After discontinuation of study drug(s) subjects will have a safety follow-up visit 30 (+3) days after the last dose of all study drug(s). After end of study, subjects may continue treatment per local standard of care at the discretion of the investigator.

All subjects will be assessed for multiple myeloma disease response according to the International Myeloma Working Group-Uniform Response Criteria (IMWG-URC) (Section 12.11) every 28 ± 7 days from cycle 1 day 1 through the end of cycle 12 or disease progression until death, loss to follow-up, withdrawal of full consent , or until first subsequent antimyeloma treatment (whichever occurs first), regardless of cycle duration, dose delays or treatment discontinuation.

Subjects who end study drug(s) before completing 12 cycles without confirmed progressive disease (PD) are required to complete disease response assessments and report new antimyeloma treatment every 28 ± 7 days until 12 months after randomization, first subsequent antimyeloma treatment, death, loss to follow-up, withdrawal of full consent, or confirmed PD, whichever occurs first. For applicable study subjects, long term follow-up will commence after the 30-day safety follow-up visit. All subjects with confirmed disease progression within 12 months of randomization will be followed for survival every 28 ± 7 days until 12 months after randomization, death, loss to follow-up, or withdrawal of full consent, whichever comes first (Section 9.1.4). For applicable study subjects, long-term follow-up will commence **28 days** after the safety follow-up visit.

The disease assessment schedule is independent of treatment schedules.

Subjects will be randomized in a 1:1 ratio to 1 of 2 arms:

- Arm 1: KRd using once-weekly carfilzomib 56 mg/m^2
- Arm 2: KRd using twice-weekly carfilzomib 27 mg/m^2

Randomization will be performed using an interactive voice/web response system (IxRS). Subjects will be stratified based on the following criteria: original (not revised) International Staging System (ISS) stage at the time of study entry (stage 1 or 2 vs stage 3), prior lenalidomide treatment (yes vs no), prior proteasome inhibitor (PI) treatment (yes vs no), prior anti-CD38 exposure (yes vs no).

All subjects enrolled will have pharmacokinetic samples assessed. Approximately 15 subjects in each arm will be invited to participate in the intensive pharmacokinetics (PK)/pharmacodynamics (PDn) substudy at selected sites. Sparse PK samples will be collected from the rest of the subjects, eg, subjects who do not consent to participate in the intensive PK/PDn substudy. See Sections 9.2.5 and 9.2.6 for more details.

An independent data monitoring committee (DMC) will be convened for this study and will act in an advisory capacity to the sponsor with respect to safeguarding the interests of study subjects, assessing interim data, monitoring the overall conduct of the study, and providing with recommendations relating to continuing, modifying, or stopping the study based on these findings (International Council for Harmonisation Good Clinical Practice [ICH GCP 5.5.2]). Details of the DMC will be described in the DMC Charter. The initial assessment from this committee will be planned after 30 subjects (approximately 15 for the experimental arm and 15 for the control arm) have been enrolled and have finished the first cycle of treatment to ensure safety of all arms. A provision will be made allowing an early follow-up DMC meeting to be decided at the time of the initial assessment. The DMC will meet approximately every 6 months to review safety data on a regular basis, and once to review the efficacy data for futility. The interim analysis for futility is planned to occur when the first 230 subjects have been randomized and had a best overall response (BOR) assessed by the date when treatment was completed, confirmed PD or death occurred, subject was lost to follow-up, withdrew consent, or started new therapy, whichever occurred first.

The individual subject disease response and disease progression for this study will be independently assessed by an Independent Review Committee (IRC) in accordance with the IMWG-URC (Section 12.11). The membership criteria and operational details of the IRC will be described in the IRC Charter. The IRC will centrally review the disease-related tests and assessments (Section 9.2.2) to evaluate disease progressions and responses without the knowledge of randomization assignments or Investigator's disease assessments. The IRC assessment will be used for the primary analysis of efficacy endpoints except for MRD rate and clinical outcome assessments (COA) endpoints.

Number of Subjects

Approximately 460 subjects will be enrolled in the study, with approximately 230 subjects per each arm.

Summary of Subject Eligibility Criteria

This study will enroll adults ≥ 18 years of age with RRMM. Subjects must have measurable disease per IMWG consensus criteria for response assessment in multiple myeloma, Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≤ 2,

and at least partial response (PR) to at least 1 line of prior therapy. Subjects must also have received at least 1 but not more than 3 prior lines of therapy for multiple myeloma including relapse or progression after the most recent myeloma treatment prior to enrollment.

For a full list of eligibility criteria, please refer to Section 6.1 to Section 6.2.

Treatments

For both arms

Each subject's first dose of carfilzomib will be calculated based upon baseline body surface area (BSA) using the Mosteller formula. In subjects with BSA > 2.2 m^2, the dose should be capped based on a BSA of 2.2 m^2. The dose for each subject should not be revised unless the subject has a change in body weight of > 20% (gain or loss) in which case the BSA should be recalculated. Carfilzomib dose is to be recalculated using the updated BSA and applied until such time that any future weight change requires further BSA recalculation. The dose can also be modified in response to toxicity following the dose modification guideline tables using the most current BSA if this has been recalculated since the first cycle due to weight change.

In subjects with normal renal function, lenalidomide will be taken once-daily orally on days 1 to 21 of each cycle at a dose of 25 mg. In subjects with renal impairment (mild to moderate or severe), please refer to the regional product label.

Dexamethasone should be taken weekly orally or by intravenous (IV) infusion at a dose of 40 mg. When dexamethasone is administered on the same day as carfilzomib, it should be started and completed within at least 4 hours of the start of carfilzomib infusion. A 30 minute interval between the end of the dexamethasone infusion and the start of the carfilzomib infusion is recommended. All doses should be administered on the scheduled days $\pm$ 2 days.

Arm 1 (once-weekly KRd 56 mg/m^2):

Carfilzomib will be administered once-weekly IV as a 30 ± 5 minute infusion using an infusion pump on days 1, 8, and 15 of each 28-day cycle. The dose will be 20 mg/m^2 on day 1 of the first cycle and 56 mg/m^2 beginning with day 8 of cycle 1 and thereafter. All carfilzomib doses should be administered on the scheduled day $\pm$ 2 days, and the day 8 and 15 doses should have at least a 5-day treatment-free interval. Dose delays > 2 days are only permitted during the start of a new cycle (for more information see Section 7.4.1).

Arm 2 (twice-weekly KRd 27 mg/m^2):

Carfilzomib will be administered twice-weekly IV as a 10 ± 5 minute infusion using an infusion pump on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. The dose will be 20 mg/m^2 on days 1 and 2 of the first cycle and 27 mg/m^2 beginning with day 8 of cycle 1 and thereafter.

Every effort should be made to maintain the days 1, 2, 8, 9, 15, and 16 every 28-day schedule. If this is not possible, then priority should be to maintain consecutive dosing days. For example, if day 1 of a new cycle is started 2 days later than originally scheduled, the entire cycle should shift by 2 days, such that the new days 1, 2, 8, 9, 15, and 16 of the next cycle are maintained. There must always be at least 5 days between the second dose of 1 week and the first dose of the following week (ie, between days 2 and 8, and days 9 and 15). Mid-cycle doses that are missed should not be made up, unless these parameters are maintained.

Procedures

Written informed consent must be obtained from all subjects or legally acceptable representatives before any study-specific screening procedures are performed. The following procedures will occur per the Schedule of Assessments: demographics, medical history, substance use history, complete physical examination, physical measurements, 12-lead electrocardiogram (ECG) with QTc interval, vital signs, ECOG PS, echocardiogram (ECHO), review of adverse events and serious adverse events, recording of concomitant medications and antimyeloma therapies. Imaging studies will be performed for bone lesions (all subjects) and soft tissue plasmacytoma evaluation (if clinically indicated). Central laboratory testing will be performed to confirm disease status and/or stage, including collection of bone marrow samples for minimal residual disease negative (MRD[-]) testing, cytomorphology, fluorescence in situ hybridization (FISH), and for confirmation of CR or sCR. Additional central laboratory testing will include hematology, serum chemistry, hepatic and renal function. Eligibility labs are to be confirmed by central laboratory prior to enrollment. Samples will also be taken to perform PK and PDn assessments. Local laboratory testing will include coagulation factors, hepatitis B serology and hepatitis B virus (HBV) DNA testing, and pregnancy testing for females of childbearing potential. Clinical outcome assessments will be measured using questionnaires and individual questions.

For a full list of study procedures, including the timing of each procedure, please refer to Section 9.2 and the Schedule of Activities in Table 2-1.

Statistical Considerations

The sample size was determined so that the primary objective could be tested via synthesis method at 1-sided 2.5% significance level with 80% power, including an interim analysis for futility when the first 230 subjects have been randomized and had a BOR assessed by the date when treatment was completed, PD/death occurred, patient dropped out or started new therapy, whichever occurred first.

A sample size of 460 subjects is needed to achieve 80% power for demonstrating that once weekly- KRd 56 mg/m^2 preserves at least 60% of twice-weekly KRd 27 mg/m^2 effect in terms of ORR at a 1-sided 2.5% significance level using the synthesis method. This calculation assumes a true relative risk (RR) of 1 with ORR = 86.6% for both arms (once weekly- KRd 56 mg/m^2 vs twice-weekly KRd 27 mg/m^2), and an interim analysis for futility at 50% information fraction using O'Brien-Fleming beta-spending function. The reference ORR = 86.6% was determined based on the BOR observed by the end of 12 cycles of treatment in ASPIRE study (Amgen data on file).

The hypotheses for the primary and key secondary objectives (ORR, PFS, and convenience after cycle 4 of treatment) will be tested using a fixed sequence hierarchical testing procedure to control the family-wise type I error rate at 1-sided 0.025 level. The testing is ordered as follows: non-inferiority of ORR, non-inferiority of PFS, and superiority of patient-reported convenience after cycle 4 of treatment. Starting with the hypothesis of ORR, if any hypothesis in the sequence is rejected at a 1-sided significance level of 0.025, then the subsequent hypothesis will be tested. Otherwise, if any hypothesis failed to be rejected, then the subsequent hypotheses will not be tested.

Primary/final analyses of efficacy endpoints will be based on the intent-to-treat population, which includes all randomized subjects.

Endpoint	Statistical Analysis Methods
Primary	Overall response over the duration of the study: Clopper-Pearson method for by treatment overall response rate (ORR) estimate and CI. Mantel-Haenszel stratified RR for the inference of treatment effect. The synthesis approach will be used to show that once-weekly KRd 56 mg/m^2 preserves at least 60% of twice-weekly KRd 27 mg/m^2 effect vs Rd.
Secondary	PFS over the duration of the study: Kaplan-Meier (KM) estimates for PFS distribution by treatment and PFS rates and CI at 6 and 12 months, stratified Cox proportional hazards (PH) model for HR and CI estimate. The synthesis approach will be used to show that once-weekly KRd 56 mg/m^2 preserves at least 50% of twice-weekly KRd 27 mg/m^2 effect vs Rd. Patient-reported convenience after cycle 4 of treatment: Cochran-Mantel-Haenszel method will be used to evaluate the treatment effect (OR) for whether carfilzomib dosing is reported as convenient or inconvenient; a logistic regression model including the randomization stratification factors and treatment group will be considered for sensitivity analysis Time to response: mean, SD, median, minimum and maximum among responders. Duration of response (DOR): KM method among responders. Time to progression (TTP): KM method and stratified Cox PH model. OS over the duration of the study: KM estimates for OS distribution by treatment and OS rates and CI at 6 and 12 months, stratified Cox PH model for HR and CI estimate. MRD[-]CR: proportion of MRD[-]CR will be reported with CI calculated using Clopper-Pearson method. MRD[-] status at 12 months from randomization: proportion of MRD[-] will be reported with CI calculated using Clopper-Pearson method. Physical functioning and role functioning (EORTC QLQ-C30) over time: repeated measures analysis of covariance adjusting for the baseline covariates. A restricted maximum likelihood-based mixed model for repeated measures (MMRM) will be considered as sensitivity analysis. Patient-reported treatment satisfaction (CTSQ) after cycle 4 of treatment: analysis of covariance at the corresponding fixed time point.
Exploratory	Will be described in the statistical analysis plan finalized before database lock.

Safety analyses will be based on the safety population (defined as all randomized subjects who have received at least 1 dose of any study treatment [carfilzomib, lenalidomide, or dexamethasone]). The number and percentage of subjects experiencing 1 or more adverse events will be summarized by treatment group, relationship to study treatment, and severity. Changes from baseline and shift in toxicity grade in safety laboratory test results, left ventricular ejection fraction and vital signs will

be summarized using descriptive statistics. Adverse events and safety laboratory test results will be graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0.

Subjects' demographics and disease characteristics, in addition to prior and concomitant medications and study treatment exposure, will be summarized descriptively for each treatment group.

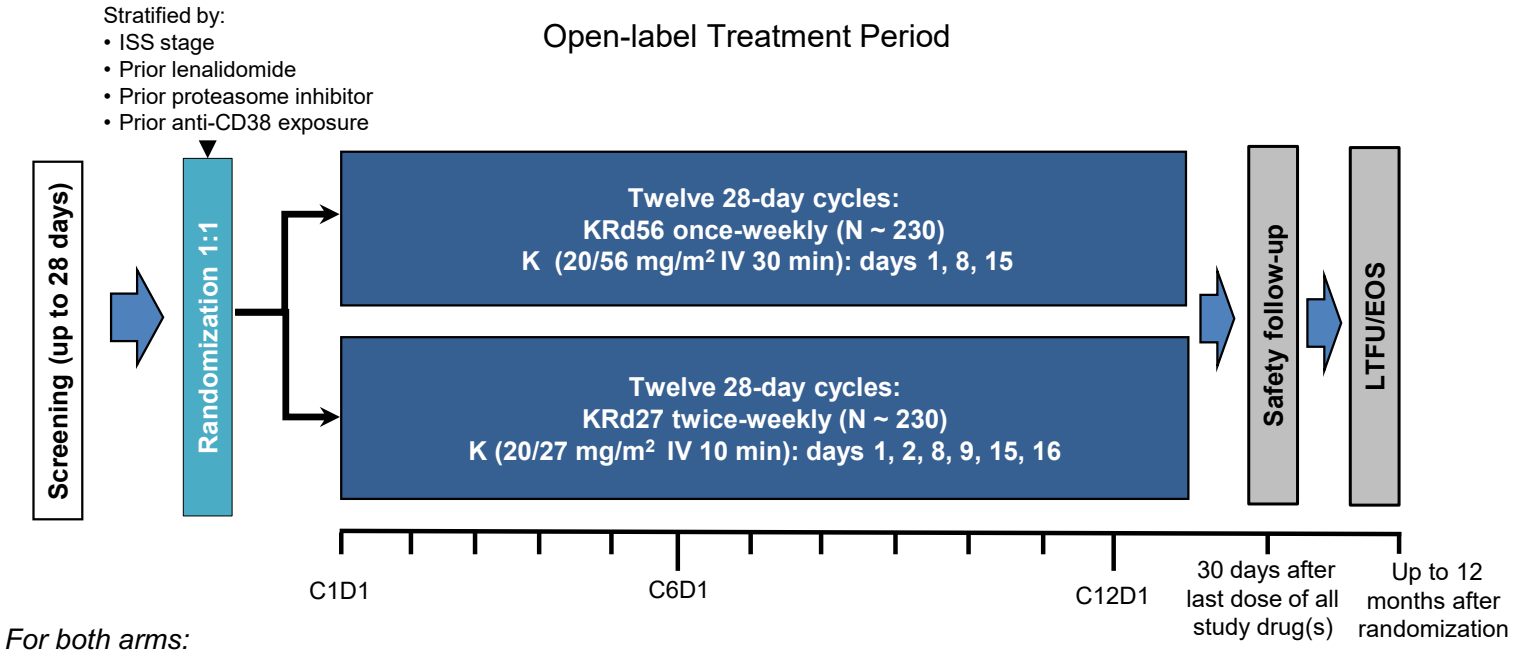
For a full description of statistical analysis methods, please refer to Section 10.

Sponsor Name: Amgen Inc.

2. Study Schema and Schedule of Activities

2.1 Study Schema

Figure 2-1. Study Schema



For both arms:
Lenalidomide (25 mg): days 1-21; Dexamethasone (40 mg weekly; oral or IV)

CxDx = cycle X day X; d = dexamethasone; EOS = End of Study; IV = intravenously; K = Kyprolis (carfilzomib); LTFU = long-term follow-up; R = lenalidomide.

2.2 Schedule of Activities

Table 2-1. Schedule of Activities

PROCEDURE			Screening[a] (up to 28 days before rand)	Treatment Period Cycles 1 to 12 Day 1	2	8	9	15	16	22	Safety FU (30 [+3] days after last dose)	LTFU[b] (every 28 ± 7 days)	Notes
GENERAL AND SAFETY ASSESSMENTS													
Informed consent			X										
Inclusion and exclusion criteria			X										
Demographics			X										
Medical history			X										Including multiple myeloma history
Substance use			X										Tobacco only
Complete physical examination			X								X		
Physical measurements	Height		X										
	BSA		X	(X)									BSA should be calculated during screening per Mosteller formula and utilized to calculate required study drug doses. BSA should be recalculated if weight changes by more than 20% (gain or loss) from weight used at the most recent BSA calculation.
	Weight		X	X									
12-lead ECG with QTc interval			X	(X)									Screening and as clinically indicated.
		cycle 1				X							To be performed at the end of carfilzomib infusion
		cycle 2		X									
Vital signs (once-weekly arm)			X	X		X		X			X		Checked prior to administration of carfilzomib in all cycles. In cycles 1 and 6, an additional blood pressure measurement post-carfilzomib infusion will be collected (within 30 minutes of the end of infusion).
Vital signs (twice-weekly arm)			X	X	X	X	X	X	X		X		
ECOG performance status			X								X		
Echocardiogram			X	(X)							X		During treatment every 6 months (± 2 weeks) from C1D1 until SFU and additionally as clinically indicated. An ECHO must be performed within 72 hours of the onset of a suspected cardiac failure event.

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Footnotes are defined on the last page of the table.

Table 2-1. Schedule of Activities

PROCEDURE		Screening[a] (up to 28 days before rand)	Treatment Period Cycles 1 to 12 Day 1	2	8	9	15	16	22	Safety FU (30 [+3] days after last dose)	LTFU[b] (every 28 ± 7 days)	Notes
Survival											(X)	Subjects who terminate early from study treatment (less than 12 complete cycles) will be followed every 28 ± 7 days after safety follow-up visit until 12 months after randomization, death, loss to follow-up or withdrawal of full consent, whichever comes first.
Subsequent antimyeloma therapies											(X)	All subjects who have ended study treatment without a confirmed PD will be followed every 28 ± 7 days until 12 months after randomization, first subsequent antimyeloma, death, loss to follow-up, withdrawal of full consent, or confirmed PD, whichever comes first.
Adverse events/serious adverse events[c]		Continuous										
Concomitant therapies review		Continuous										
LABORATORY ASSESSMENTS												
Pregnancy test (FCBP only)	Serum	X								X		At screening: 10 to 14 days prior to C1D1
	Urine or serum cycle 1 (predose)		X		X		X		X			Within 24 hours prior to dose of lenalidomide.
	Urine or serum cycle 2 to 12 (predose; regular menses)		X									
	Urine or serum cycle 2 to 12 (irregular menses)		X				X					
Hematology		X	X							X		Hematology and chemistry samples from screening may be used for C1D1 if taken within 3 days prior to C1D1. Hematology and chemistry samples taken within 48 hours of D1 of subsequent cycles may be used for treatment decisions. Laboratory results must be evaluated for potential dose modification assessment prior to dosing.
Chemistry		X	X							X		

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Footnotes are defined on the last page of the table.

Table 2-1. Schedule of Activities

PROCEDURE	Screening[a] (up to 28 days before rand)	Treatment Period Cycles 1 to 12 Day 1	2	8	9	15	16	22	Safety FU (30 [+3] days after last dose)	LTFU[b] (every 28 ± 7 days)	Notes
LABORATORY ASSESSMENTS (CONTINUED)											
Screening laboratory assessments	X										Assessments must be done within 28 days prior to randomization See Table 12-1 for more details.
Coagulation tests	X										
β2 microglobulin	X	(X)									At screening and as clinically indicated.
NT-proBNP	X										At screening.
Quantitative immunoglobulins	X	(X)									During screening, assessments must be done within 28 days prior to randomization. To be repeated only in case of clinical need, such as recurrent infections
Hepatitis B virus	X	(X)							(X)		For subjects with unknown hepatitis serology status or who have not had hepatitis serology tested within 6 months of screening: perform local serology testing for HBsAg, anti-HBs, and anti-HBc. Local testing for HBV DNA will be performed for subjects with any of the following: a known history of hepatitis B, positive serology, or who seroconvert to positive status during treatment. HBV DNA testing will be repeated every 12 weeks (± 2 weeks) or more frequently if clinically indicated through SFU. An appropriate specialist should be consulted for all subjects who test positive. See Section 9.2.3.4.3

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Footnotes are defined on the last page of the table.

Table 2-1. Schedule of Activities

PROCEDURE	Screening[a] (up to 28 days before rand)	Treatment Period Cycles 1 to 12 Day 1	2	8	9	15	16	22	Safety FU (30 [+3] days after last dose)	LTFU[b] (every 28 ± 7 days)	Notes
DISEASE-SPECIFIC ASSESSMENTS											
SPEP/UPEP/SFLC/SIFE/UIFE[d]	X	(X)							X	(X)	Screening disease-specific assessments must be done within 28 day screening window and repeated on C1D1 if not performed within 14 days (of C1D1). See Section 9.2.2.1. Disease assessments at the safety follow-up visit and during LTFU are not required for subjects with confirmed PD or have started new antimyeloma therapy or if assessments were performed within 14 days prior to the safety follow-up visit.
Serum calcium											
Bone lesion assessment	X	(X)								(X)	A standard of care bone lesion radiographic assessment performed within 45 days of Cycle 1 Day 1 may be used as the Screening assessment, and does not need to be repeated, unless standard of care method of assessment is different from as specified above, ie, MRI bone lesion assessment would not be allowed to substitute for the Screening bone lesion assessment. It will be repeated if worsening clinical symptoms suggest PD or as clinically indicated. Not required during LTFU for subjects with confirmed PD.
Plasmacytoma evaluation	(X)	(X)								(X)	Will be done at screening only if clinically suspected. Screening evaluation may be done within the 28 day screening window, if performed as a part of standard of care. For subjects with a history of plasmacytoma, clinical assessment will be performed locally every 28 (± 7) days from C1D1. Radiological exam will be performed only to confirm a response of PR or better, or to confirm PD, or as clinically indicated (see Section 9.2.2.4 for more detail) Not required during LTFU for subjects with confirmed PD.

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Footnotes are defined on the last page of the table.

Table 2-1. Schedule of Activities

PROCEDURE		Screening[a] (up to 28 days before rand)	Treatment Period Cycles 1 to 12 Day 1	2	8	9	15	16	22	Safety FU (30 [+3] days after last dose)	LTFU[b] (every 28 ± 7 days)	Notes
DISEASE-SPECIFIC ASSESSMENTS (CONTINUED)												
Bone marrow sample	For MRD[-] assessment	X	(X)									Within the 28-day screening window, at CR or better, and at 12 months from randomization (± 4 weeks) for all subjects regardless of cycles. A bone marrow aspirate is required for MRD analysis. MRD sample is sent frozen (12-month sample may be omitted if an MRD analysis with confirmed results was performed within 4 months of the scheduled test at 12 months from randomization, or if the subject has started new anti-myeloma therapy prior to 12-month landmark, or if disease progression is recorded).
	Cytomorphology	X	(X)								(X)	Screening, bone marrow aspirate slides for cytomorphology obtained be used as baseline if taken within 45 days prior to randomization and are sent to the central laboratory for processing (see Section 9.2.2.2).
	FISH analysis for cytogenetic risk	X										See Section 9.2.2.2. A bone marrow aspirate is required and will be taken no later than C1D1 predose (ie, during 28-day screening period or C1D1). Note: DO NOT FREEZE the FISH sample tube.
	Immunohistochemisty to confirm sCR		(X)								(X)	When parameters suggest CR has been reached, collect a bone marrow sample: a biopsy or an aspirate clot to enable immunohistochemistry to assess sCR. (At minimum a bone marrow aspirate is required for plasma cell% and MRD).

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Footnotes are defined on the last page of the table.

Table 2-1. Schedule of Activities

PROCEDURE	Screening[a] (up to 28 days before rand)	Treatment Period Cycles 1 to 12 Day 1	2	8	9	15	16	22	Safety FU (30 [+3] days after last dose)	LTFU[b] (every 28 ± 7 days)	Notes
SPARSE PHARMACOKINETIC ASSESSMENTS (ONLY FOR SUBJECTS NOT PARTICIPATING IN OPTIONAL INTENSIVE PK/PDN SUBSTUDY)											
Cycle 2 only		X									• Predose (within 5 min before the start of infusion) • 15 minutes after the start of infusion (± 5 min) for once-weekly arm only • Immediately prior to (within 2 min before) the end of infusion • 30 min after the end of infusion (± 5 min)
INTENSIVE PHARMACOKINETIC ASSESSMENTS (ONLY FOR SUBJECTS IN OPTIONAL INTENSIVE PK/PDN SUBSTUDY)											
Cycle 1		X		X							Day 1 only: • Predose (within 5 min before the start of infusion) • Immediately prior to (within 2 min before) the end of infusion Day 8 only: • Predose (within 5 min before the start of infusion) • 15 minutes after the start of infusion (± 5 min) for once-weekly arm only • Immediately prior to (within 2 min before) the end of infusion • 15 min, 60 min, and 2 hr after the end of infusion (± 5 min)
Cycle 2		X		X							• Predose (within 5 min before the start of infusion) • Immediately prior to (within 2 min before) the end of infusion • 60 minutes after the end of infusion (± 5 min)

Footnotes are defined on the last page of the table.

Table 2-1. Schedule of Activities

PROCEDURE	Screening[a] (up to 28 days before rand)	Treatment Period Cycles 1 to 12 Day 1	2	8	9	15	16	22	Safety FU (30 [+3] days after last dose)	LTFU[b] (every 28 ± 7 days)	Notes
PHARMACODYNAMIC ASSESSMENTS (ONLY FOR SUBJECTS IN OPTIONAL INTENSIVE PK/PDN SUBSTUDY)											
Cycle 1		X		X							Day 1 only: • Predose (within 5 min before the start of infusion) Day 8 only: • Predose (within 5 min before the start of infusion) • 60 minutes (± 5 min) after the end of infusion
Cycle 2		X		X		X					• Predose (within 5 min before the start of infusion) • 60 min after the end of infusion (± 5 min)
Cycle 3 to 7		X									• Predose (within 5 min before the start of infusion) • 60 min after the end of infusion (± 5 min)
CLINICAL OUTCOME ASSESSMENTS – TO BE COMPLETED PRIOR TO ANY STUDY PROCEDURE											
EORTC QLQ-C30		(X)							X		[redacted] Before dosing on day 1 of cycle 1, 3, 5, 7, 9, and 12
Patient-reported convenience with carfilzomib-dosing schedule single-item question		(X)							X		Before dosing on C2D1, C5D1, and C12D1 for subjects still receiving carfilzomib.
[redacted]											
CTSQ		(X)							X		Before dosing on C2D1, C5D1, and C12D1.
[redacted]											

Footnotes are defined on the last page of the table.

Table 2-1. Schedule of Activities

PROCEDURE	Screening[a] (up to 28 days before rand)	Treatment Period Cycles 1 to 12 Day 1	2	8	9	15	16	22	Safety FU (30 [+3] days after last dose)	LTFU[b] (every 28 ± 7 days)	Notes
STUDY TREATMENT ADMINISTRATION											
Once-weekly arm											
Carfilzomib		X		X		X					Cycle 1: 20 mg/m^2 on days 1; 56 mg/m^2 on days 8, 15 Cycles 2-12: 56 mg/m^2 each dosing day
Dexamethasone		X		X		X		(X)			40 mg (oral or IV) weekly. Day 22 administration is for cycles 1 to 9 only and may be self-administered at home
IV prehydration		(X)		(X)		(X)					As clinically indicated (Section 7.1.1.3)
Lenalidomide		Days 1 to 21									In subjects with normal renal function, lenalidomide will be taken once-daily on days 1 to 21 at a dose of 25 mg. In subjects with renal impairment (mild to moderate or severe), please refer to the regional product label.
Twice-weekly arm											
Carfilzomib		X	X	X	X	X	X				Cycle 1: 20 mg/m^2 on days 1 and 2; 27 mg/m^2 on days 8, 9, 15, and 16 Cycles 2 to 12: 27 mg/m^2 each dosing day
Dexamethasone		X		X		X		(X)			40 mg (oral or IV) weekly. Day 22 administration is for cycles 1 to 9 only and may be self-administered at home
IV prehydration		(X)	(X)	(X)	(X)	(X)	(X)				As clinically indicated (Section 7.1.1.3)
Lenalidomide		Days 1 to 21									In subjects with normal renal function, lenalidomide will be taken once-daily on days 1 to 21 at a dose of 25 mg. In subjects with renal impairment (mild to moderate or severe), please refer to the regional product label.

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anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; BSA = body surface area; C = cycle; CR = complete response; CTSQ = Cancer Therapy Satisfaction Questionnaire; CxDx = cycle X day X; D = day; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; EORTC = European Organization for Research and Treatment of Cancer; EORTC QLQ-C30 = EORTC Quality-of-life Questionnaire Core 30; [redacted] FCBP = females of childbearing potential; FISH = fluorescence in-situ hybridization; FU = follow-up; IV = intravenously; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; LTFU = long-term follow-up; MRD [-] = minimal residual disease negative; NT-proBNP = N terminal of the prohormone brain natriuretic peptide; PD = progressive disease; PDn = pharmacodynamics; PK = pharmacokinetics; PR = partial response; rand = randomization; sCR = stringent complete response; [redacted] SFLC = serum-free light chain; SIFE = serum immunofixation; SOC = standard of care; SPEP = serum protein electrophoresis; UIFE = urine immunofixation; UPEP = urine protein electrophoresis

(X) = Parentheses indicate that the particular test is situational at that time point, as specified in the respective notes.

[a] If the assessments are repeated during screening, then the most recent result prior to randomization should be used to determine eligibility.

[b] LTFU is up to 12 months after randomization.
[c] If the investigator becomes aware of serious adverse events suspected to be related to IP or fatal serious adverse events (regardless of causality) after completion of the protocol-required reporting period, then these serious adverse events will be reported to Amgen within 24 hours following the investigator's awareness of the event on the Events CRF. Please refer to Section 9.2.3.1.1.3 for additional details.
[d] Disease response assessments are to be performed every 28 ± 7 days from C1D1 through the end of C12 or until confirmed PD, whichever comes first, regardless of cycle duration, dose delays, or treatment discontinuation. After discontinuation from study treatment, subjects who do not have confirmed PD are required to continue disease response assessments and report new antimyeloma treatment and will be followed every 28 ± 7 days until 12 months after randomization, first subsequent antimyeloma treatment, death, loss to follow-up, withdrawal of full consent, or confirmed PD, whichever comes first.

3. Introduction

3.1 Study Rationale

Recently, the International Myeloma Working Group (IMWG) published recommendations on management of relapsed multiple myeloma and advocated a regimen containing carfilzomib (K), preferably in combination with lenalidomide (R) and dexamethasone (d) (Laubach et al, 2016); such a regimen (27 mg/m^2 KRd, twice-weekly) was approved for treatment of relapsed multiple myeloma based on the results of ASPIRE study (Stewart et al, 2015).

ASPIRE was the first phase 3 randomized study demonstrating that a triplet combining non-conventional chemotherapy agents and carfilzomib had significant improvement in outcomes when compared with a doublet in patients who had received 1 to 3 prior lines of therapy and whose disease had not progressed during treatment with bortezomib or lenalidomide plus dexamethasone (if it was their most recent treatment). In this study, the addition of carfilzomib to lenalidomide and dexamethasone reduced the risk of death or progression by 31% when compared with lenalidomide and dexamethasone alone (hazard ratio [HR] = 0.69, $p < 0.0001$) which translated into a median progression-free survival (PFS) of 26.3 months. Further, KRd 27 mg/m^2 twice-weekly was associated with a high overall response rate (ORR) of 87.1% (odds ratio [OR] = 3.47; $p < 0.0001$) (Stewart et al, 2015), increasing rapidly by end of cycle 4 of treatment, and demonstrated a statistically significant 8-month improvement in median overall survival (OS) (HR = 0.794; $p = 0.0045$) (Siegel et al, 2018). Also, the rate of complete or stringent complete response (CR/sCR) has a steep increase by end of 12 cycles of KRd 27 mg/m^2 twice-weekly (Dimopoulos et al, 2018). These positive results were seen despite a less intensified carfilzomib dosing after 12 cycles of therapy and limiting carfilzomib treatment to the first 18 cycles of therapy.

For the approved dose schedule of KRd, carfilzomib is administered intravenously (IV) on 2 consecutive days for 3 weeks (ie, days 1, 2, 8, 9, 15, and 16) of each 28-day cycle. The frequency of dosing in this regimen demands a substantial time commitment and potential financial challenges for patients and caregivers, as carfilzomib is generally administered in an outpatient clinic. This time commitment can be particularly burdensome for patients with transportation or mobility challenges (Barrett-Lee et al, 2007). As a result, compliance with the currently available twice-weekly dose schedule for the KRd regimen may be less optimal and can reduce the ability to achieve deep responses and the longest possible survival.

A more time-efficient once-weekly dosing schedule can help improve patient adherence to treatment with antimyeloma IV agents. Two studies of once-weekly vs twice-weekly dosing schedules of bortezomib as combination therapy showed similar efficacy between the 2 regimens; however, patients with multiple myeloma treated once-weekly were more concordant, received higher doses, had fewer dose reductions, and were treated for longer durations compared with patients treated twice-weekly (Bringhen et al, 2010; Reeder et al, 2010). These studies provide clinical evidence that a once-weekly schedule can result in improved dosing and longer duration of therapy when compared with a twice-weekly schedule, while preserving benefit to the patients and allowing for a schedule that is less burdensome.

Exploring a KRd regimen aimed at improving tolerability, treatment convenience, and patient satisfaction while preserving clinical benefit to the patients is expected to address the challenges patients may face with the on-label twice-weekly KRd 27 mg/m^2 dose regimen and is an important consideration for improving treatment outcomes.

3.1.1 Justification for Primary Endpoint

The ORR over the duration of the study is used as the primary endpoint to establish non-inferiority in terms of efficacy of a once-weekly KRd regimen (56 mg/m^2) when compared with weekly KRd dose regimen with the on-label twice-weekly KRd 27 mg/m^2 dose regimen. A positive correlation between ORR and PFS is supported by ASPIRE overall response and PFS rates (Stewart et al, 2015), as well as by the data from meta-analysis of 7 phase 3 studies with different treatment regimens for this study population (Teng et al, 2018).

In the pivotal ASPIRE study (the historical study for the non-inferiority analysis), the analysis of ORR was statistically significant and consistent with the treatment effect observed in PFS (primary endpoint) and OS. The ORR was 87.1% (95% CI: 83.4, 90.3) in the KRd arm versus 66.7% (95% CI: 61.8, 71.3) in the Rd arm (OR [95% CI]: 3.47 [2.41, 5.00]; $p < 0.0001$) and corresponded with a 9-month improvement in median PFS and an 8-month improvement in OS. The mean time to response (TTR) was 1.6 months in the KRd arm (Siegel et al, 2018; Stewart et al, 2015) and the response rate increased rapidly by end of cycle 4 plateauing after that. By the end of 12 cycles of treatment in the ASPIRE study, the best ORR was 86.6% (Amgen data on file), with a CR/ sCR rate steeply increasing (Dimopoulos et al, 2018), and Kaplan-Meier event-free rate for PFS was 74.6% (HR = 0.55) (Amgen data on file)

In the supplementary appendix of the e-publication, Stewart et al present a landmark analysis of PFS within the KRd group among patients who achieved partial response (PR) or better compared with patients who did not achieve a response of PR or better, providing evidence that the responders had significantly longer subsequent PFS than nonresponders ($p < 0.001$). The Simon-Makuch landmark transient-state method at the end of 2 months from randomization was used to minimize the bias in favor of responders represented by the time necessary to reach the response (Simon and Makuch, 1984).

Results of an ongoing Study 20140241 (CFZ013) evaluating once-weekly dosing regimens of KRd (56 and 70 mg/m^2) support the proposed ORR as a primary endpoint. After a median treatment time of 39 weeks, ORR was 90% for subjects treated with 56 mg/m^2. The combined dose cohort, including subjects that were treated with weekly doses of 56 and 70 mg/m^2 (N = 56) reached an ORR of 89.3% after a median treatment time of 33 weeks (Amgen data on file).

Additional supportive evidence for the appropriateness of the primary endpoint ORR involves a model-based meta-analysis of 7 phase 3 studies in subjects with relapsed and refractory multiple myeloma (RRMM), which included ASPIRE and ENDEAVOR studies (Teng et al, 2018). This meta-analysis assessed the relationship between ORR and PFS. The results from these phase 3 studies showed that responses are attainable within the first 4 months of treatment and demonstrated a linear relationship between ORR and median PFS, with a strong correlation (R2 = 0.84) (Teng et al, 2018). The selected studies encompass a broad representation of treatment regimens, with 12 treatment arms used to evaluate the relationship of ORR and PFS. The median time to response (defined as achievement of PR or better) in this meta-analysis was $\leq$ 4 months in 6 of the 7 studies with available information (Teng et al, 2018).

These evidences indicate that ORR over duration of the study is an appropriated predictor of PFS and will be a suitable indicator of efficacy to establish non-inferiority between once-weekly and twice-weekly KRd dose regimens.

3.1.2 Justification for the Clinical Outcome Assessments Endpoints

Treatment convenience and satisfaction are significant endpoints adding to the health-related quality-of-life (HRQOL) of RRMM patients (Moreau et al, 2011). Results of the phase 3 A.R.R.O.W. study comparing once-weekly dosing of Kd (70 mg/m^2) with twice-weekly Kd (27 mg/m^2) demonstrated that subjects who were receiving once-weekly carfilzomib reported higher odds of convenience and satisfaction than

subjects receiving twice-weekly carfilzomib (Study 20140355). However; this clinical outcome assessment (COA) was exploratory and was not corrected for multiplicity. Therefore, the same patient-reported convenience with carfilzomib-dosing schedule question will be used in this study as a secondary endpoint (corrected for multiplicity) to compare patient-reported convenience with carfilzomib-dosing schedule between treatment arms. Response categories include 'very convenient, convenient, inconvenient, and very inconvenient,' and differ from the response categories to the question in ARROW, which also included 'neutral' as a response.

3.2 Background

3.2.1 Disease

Multiple myeloma, a clonal neoplastic proliferation of plasma cells, is the second most common hematologic malignancy and is responsible for approximately 80 000 annual deaths worldwide (1% of all cancer deaths). The estimated incidence of multiple myeloma worldwide was 114 000 patients, which represents 0.8% of all cancers. The 5-year prevalence of multiple myeloma worldwide was estimated 229 000 persons (Ferlay et al, 2015). Multiple myeloma is a disease of older adults, with a median age at diagnosis of 69 years (Noone et al, 2018). As the world's older population (age $\geq$ 65 years) continues to grow (from 8.5% [617 million] of the world's population in 2013 to a projected 17% [1.6 billion] in 2015) (He et al, 2016), the incidence of multiple myeloma is expected to increase.

3.2.2 Amgen Investigational Product Background: Carfilzomib

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor (PI) that binds selectively and irreversibly to the 20S proteasome, the proteolytic core particle within the 26S proteasome. Consequently, proteasome function after therapy can only be regained by de novo proteasome synthesis. Specifically, carfilzomib inhibits the chymotrypsin-like catalytic activity of the β5 subunit over the caspase-like catalytic activity of the β1 subunit or the trypsin-like catalytic activity of the β2 subunit, resulting in the accumulation of proteasome substrates and ultimately growth arrest and apoptosis (Hoy, 2016). Carfilzomib extensively penetrates all tissues, but the brain. It is metabolized largely extra-hepatically and rapidly cleared from the circulation by biliary and renal excretion ($t_{1/2}$ = 15 to 30 minutes); < 1% is excreted intact (Kortuem and Stewart, 2013).

Carfilzomib entered clinical studies in September 2005. On 20 July 2012, Kyprolis® (carfilzomib for injection) was granted accelerated approval by the US Food and Drug

Administration (FDA) for the treatment of patients with multiple myeloma who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agents (IMiD), and have demonstrated disease progression on or within 60 days of completion of the last therapy. The initial accelerated approval was based on the results of the phase 2 PX-171-003-A1 study in the United States. Subsequent full approval in the United States and globally were based on 2 phase 3 studies: PX-171-009 ASPIRE and 2011-003 ENDEAVOR. Following these approvals, Kyprolis in combination with either lenalidomide and dexamethasone or dexamethasone alone is indicated for the treatment of RRMM. The exact indication wording varies by region.

As of 19 July 2018, an estimated 4132 subjects have been treated with carfilzomib in company-sponsored clinical studies since the beginning of the development program and approximately 88 964 patients have been exposed to carfilzomib in the postmarketing setting.

A detailed description of the chemistry, pharmacology, efficacy, and safety of carfilzomib is provided in the Carfilzomib Investigator's Brochure (IB).

3.3 Benefit/Risk Assessment

The following benefit-risk assessment supports the conduct of this clinical study.

Reference should be made to the Carfilzomib IB for further data on carfilzomib.

3.3.1 Therapeutic Context

Relapsed or refractory multiple myeloma treatment has evolved rapidly in recent years. Progress has been made in autologous stem cell transplantation along with the introduction of several breakthrough drugs, including IMiD and PI, which led to a significant increase in response rate as well as survival rate (Kumar et al, 2012). While treatment for multiple myeloma will typically induce remission, multiple myeloma is characterized by a recurring pattern of remission and relapse. With each subsequent line of treatment, the duration and depth of response decreases (Cook et al, 2018) and patients eventually develop treatment resistance (Papadas and Asimakopoulos, 2017). It is not uncommon for patients to be treated with 3 or more lines of therapy.

The goal of treatment for RRMM is to achieve the longest PFS and subsequently OS. The depth of response is associated with OS and a critical factor to achieving that goal (Chanan-Khan and Giralt, 2010; Richardson et al, 2007). Additional goals include: control disease to prevent or delay associated complications (such as bone fractures,

renal insufficiency, and infections), to maintain an acceptable HRQOL, and to provide relief of pain and other disease-related symptoms.

3.3.2 Key Benefits

Triplet therapy combining a PI with an IMiD and steroid remains an important and commonly used option for many patients with RRMM. The key benefits of carfilzomib as a triplet therapy for patients RRMM include: increases in OS, PFS, and ORR; as well as improvements in quality-of-life. The evidence for these benefits is based on the pivotal, phase 3 randomized study (Study PX-171-009 [hereafter referred to as ASPIRE], N = 792 subjects) and an ongoing open-label, multicenter, phase 1b dose-finding and dose evaluation study (NCT02335983; Study CFZ 013, N = 56).

ASPIRE evaluated KRd 20/27 mg/m^2 twice-weekly vs Rd for treatment of relapsed multiple myeloma: the addition of carfilzomib to lenalidomide and dexamethasone reduced the risk of death or progression by 31% when compared with lenalidomide and dexamethasone alone. The median PFS with carfilzomib was 26.3 months compared with 17.6 months without carfilzomib (HR = 0.69, 95% CI: 0.57, 0.83; p < 0.0001). Further, KRd 27 mg/m^2, twice-weekly was associated with a higher ORR of 87.1% vs 66.7% in the control arm (OR = 3.47; p < 0.0001) (Stewart et al, 2015) and improved OS by 8-month (median OS 48.3 vs 40.4 months; HR = 0.79; p = 0.0045) (Siegel et al, 2018).

The ongoing Study CFZ013 evaluates once-weekly KRd in patients with RRMM and newly diagnosed multiple myeloma (NDMM). As of data cut-off 22 February 2018, available efficacy results from 56 subjects with either RRMM or NDMM treated with weekly KRd 56 mg/m^2 or KRd 70 mg/m^2 has shown similar efficacy (as determined by ORR) with either KRd 56 mg/m^2 or KRd 70 mg/m^2 (90.0% versus 89.1%, respectively) to the effect previously reported for twice-weekly KRd (27 mg/m^2) in the randomized phase 3 ASPIRE study (Biran et al, 2018). These results complement the significant efficacy results of carfilzomib as a triplet therapy.

The European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30) instrument with a GHS/QOL subdomain was used to assess HRQOL as a secondary endpoint in ASPIRE. Subjects had higher QLQ-C30 global health status/quality of life (GHS/QOL) scores in the KRd group versus the Rd group over 18 cycles of treatment (overall treatment difference: 4.23, 95% CI: 2.09, 6.37 [Stewart et al, 2016]), with a nominal 1-sided p = 0.0001. Thus, in ASPIRE KRd improved overall health and quality-of-life compared with Rd, respectively.

3.3.3 Key Risks

Multiple important identified and potential risks for carfilzomib have been identified based on pooled safety data from completed studies where carfilzomib was used in combination (with lenalidomide-dexamethasone, cyclophosphamide dexamethasone, melphalan prednisone, or carboplatin etoposide), with dexamethasone alone, or in monotherapy studies (n = 2944). Dose modification instructions for the management of toxicities is provided in Section 7.4.

Although the key identified risks (ie, cardiac failure, acute renal failure, and hypertension) are underlying comorbidities in patients with multiple myeloma (Kistler et al, 2014; Christiansen et al, 2011; Knauf et al, 2009), these risks were identified as key risks with carfilzomib based on a greater incidence and severity of adverse events in the carfilzomib treatment groups versus the comparators in the randomized clinical studies. The combination of KRd has been studied in the randomized clinical study ASPIRE (A Randomized, Multicenter, Phase 3 Study Comparing Carfilzomib, Lenalidomide, and Dexamethasone [KRd] vs Lenalidomide and Dexamethasone [Rd] in Subjects with Relapsed Multiple Myeloma). The information about the key risks from this study has been summarized below in Section 3.3.3.1.

Additional information regarding important identified risks as well as adverse drug reactions for carfilzomib are detailed in the Carfilzomib IB.

Embryo-fetal toxicity is associated with REVLIMID® (lenalidomide) treatment. Investigators and subjects must comply with the requirements of restricted distribution programs if one is present in the local region; (eg, REVLIMID Risk Evaluation and Mitigation Strategy [REMS] program in the United States). Additional information regarding risks for lenalidomide are described in REVLIMID United States Prescribing Information (USPI) and REVLIMID Summary of Product Characteristics (SmPC) or local prescribing information.

Warnings for dexamethasone include anaphylactoid reactions, cardio-renal toxicities, endocrine toxicities, infections, and ophthalmic toxicities. Dexamethasone is approved for the palliative treatment of neoplastic diseases. Additional details regarding the risks of dexamethasone are provided in the prescribing information (Dexamethasone USPI, Dexamethasone SmPC). The risks of dexamethasone in this study are expected to be similar with the overall safety profile described in the labeling information.

3.3.3.1 Risks

3.3.3.1.1 Cardiac Toxicity

New onset or worsening of pre-existing cardiac failure (eg, congestive heart failure, pulmonary edema, decreased ejection fraction), including fatalities, have occurred after administration of carfilzomib. In clinical studies with carfilzomib, these events occurred throughout the course of carfilzomib therapy.

Incidence of cardiac failure events reported in ASPIRE was as follows: all grades: KRd: 7.1%, Rd: 4.1%; serious adverse events: KRd: 4.1%, Rd: 2.1%; grade ≥ 3 adverse events: KRd: 4.3%, Rd: 2.1%. Most of the cardiac failure adverse events (all grades) were resolved (KRd: 3.3%, Rd: 1.5%) or stabilized/not resolving (KRd: 2.6%, Rd: 1.5%) or resolved with sequelae (KRd: 0.5%, Rd: 0%). Fatal outcomes were reported for 0.8% subjects from the KRd group and 1.0% from the Rd group. Cardiac failure adverse events (all grades) leading to discontinuation of any investigational product were reported for 0.5% of subjects from the KRd group and 0.8% of subjects from the Rd group.

Once-weekly carfilzomib has been evaluated in A.R.R.O.W study (a randomized phase 3 study in 478 subjects with relapsed and refractory multiple myeloma receiving carfilzomib in combination with dexamethasone, comparing once-weekly versus twice-weekly carfilzomib dosing). Incidence of cardiac failure events reported in this study was as follows: all grades: Kd 20/70 mg/m^2 once-weekly: 3.8%, Kd 20/27 mg/m^2 twice-weekly: 5.1%; serious adverse events: Kd 20/70 mg/m^2 once-weekly: 3.4%, Kd 20/27 mg/m^2 twice-weekly 3.4%; grade ≥ 3 adverse events: Kd 20/70 mg/m^2 once-weekly: 2.9%, Kd 20/27 mg/m^2 twice-weekly: 4.3%. Adverse event outcomes were reported for serious adverse events only in A.R.R.O.W. Almost all the cardiac failure serious adverse events were resolved (Kd 20/70 mg/m^2 once-weekly: 2.9%, Kd 20/27 mg/m^2 twice-weekly: 1.7%) or not resolved (Kd 20/70 mg/m^2 once-weekly: 0.4%, Kd 20/27 mg/m^2 twice-weekly: 1.3%). One fatal outcome was reported (Kd 20/70 mg/m^2 once-weekly: 0%, Kd 20/27 mg/m^2 twice-weekly: 0.4%). Cardiac failure adverse events (all grades) leading to discontinuation of any investigational product were reported for 2.9% of subjects from the Kd 20/70 mg/m^2 once-weekly group and 2.6% of subjects from the Kd 20/27 mg/m^2 twice-weekly group.

The risk of cardiac failure is increased in elderly patients (≥ 75 years) and in Asian patients. Subjects with New York Heart Association Class III and IV heart failure, recent myocardial infarction, and conduction abnormalities uncontrolled by medications were

not eligible for the clinical study and may be at greater risk for cardiac complications. While adequate hydration is required prior to dosing in cycle 1, all subjects should be monitored for evidence of volume overload, especially subjects at risk for cardiac failure. The total volume of fluids may be adjusted as clinically indicated in subjects with baseline cardiac failure or who are at risk for cardiac failure.

3.3.3.1.2 Hypertension

Hypertension has been reported as one of the common comorbidities in patients with multiple myeloma. Based on the MarketScan claims database, the prevalence of hypertension as a comorbidity among multiple myeloma patients is 46.9% (Song et al, 2016) and there was a 30% increase in the risk of hypertension in multiple myeloma versus non-multiple myeloma patients (Chari et al, 2016). The incidence of hypertension adverse events in ASPIRE was as follows: all grades: KRd: 17.1%, Rd: 8.7%, serious adverse events: KRd: 0%, Rd: 0.3%; grade ≥ 3 adverse events: KRd: 6.4%, Rd: 2.3%. The incidence of hypertension (all grades) was higher in subjects with a history of hypertension: with history of hypertension: KRd: 20.5%, Rd: 10.7%; without history of hypertension: KRd: 13.7%, Rd: 7.1%. No fatal outcomes for hypertension adverse events (all grades) were reported in ASPIRE. Almost all the hypertension adverse events (all grades) were stabilized/not resolving (KRd: 8.7%; Rd: 4.4%) or resolved (KRd: 8.4%, Rd: 4.1%); resolved with sequelae was also reported (KRd: 0%, Rd: 0.3%). Hypertension adverse events (all grades) led to discontinuation of any investigational product in 0.3% subjects from the KRd and Rd groups each. Hypertensive crisis occurred in ≤ 0.5% of subjects (KRd: 0.5%, Rd: 0.3%), all these adverse events were ≥ grade 3.

The incidence of hypertension adverse events in A.R.R.O.W was as follows: all grades: Kd 20/70 mg/m2 once-weekly: 21.8%, Kd 20/27 mg/m^2 twice-weekly: 21.3%, serious adverse events: Kd 20/70 mg/m^2 once-weekly: 0%, Kd 20/27 mg/m^2 twice-weekly: 0.4%; grade ≥ 3 adverse events: Kd 20/70 mg/m^2 once-weekly: 5.9%, Kd 20/27 mg/m^2 twice-weekly: 5.5%. In A.R.R.O.W., the difference in incidence of hypertension (all grades) among subjects with or without a history of hypertension was similar between treatment groups (with history of hypertension: Kd 20/70 mg/m^2 once-weekly: 22.2%, Kd 20/27 mg/m^2 twice-weekly: 20.6%; subjects without history of hypertension: Kd 20/70 mg/m^2 once-weekly: 21.6%, Kd 20/27 mg/m^2 twice-weekly: 21.9%. Adverse event outcomes were reported for serious adverse events only in A.R.R.O.W. The only hypertension serious adverse event was resolved (Kd 20/70 mg/m^2 once-weekly: 0%,

Kd 20/27 mg/m^2 twice-weekly: 0.4%). Hypertension adverse events (all grades) led to discontinuation of any investigational product in 1.3% subjects from the Kd 20/70 mg/m^2 once-weekly and 0% from the Kd 20/27 mg/m^2 twice-weekly group. Hypertensive crisis occurred in ≤ 0.5% of subjects (Kd 20/70 mg/m^2 once-weekly: 0%, Kd 20/27 mg/m^2 twice-weekly: 0.4%), all these adverse events were ≥ grade 3.

Blood pressure is monitored while on study and hypertension should be treated as needed. If hypertension cannot be controlled, the carfilzomib dose should be held. In case of hypertensive crisis, carfilzomib should be stopped until the hypertensive crisis resolved. The investigator may consider restarting carfilzomib based on an individual benefit-risk assessment.

3.3.3.1.3 Acute Renal Failure

Renal failure is a relatively common problem in patients with multiple myeloma (Dimopoulos et al, 2016; Bladé and Rosiñol, 2005). Acute renal failure occurs most often in patients with multiple myeloma who have high rates of production and excretion of immunoglobulin (Ig)-free light chains, which may be toxic to the basement membranes of the glomeruli and/or the renal tubules and form obstructing tubular casts, particularly if the patient is dehydrated (Dimopoulos et al, 2016; Sanders and Booker, 1992).

Incidence of acute renal failure in ASPIRE was as follows: all grades: KRd: 9.2%, Rd: 7.7%; serious adverse events: KRd: 2.6%, Rd: 1.8%; grade ≥ 3 adverse events: KRd: 3.8%, Rd: 3.3%. Most of the acute renal failure adverse events (all grades) were resolved (KRd: 6.1%, Rd: 5.7%) or stabilized/not resolving (KRd: 2.8%, Rd: 1.8%) or resolved with sequelae (KRd: 0.3%, Rd: 0%). No fatal outcomes were reported for the KRd group; in the Rd group, fatal outcomes were reported for 0.3% of the subjects. Acute renal failure adverse events (all grades) leading to discontinuation of any investigational product were reported for 0.5% subjects in the KRd group and 1.0% in the Rd group.

The incidence of acute renal failure adverse events in A.R.R.O.W was as follows: all grades: Kd 20/70 mg/m^2 once-weekly: 7.1%, Kd 20/27 mg/m^2 twice-weekly: 6.8%, serious adverse events: Kd 20/70 mg/m^2 once-weekly: 4.6%, Kd 20/27 mg/m^2 twice-weekly: 5.1%; grade ≥ 3 adverse events: Kd 20/70 mg/m^2 once-weekly: 3.8%, Kd 20/27 mg/m^2 twice-weekly: 5.5%. Adverse event outcomes were reported for serious adverse events only in A.R.R.O.W. All of the acute renal failure serious adverse events were resolved (Kd 20/70 mg/m^2 once-weekly: 3.8%, Kd 20/27 mg/m^2 twice-weekly: 3.8%) or not resolved (Kd 20/70 mg/m^2 once-weekly: 0.8%, Kd 20/27 mg/m^2

twice-weekly: 1.3%). None were reported as fatal or unknown in either treatment group. Acute renal failure adverse events (all grades) leading to discontinuation of any investigational product were reported for 2.1% subjects in the Kd 20/70 mg/m^2 once-weekly and Kd 20/27 mg/m^2 twice-weekly groups, each.

Acute renal failure was reported more frequently in patients with advanced RRMM who received carfilzomib monotherapy. The incidence was increased in patients with a decrease in estimated creatinine clearance, calculated using Cockcroft and Gault equation, prior to receiving carfilzomib. Renal function should be monitored with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or stop dose as described in the dose modification Section 7.4.

4. Objectives, Endpoints and Hypotheses

4.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• compare efficacy of 56 mg/m^2 carfilzomib administered once-weekly in combination with lenalidomide and dexamethasone (KRd 56 mg/m^2) to 27 mg/m^2 carfilzomib administered twice-weekly in combination with lenalidomide and dexamethasone (KRd 27 mg/m^2) in subjects with relapsed or refractory multiple myeloma (RRMM) with 1 to 3 prior lines of therapy	• overall response, defined as the best overall response of stringent complete response [sCR], complete response [CR], very good partial response [VGPR], and partial response [PR] per International Myeloma Working Group Uniform Response Criteria [IMWG-URC] over the duration of the study
Key Secondary	
• compare progression-free survival (PFS) between treatment arms	• PFS over the duration of the study
• compare patient-reported convenience with carfilzomib-dosing schedule between treatment arms	• convenience as measured by the Patient-reported Convenience With Carfilzomib-dosing Schedule Question after cycle 4 of treatment
Secondary	
• describe safety and tolerability in treatment arms	• incidence of treatment-emergent adverse events
• compare additional efficacy parameters between treatment arms	• time to response (TTR) • duration of response (DOR) • time to progression (TTP)

Objectives	Endpoints
• compare overall survival (OS) between treatment arms	• OS over the duration of the study
• compare rate of minimal residual disease negative (MRD[-]) in bone marrow aspirates between treatment arms	• MRD[-]CR, defined as achievement of CR or better by Independent Review Committee (IRC) per IMWG-URC and achievement of MRD negativity as assessed by next-generation sequencing method at a 10^{-5} threshold over the duration of the study • MRD[-] status at 12 months, defined as achievement of MRD negativity at 12 months (± 4 weeks) from randomization, as assessed by next-generation sequencing method at a 10^{-5} threshold
Secondary (continued)	
• compare patient-reported physical functioning and role functioning between treatment arms	• physical functioning and role functioning over time as measured by the Physical Functioning and Role Functioning scales of the European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30) over the duration of the study
• compare patient-reported treatment satisfaction between treatment arms	• treatment satisfaction as measured by the Satisfaction With Therapy (SWT) scale of the Cancer Therapy Satisfaction Questionnaire (CTSQ) after cycle 4 of treatment

Exploratory	
Objectives	**Endpoints**
[redacted]	

Exploratory	
Objectives	**Endpoints**
[redacted]	

4.2 Hypotheses

Once-weekly KRd 56 mg/m^2 is non-inferior in terms of efficacy when compared with twice-weekly KRd 27 mg/m^2.

5. Study Design

5.1 Overall Design

This is a phase 3, multicenter, open-label, randomized study in subjects with RRMM who have received 1 to 3 prior therapies. The study will consist of a screening period of up to 28 days, a treatment duration of up to 12 cycles of 28 days, and a 30-day safety follow-up period.

Subjects will receive the study drug(s) determined by randomization for a maximum of 12 cycles. No crossover between the treatment arms is allowed. After discontinuation of study drug(s) subjects will have a safety follow-up visit 30 (+3) days after the last dose of all study drug(s). After end of study, subjects may continue treatment per local standard of care at the discretion of the investigator.

All subjects will be assessed for multiple myeloma disease response according to the IMWG-URC (Section 12.11) every 28 ± 7 days from cycle 1 day 1 through the end of cycle 12 or disease progression until death, loss to follow-up, withdrawal of full , or until first subsequent antimyeloma treatment consent (whichever occurs first), regardless of cycle duration, dose delays or treatment discontinuation.

Subjects who end study drug(s) before completing 12 cycles without confirmed progressive disease (PD) are required to complete disease response assessments and report new antimyeloma treatment every 28 ± 7 days until 12 months after randomization, first subsequent antimyeloma treatment, death, loss to follow-up, withdrawal of full consent, or confirmed PD, whichever comes first. All subjects with

confirmed disease progression within 12 months of randomization will be followed for survival every 28 ± 7 days until 12 months after randomization, death, loss to follow-up, or withdrawal of full consent, whichever occurs first.

The disease assessment schedule is independent of treatment schedules.

Subjects will be randomized in a 1:1 ratio to 1 of 2 arms:

- Arm 1: KRd using once-weekly carfilzomib 56 mg/m^2
- Arm 2: KRd using twice-weekly carfilzomib 27 mg/m^2

Randomization will be performed using an interactive voice/web response system (IxRS). Subjects will be stratified based on the following criteria: original (not revised) International Staging System (ISS) stage at the time of study entry (stage 1 or 2 vs stage 3), prior lenalidomide treatment (yes vs no), prior PI treatment (yes vs no), prior anti-CD38 exposure (yes vs no).

All subjects enrolled will have pharmacokinetic samples assessed. Approximately 15 subjects in each arm will be invited to participate in the intensive pharmacokinetics (PK)/pharmacodynamics (PDn) substudy at selected sites. Sparse PK samples will be collected from the rest of the subjects, eg, subjects who do not consent to participate in the intensive PK/PDn substudy. See Sections 9.2.5 and 9.2.6 for more details.

An independent data monitoring committee (DMC) will be convened for this study and will act in an advisory capacity to the sponsor with respect to safeguarding the interests of study subjects, assessing interim data, monitoring the overall conduct of the study, and providing with recommendations relating to continuing, modifying, or stopping the study based on these findings (International Council for Harmonisation Good Clinical Practice [ICH GCP 5.5.2]). Details of the DMC will be described in the DMC Charter. The initial assessment from this committee will be planned after 30 subjects (approximately 15 for the experimental arm and 15 for the control arm) have been enrolled and have finished the first cycle of treatment to ensure safety of all arms. A provision will be made allowing an early follow-up DMC meeting to be decided at the time of the initial assessment. The DMC will meet approximately every 6 months to review safety data on a regular basis, and once to review the efficacy data for futility. The interim analysis for futility is planned to occur when the first 230 subjects have been randomized and had a best overall response (BOR) assessed by the date when treatment was completed, confirmed PD or death occurred, subject was lost to follow-up, withdrew full consent, or started new therapy, whichever occurred first.

The individual subject disease response and disease progression for this study will be independently assessed by an Independent Review Committee (IRC) in accordance with the IMWG-URC (Section 12.11). The membership criteria and operational details of the IRC will be described in the IRC Charter. The IRC will centrally review the disease-related tests and assessments (Section 9.2.2) to evaluate disease progressions and responses without the knowledge of randomization assignments or Investigator's disease assessments. The IRC assessment will be used for the primary analysis of efficacy endpoints except for MRD rate and COA endpoints.

The overall study design is outlined in the study schema in Section 2.1. The endpoints are defined in Section 4.1.

5.2 Number of Subjects

Approximately 460 subjects will be enrolled in the study, with approximately 230 subjects per arm.

Subjects in this clinical investigation shall be referred to as "subjects". For the sample size justification, see Section 10.1.

5.2.1 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study will not be replaced.

5.2.2 Number of Sites

Approximately 100 investigative sites in North America, Europe, and Asia, including Japan are planned for inclusion in the study. Sites that do not enroll subjects within 3 months of site initiation may be closed.

5.3 End of Study

5.3.1 End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject across all sites is assessed or receives an intervention for the final collection of data for the primary endpoint(s), whether the study concluded as planned in the protocol or was terminated early.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

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), following any additional parts in the study (eg, long-term follow-up), as applicable.

5.3.2 Study Duration for Subjects

The duration of screening is up to 28 days, and the duration of treatment for an individual subject is anticipated to be 12 cycles (or approximately 12 months from randomization), followed by safety follow-up visit that occurs 30 (+3) days after the last dose of all study drug(s). Following 12 cycles and the safety follow-up visit the study is completed for that subject.

The total study duration for an individual subject is estimated to be approximately 14 months. If a subject experiences treatment delays requiring in excess of 14 months to complete all 12 cycles the investigator must contact the medical monitor to discuss in order to approve treatment continuation.

5.4 Justification for Investigational Product Dose

The carfilzomib dose (56 mg/m^2) in the once-weekly KRd arm is based on the objective to evaluate the benefit-risk profile of a weekly KRd dose regimen that will address the patient need for more convenient dosing schedule and to establish non-inferiority with the on-label twice-weekly KRd 27 mg/m^2 dose regimen.

Once-weekly carfilzomib has been evaluated in clinical studies at doses as high as 88 mg/m^2 and data have shown that weekly carfilzomib in combination with dexamethasone (Kd) can be used safely and effectively in patients with RRMM (Berenson et al, 2016).

In the phase 1/2 CHAMPION1 study, the maximum tolerated dose of carfilzomib administered once-weekly with dexamethasone was 70 mg/m^2 and an overall response rate of 77% was observed at this dose (Berenson et al, 2016). The randomized phase 3 A.R.R.O.W. study demonstrated that treatment with carfilzomib (70 mg/m^2) administered once-weekly with dexamethasone led to an improvement in PFS compared with carfilzomib (27 mg/m^2) administered twice-weekly with dexamethasone (11.2 vs 7.6 months; HR = 0.69; 95% CI, 0.54, 0.88) (Mateos et al, 2018).

The safety experience from 56 subjects with RRMM with weekly KRd 56 mg/m^2 (n = 10) or 70 mg/m^2 (n= 46) in Study CFZ013 (NCT02335983) has not identified any safety concerns which would preclude the investigation of KRd 56 mg/m^2 weekly in this study.

The subject incidence of grade ≥ 3 treatment-emergent adverse events was 70.0% in the KRd 56 mg/m^2 group and 69.6% in the KRd 70 mg/m^2 group. Grade ≥ 3 adverse events reported in more than 2 patients were thrombocytopenia (56 mg/m^2, n = 2; 70 mg/m^2, n = 4), neutropenia (56 mg/m^2, n = 1; 70 mg/m^2, n = 4), anemia (56 mg/m^2, n = 2; 70 mg/m^2, n = 3), pneumonia (70 mg/m^2, n = 4), decreased platelet count (56 mg/m^2, n = 1; 70 mg/m^2, n = 3), decreased neutrophil count (56 mg/m^2, n = 2; 70 mg/m^2, n = 2), hypertension (56 mg/m^2, n = 1; 70 mg/m^2, n = 3), and hypophosphatemia (70 mg/m^2, n = 4). There were 3 deaths in the KRd 70 mg/m^2 group (1 each due to cardiac arrest, cardiac disorder, and disease progression). No deaths occurred in the KRd 56 mg/m^2 group (Biran et al, 2018). The median weekly dose of carfilzomib was 53.2 mg/m^2 for subjects administered 20/56 mg/m^2 and 62.4 mg/m^2 for subjects administered 20/70 mg/m^2. The median relative dose intensity of carfilzomib was 90.7 for subjects administered 20/56 mg/m^2 and 88.2 for subjects administered 20/70 mg/m^2. The median weekly dose and the relative dose intensity suggest that 20/56 mg/m^2 weekly dose was tolerable.

Available efficacy results indicated similar efficacy (as determined by ORR) with either KRd 56 mg/m^2 or KRd 70 mg/m^2 (90.0% versus 89.1%, respectively) to the effect previously reported for twice-weekly KRd (27 mg/m^2) in the randomized phase 3 ASPIRE study (Biran et al, 2018). In ASPIRE, KRd 27 mg/m^2 was compared with Rd alone in a similar patient population proposed in this phase 3 study (Study 20180015). The carfilzomib arm proved superior at the first interim analysis for efficacy reducing the risk of progression or death by 31% (median PFS [KRd vs Rd]: 26.3 months vs 17.6 months). The ORR was 87.1% in the KRd versus 66.7% in the Rd arm. The OS benefit seen at the final analysis was 8 months (median OS was 48.3 months for KRd arm vs 40.4 months for Rd arm; Siegel et al, 2018; Stewart et al, 2015).

Given these data, this phase 3 study will evaluate the 56 mg/m^2 once-weekly dose schedule for carfilzomib in combination with lenalidomide and dexamethasone to establish non-inferiority to KRd 27 mg/m^2 twice-weekly.

5.5 Patient Input on Study Design

No patient input was obtained for this study design.

6. Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening).

Eligibility criteria will be evaluated during screening. Eligibility labs are to be confirmed by central laboratory prior to enrollment.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 12.3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, will not be provided.

6.1 Inclusion Criteria

All screening laboratory assessments must done in accordance with Table 12-1. Local laboratory assessments may not be used in place of central laboratory assessments where required.

Subjects are eligible to be included in the study only if all the following criteria apply:

101 Subject has provided informed consent prior to initiation of any study-specific activities or procedures or subject's legally acceptable representative has provided informed consent prior to any study-specific activities/procedures being initiated when the subject has any kind of condition that, in the opinion of the Investigator, may compromise the ability of the subject to give written informed consent.

102 Males or females ≥ 18 years of age.

103 Subject has multiple myeloma with documented relapse or progression after most recent myeloma treatment. Subjects refractory to the most recent line of therapy are eligible, unless last treatment contained PI or lenalidomide and dexamethasone.

- Refractory is defined as disease that is nonresponsive or progresses within 60 days of last therapy

104 Subjects must have at least PR to at least 1 line of prior therapy.

105 Subjects must have received at least 1 but not more than 3 prior lines of therapy for multiple myeloma (induction therapy followed by stem cell transplant and consolidation maintenance therapy will be considered as 1 line of therapy). See Section 12.8 for guidelines for documenting prior treatment.

106 Prior therapy with a PI is allowed if the patient achieved at least a PR to most recent treatment with a PI, did not relapse within 60 days of discontinuation of the PI and the PI was not removed due to toxicity. A history of prior neuropathy is permitted if this was not grade 3, grade 4 or grade 2 with pain and if not resolved within the 14 days before enrollment, is less than or equal to grade 2 without pain.

107 Prior therapy with a lenalidomide and dexamethasone containing regimen is allowed if the patient achieved at least a PR to most recent treatment with lenalidomide and dexamethasone, did not progress within the first 3 months of initiating a lenalidomide and dexamethasone containing treatment or relapse within 60 days of discontinuation of lenalidomide and dexamethasone containing treatment and treatment was not discontinued due to toxicity. A history of prior

neuropathy is permitted if this was not grade 3, grade 4 or grade 2 with pain and if not resolved within the 14 days before enrollment, is less than or equal to grade 2 without pain. Patients are permitted to have received single agent lenalidomide as maintenance therapy within 60 days of enrollment.

108 Measurable disease with at least 1 of the following assessed within 28 days prior to randomization:

- IgG multiple myeloma: serum monoclonal protein (M-protein) level ≥ 1.0 g/dL
- IgA, IgD, IgE multiple myeloma: serum M-protein level ≥ 0.5 g/dL
- urine M-protein ≥ 200 mg per 24 hours
- in subjects without measurable serum or urine M-protein, serum-free light chain (SFLC) ≥ 100 mg/L (involved light chain) and an abnormal serum kappa lambda ratio

109 Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≤ 2 (see Section 12.9).

6.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Disease-related

201 Waldenström macroglobulinemia.

202 Multiple myeloma of IgM subtype.

203 POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).

204 Plasma cell leukemia (> 2.0 × 10^9/L circulating plasma cells by standard differential).

205 Primary amyloidosis (patients with multiple myeloma with asymptomatic deposition of amyloid plaques found on biopsy would be eligible if all other criteria are met).

206 Myelodysplastic syndrome.

Other Medical Conditions

207 History of other malignancy within the past 5 years, with the following exceptions:

- Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before enrollment and felt to be at low risk for recurrence by the treating physician
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated cervical carcinoma in situ without evidence of disease
- Adequately treated breast ductal carcinoma in situ without evidence of disease
- Prostatic intraepithelial neoplasia without evidence of prostate cancer

- Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ
- Treated medullary or papillary thyroid cancer
- Similar neoplastic conditions with an expectation of > 95% 5-year disease-free survival

208 Known HIV infection, hepatitis C infection (subjects with hepatitis C that achieve a sustained virologic response after antiviral therapy are allowed), or hepatitis B infection (subjects with hepatitis B surface antigen or core antibody that achieve sustained virologic response with antiviral therapy are permitted with a requirement for regular monitoring for reactivation for the duration of treatment on the study).

209 Ongoing graft-vs-host disease.

210 Acute active infection requiring systemic antibiotics, antifungal, antiviral (except antiviral therapy directed at hepatitis B) agents within 14 days prior to randomization.

211 Known cirrhosis.

212 Significant neuropathy (grades 3 to 4, or grade 2 with pain) within 14 days prior to randomization.

213 Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 14 days prior to randomization.

Cardiopulmonary Conditions

214 Uncontrolled hypertension, defined as a subject whose blood pressure **is greater than or equal to** 160 mmHg systolic or **greater than or equal to** 100 mmHg diastolic when taken in accordance with the European Society of Hypertension/European Society of Cardiology 2018 guidelines (Section 12.10; Williams et al, 2018).

215 Active congestive heart failure (New York Heart Association Class III to IV), symptomatic ischemia, uncontrolled arrhythmias, screening ECG with corrected QT interval (QTc) of > 470 msec, pericardial disease, or myocardial infarction within 4 months prior to randomization.

216 Intolerance to hydration due to pre-existing pulmonary or cardiac impairment.

217 History of interstitial lung disease or ongoing interstitial lung disease.

Prior/Concomitant Therapy

218 Immunotherapy within 28 days prior to randomization.

219 Monoclonal antibody therapy within 28 days prior to randomization.

220 Chemotherapy with approved anticancer therapeutic within 28 days prior to randomization.

221 Glucocorticoid therapy within 14 days prior to randomization that exceeds a cumulative dose of 160 mg of dexamethasone or equivalent dose of other corticosteroids.

222 Focal radiation therapy within 7 days prior to randomization. Radiation therapy to an extended field involving a significant volume of bone marrow within 28 days prior to randomization (ie, prior radiation must have been to < 30% of the bone marrow).

223 Major surgery (except kyphoplasty) within 28 days prior to randomization.

224 Autologous or allogeneic stem cell transplant within 90 days prior to randomization.

225 Contraindication or intolerance to lenalidomide, dexamethasone, or carfilzomib.

226 Known history of allergy to Captisol (a cyclodextrin derivative used to solubilize carfilzomib).

227 Subject has known hypersensitivity to any of the products or components to be administered during dosing, including hypersensitivity to antiviral drugs.

Prior/Concurrent Clinical Study Experience

228 Currently receiving treatment in another investigational device or drug study, or < 28 days since ending treatment on another investigational device or drug study(ies).

Organ Function Assessments

229 Hepatic dysfunction within 28 days prior to randomization:

- direct bilirubin $\geq$ 1.5x the upper limit of normal (ULN)
- aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq$ 2.5 x ULN

230 Left ventricular ejection fraction < 40% assessed by transthoracic echocardiogram (ECHO).

231 Absolute neutrophil count (ANC) < 1 x 10^9/L within 28 days prior to randomization. Screening ANC should be independent of growth factor support for ≥ 1 week.

232 Hemoglobin < 80 g/L within 28 days prior to randomization. Use of erythropoietic stimulating factors and red blood cell (RBC) transfusions per institutional guidelines is allowed; however, most recent RBC transfusion must not have been performed within 7 days prior to obtaining screening hemoglobin.

233 Platelet count < 50 x 10^9/L (≤ 30 x 10^9/L if myeloma involvement in the bone marrow is > 50%) within 28 days prior to randomization. Subjects should not have received platelet transfusions for at least 1 week prior to obtaining the screening platelet count.

244 Calculated or measured creatinine clearance < 30 mL/min (calculation must be based on the Cockcroft and Gault formula) within 28 days prior to randomization.

Other Exclusions

235 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 30 days after the last dose of all study drug(s). (Females of childbearing potential should only be included in

the study after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test).

236 Female subjects of childbearing potential unwilling to use 2 methods of contraception (1 highly effective form of contraception and 1 additional effective contraceptive method) for at least 28 days before starting study drug(s), during treatment, during treatment interruptions, and for an additional 30 days after the last dose of all study drug(s). Refer to Section 12.5 for additional contraceptive information.

237 Female subjects of childbearing potential with a positive pregnancy test assessed at screening (by a highly sensitive serum pregnancy test 10 to 14 days prior to first dose of study drugs).

238 Male subjects with a female partner of childbearing potential who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use a condom with spermicide during treatment and for an additional 90 days after the last dose of all study drug(s), even if they have undergone a successful vasectomy. Refer to Section 12.5 for additional contraceptive information.

239 Male subjects with a pregnant partner who are unwilling to practice abstinence or use a condom with spermicide during treatment and for an additional 90 days after the last dose of all study drug(s).

240 Male subjects unwilling to abstain from donating blood, semen, or sperm during treatment and for an additional 90 days after the last dose of all study drug(s).

241 Females subjects unwilling to abstain from donating blood during treatment and for an additional 90 days after the last dose of all study drug(s).

242 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study assessments (including COA) to the best of the subject and investigator's knowledge.

243 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

6.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 12.3).

The subject or the subject's legally acceptable representative must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date in the subject's medical record and in/on the enrollment electronic case report form (eCRF).

Each subject who enters into the screening period for the study (defined as the point when the subject signs the informed consent) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned via Interactive Voice/Web Response System (IxRS). This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. This number will not necessarily be the same as the randomization number assigned for the study.

6.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demographics, screen failure details, eligibility criteria, and any serious adverse events. If a serious adverse event is observed from the time informed consent is signed up to the point of screen failure, then serious adverse events, medical history, and concomitant medications will also be collected.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Refer to Section 9.1.1.

Subjects who experience a technical failure of central laboratory samples at screening (for example sample is lost or damaged in transit, or otherwise cannot be analyzed) will not be considered a screen failure. Central lab samples may be retested during screening in such cases, subject to the screening window not being exceeded.

7. Treatments

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

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown below.

7.1 Treatment Procedures

7.1.1 Investigational Product: Carfilzomib

7.1.1.1 Dosage Formulation

Carfilzomib will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

Carfilzomib is supplied as a sterile, lyophilized, white to off-white powder ready for reconstitution. It is supplied for single use in 50 mL Type 1 glass vials containing 60 mg of carfilzomib drug product with an elastomeric stopper and flip-off lid.

7.1.1.2 Dosage, Administration, and Schedule

Hematology and chemistry samples will be repeated within 3 days prior to cycle 1 day 1 and reviewed by the investigator before first dose.

Baseline laboratories for SPEP/UPEP/SIFE/UIFE/SFLC, will also be collected and checked by the investigator or treating physician before treatment is administered on cycle 1 day 1 if the screening laboratory assessments were not performed within 14 days of randomization.

Both arms:

Each subject's first dose of carfilzomib will be calculated based upon baseline body surface area (BSA) using the Mosteller formula. In subjects with BSA > 2.2 m^2, the dose should be capped based on a BSA of 2.2 m^2. The dose for each subject should not be revised unless the subject has a change in body weight of > 20% (gain or loss) in which case the BSA should be recalculated. Carfilzomib dose is to be recalculated using the updated BSA and applied until such time that any future weight change requires further BSA recalculation. The dose can also be modified in response to toxicity following the dose modification guideline tables using the most current BSA if this has been recalculated since the first cycle due to weight change.

Carfilzomib will be administered as an IV infusion. Mechanical infusion pumps are recommended, but gravity-dependent infusions are permitted if the infusion duration can be reliably maintained.

The planned dose (mg/m^2), quantity administered (mg), start date/time, stop date/time, reason for change in planned dose, reason for dose change/withheld, reason for dose delay, reason for dose interruption and package lot number of carfilzomib are to be recorded on each subject's eCRF.

Arm 1 (once-weekly KRd 56 mg/m^2):

Carfilzomib will be administered once-weekly IV as a 30 ± 5 minute infusion using an infusion pump on days 1, 8, and 15 of each 28-day cycle. The dose will be 20 mg/m^2 on day 1 of the first cycle and 56 mg/m^2 beginning with day 8 of cycle 1 and thereafter. All carfilzomib doses should be administered on the scheduled day ± 2 days, and the day 8 and 15 doses should have at least a 5-day treatment-free interval. Dose delays > 2 days are only permitted during the start of a new cycle.

Arm 2 (twice-weekly KRd 27 mg/m^2):

Carfilzomib will be administered twice-weekly IV as a 10 minute ± 5 minute infusion using an infusion pump on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. The dose will be 20 mg/m^2 on days 1 and 2 of the first cycle and 27 mg/m^2 beginning with day 8 of cycle 1 and thereafter.

Every effort should be made to maintain the days 1, 2, 8, 9, 15, and 16 of 28-day schedule. If this is not possible, then priority should be to maintain consecutive dosing days. For example, if day 1 of a new cycle is started 2 days later than originally scheduled, the entire cycle should shift by 2 days, such that the new days 1, 2, 8, 9, 15, and 16 of the next cycle are maintained. There must always be at least 5 days between the second dose of 1 week and the first dose of the following week (ie, between days 2 and 8, and days 9 and 15). Mid-cycle doses that are missed should not be made up unless these parameters are maintained.

7.1.1.3 Intravenous Prehydration

Subjects may receive IV prehydration (normal saline or other appropriate IV fluid) prior to each carfilzomib infusion during cycle 1. Investigators must consider IV prehydration in subjects at high-risk for tumor lysis or renal toxicity. All subjects must be monitored for fluid overload and hydration should be tailored to individual needs

Thereafter, carfilzomib prehydration may only be administered if the subject’s condition and/or risk factors require it. The total volume of prehydration and the indication will be recorded on the Concomitant Medications eCRF.

Carfilzomib infusion must occur at a facility capable of managing hypersensitivity reactions.

7.1.1.4 Starting Dose in Hepatic Insufficiency

For subjects with baseline chronic hepatic impairment (mild, moderate), reduce the starting and subsequent doses of carfilzomib by 25% (Brown et al, 2017):

- for once-weekly arm: 15 mg/m^2 day 1 of cycle 1 and 42 mg/m^2 day 8 of cycle 1 and thereafter;
- for twice-weekly arm: 15 mg/m^2 day 1 and 2 of cycle 1 and 20 mg/m^2 day 8 of cycle 1 and thereafter.

If hepatic function returns to normal, the dose may be re-escalated to 56 mg/m^2 (for once-weekly arm) and 27 mg/m^2 (for twice-weekly arm) after the first cycle. For dose modification due to subsequent changes in hepatic function, refer to Section 7.4.1.1.2.

Mild and moderate hepatic dysfunction is defined as:

- Mild: 1.0 x ULN < bilirubin ≤ 1.5 x ULN; or AST > ULN with bilirubin ≤ ULN
- Moderate: 1.5 x ULN < bilirubin < 3 x ULN with any AST

7.1.2 Non-investigational Products

7.1.2.1 Dexamethasone: Dosage, Administration, and Schedule

Dexamethasone, a non-Amgen non-investigational product, will also be used in this study. Dexamethasone should be taken weekly orally or by IV infusion at a dose of 40 mg. When dexamethasone is administered on the same day as carfilzomib, it should be started and completed within 4 hours of the start of carfilzomib infusion. A 30 minute interval between the end of the dexamethasone infusion and the start of the carfilzomib infusion is recommended. All doses should be administered on the scheduled days ± 2 days.

The planned dose, quantity administered, start date/time, stop date/time, route, reason for dose change/withheld, reason for dose delay, reason for dose interruption are to be recorded on each subject's eCRF.

7.1.2.2 Lenalidomide

7.1.2.2.1 Prescribing Requirements

Lenalidomide, a non-Amgen non-investigational product, will also be used in this study.

Within the United States, lenalidomide should be administered in accordance with the REVLIMID REMS® program of Celgene Corporation (http://www.revlimidrems.com/.) All physicians who prescribe lenalidomide for research subjects enrolled into this study, and

all research subjects enrolled on this study, must be registered in and comply with all requirements of the REVLIMID REMS® program.

Females of childbearing potential (FCBP) must agree to monitoring for pregnancy. In addition, males and FCBP are subject to certain restrictions as detailed in Section 12.5 while receiving lenalidomide.

Outside the United States, all investigators and subjects must adhere to the requirements of the lenalidomide restricted distribution program in effect in their local country.

7.1.2.2.2 Dosage, Administration, and Schedule

In subjects with normal renal function, lenalidomide will be taken once-daily orally on days 1 to 21 of each cycle at a dose of 25 mg. In subjects with renal impairment (mild to moderate or severe), please refer to the regional product label. Lenalidomide should be taken at home by the subject at about the same time each day. Lenalidomide capsules should be swallowed whole with water. The capsules should not be opened, broken, or chewed. If a planned dose is missed, it should be taken as soon as possible within the same calendar day and with a return to the regular schedule the following day. If a planned dose is missed for more than a calendar day, subjects should not make up doses, but should resume the dosing regimen as per schedule. Dose modifications are permitted in response to toxicity following the dose modification guideline tables.

The planned dose, quantity administered, start date, and reason for dose change are to be recorded on each subject's eCRF.

7.1.3 Medical Devices

No investigational medical devices will be used.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

7.1.4 Other Protocol-required Therapies

All other protocol-required therapies including, antiviral prophylaxis, thromboprophylaxis, tumor lysis prophylaxis, proton pump inhibitor, bisphosphonate therapy, and prophylaxis

for *Pneumocystis jirovenci* pneumonia, that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies.

7.1.4.1 Antiviral Prophylaxis

An antiviral is a required concomitant medication for the duration of treatment with carfilzomib. Acyclovir (eg, 400 mg orally 3 times a day, or 800 mg orally 2 times a day or per institutional standards), famcyclovir (eg, 125 mg orally given 3 days, twice a day or per institutional standards), or valacyclovir (eg, 500 mg orally, twice a day or per institutional standards), dose adjustments for renal function where appropriate, initiated within 1 week of the first dose of carfilzomib and should continue for the duration of treatment with carfilzomib.

7.1.4.2 Prophylaxis for Hepatitis B Reactivation

Hepatitis B virus (HBV) reactivation prophylaxis should be considered for patients at risk (ie, patients tested positive on serology or had a prior history of HBV infection) as per institutional standards.

7.1.4.3 Thromboprophylaxis

It is strongly recommended that all subjects receive an anticoagulant (eg, low molecular weight heparin, direct oral anti-coagulant, warfarin, enteric-coated aspirin at standard prophylactic dose or other anticoagulant or antiplatelet medication). Additional or secondary thromboprophylaxis medication is strongly recommended in subjects with elevated risk of thrombosis, based on an individual benefit/risk assessment (Li et al, 2017).

7.1.4.4 Tumor Lysis Syndrome Prophylaxis

An approved uric acid-lowering agent (eg, allopurinol) in subjects at high-risk for tumor lysis syndrome (TLS) due to high tumor burden may be prescribed at the investigator's discretion, according to the package insert.

Subjects should be well hydrated to reduce the risk of TLS and decline in renal function; refer to the current Carfilzomib IB for safety guidance regarding TLS.

7.1.4.5 Proton-pump Inhibitor

Proton-pump inhibitor (omeprazole or equivalent) is required while on dexamethasone.

7.1.4.6 Bisphosphonate or Monoclonal Antibody Therapy

Concomitant therapy should be administered to all subjects with evidence of lytic destruction of bone or with osteopenia (Gralow et al; 2013; Terpos et al, 2013) unless

contraindicated. Commercially available therapies are preferred when available and should be used for subjects with osteolytic or osteopenic myelomatous bone disease according to the manufacturer's recommendations, as described in the prescribing information.

Subjects who are using bisphosphonate or monoclonal antibody therapy when they enter the study should continue the same treatment. Subjects with evidence of lytic destruction of bone or with osteopenia who are not using a bisphosphonate or monoclonal antibody therapy at the time of randomization should start therapy as soon as possible during cycle 1 or 2 of treatment. Investigators should not start bisphosphonate or monoclonal antibody therapy during the study, unless it has been agreed with the sponsor that there is no sign of disease progression.

7.1.4.7 Prophylaxis for *Pneumocystis Jirovenci*

Pneumocystis jirovenci pneumonia prophylaxis should be considered, as per institutional guidelines while on dexamethasone.

7.1.5 Other Treatment Procedures

No other treatment procedures are required.

7.1.6 Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic by either (1) Amgen or (2) distributors or partners for whom Amgen manufactures the material. This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.

This includes any investigational products provisioned and/or repackaged/modified by Amgen: carfilzomib.

Any product complaint(s) associated with an investigational product(s) or non-investigational products(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

7.1.7 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

7.1.7.1 Anticancer Therapeutic or Radiation

Concurrent therapy with a marketed or investigational anticancer therapeutic or radiation to large marrow reserves for either a palliative or therapeutic intent is excluded.

7.1.7.2 Corticosteroids

Long-term corticosteroids for nonmalignant conditions (eg, asthma, inflammatory bowel disease) equivalent to a dexamethasone dose > 4.0 mg/day or prednisone > 20 mg/day are not permitted. Corticosteroids given short-term (up to 2 weeks) for non-malignant conditions are permitted provided that the cumulative dose is less than 40 mg per week dexamethasone equivalent. Medical monitor should be contacted if short-term corticosteroid use is required > 2 weeks or at cumulative dose of more than 40 mg dexamethasone equivalent.

7.1.7.3 Plasmapheresis

Plasmapheresis is not permitted at any time while the subject is receiving study treatment. For subjects requiring plasmapheresis while on study treatment, every attempt should be made to document disease status by IMWG criteria first. Study treatment must be discontinued.

7.1.7.4 Myeloid Growth Factors

The prophylactic use of myeloid growth factors is prohibited, but they may be used for management of neutropenia in accordance with American Society of Clinical Oncology Guidelines (Smith et al, 2015).

7.2 Method of Treatment Assignment

Subjects will be randomized in 1:1 allocation ratio to 1 of the 2 treatment arms in an open-label manner:

- Arm 1: KRd using once-weekly carfilzomib 56 mg/m^2 (days 1, 8, 15; 30 minutes [± 5 minutes] IV)
- Arm 2: KRd using twice-weekly carfilzomib 27 mg/m^2 (days 1, 2, 8, 9, 15, 16; 10 minutes [± 5 minutes] IV)

The randomization will be performed using an IxRS. The randomization number will be provided on the IxRS randomization confirmation document and the randomization date is to be documented in the subject's medical record and on the enrollment eCRF.

The randomization will be stratified based on the following criteria:

- original ISS stage at study entry (stage 1 or 2 vs stage 3)
- prior lenalidomide treatment (yes vs no)
- prior PI treatment (yes vs no)
- prior anti-CD38 exposure (yes vs no)

Subjects will receive the treatment determined by randomization for the duration of 12 cycles or until treatment discontinuation for reasons outlined in Section 8.1. No crossover between the treatment arms will be allowed.

7.3 Blinding

This is an open-label study; blinding procedures are not applicable.

7.4 Dose Modification

7.4.1 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

7.4.1.1 Amgen Investigational Product: Carfilzomib

Carfilzomib will be discontinued, temporarily delayed, or dosage temporarily reduced, in the event of a treatment-related toxicity that, in the opinion of the investigator, warrants the discontinuation, temporary delay or dose reduction as indicated in Table 7-2 and Table 7-3. Dose reduction levels of carfilzomib for toxicity management of individual subjects are provided in Table 7-1. Subjects that require a dose level reduction and tolerate the reduced dose for 1 full cycle may at the discretion of the treating physician increase the dose to a prior dose starting with the next cycle except when the dose reduction is due to: pulmonary hypertension, pulmonary toxicity, grade 3 or worse cardiac failure, and drug-induced hepatotoxicity.

Table 7-1. Dose Decrements for Carfilzomib

Nominal Dose (mg/m^2)	Reduced Carfilzomib Doses (mg/m^2)			
	Dose -1	Dose -2	Dose -3	Dose -4
20[a, b]	15	11	Discontinue	-
27	20	15	11	Discontinue
56	45	36	27	20

[a] If dose reduction of carfilzomib is required on cycle 1 day 1 or cycle 1 day 2, the investigator should contact the medical monitor to discuss the situation before any additional doses of carfilzomib are administered.

[b] For subjects with baseline chronic hepatic impairment (mild, moderate), reduce the starting and subsequent doses of carfilzomib by 25% (ie, for once-weekly arm: 15 mg/m^2 day 1 of cycle 1 and 42 mg/m^2 day 8 of cycle 1 and thereafter; for twice-weekly arm: 15 mg/m^2 day 1 and 2 of cycle 1 and 20 mg/m^2 day 8 of cycle 1 and thereafter).

The subject will be considered on protocol treatment while receiving carfilzomib or lenalidomide.

If day 1 of a cycle is delayed, all subsequent doses within the cycle and also day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. However, if a within-cycle dose is delayed, then the dates of the subsequent within-cycle doses should not be adjusted. For within-cycle doses, if administration does not

commence within the allowable window of the scheduled administration date, then the dose will be considered a missed dose and this missed dose will not be made up. Administration may resume at the next planned dosing date.

If a subject requires interruption of carfilzomib for more than 6 consecutive weeks due to unresolved toxicities, the subject must be discontinued permanently from study treatment.

If a subject requires interruption of carfilzomib for more than 6 weeks for reasons other than toxicity, medical monitor approval is required prior to resuming treatment. The reason for dose change of carfilzomib is to be recorded on each subject's eCRF.

7.4.1.1.1 Carfilzomib: Guidelines for Hematologic Toxicity

Guidelines for carfilzomib dose modification in the event of thrombocytopenia and neutropenia are summarized in Table 7-2.

Table 7-2. Dose Modification Guidelines for Thrombocytopenia and Neutropenia

Hematologic toxicity	Recommended Action	
Thrombocytopenia		
When platelets fall to < 30 x 10^9/L and for each subsequent drop to < 30 x 10^9/L	If platelets 10 to 30 x 10^9/L without evidence of bleeding	• hold • restart at previous dose when platelets > 30 x 10^9/L
	If evidence of bleeding or platelets < 10 x 10^9/L	• hold • restart at 1 dose decrement when platelets > 30 x 10^9/L
Neutropenia		
When ANC falls to < 0.75 x 10^9/L and for each subsequent drop to < 0.75 x 10^9/L	If ANC 0.5 to 0.75 x 10^9/L	• continue at full dose
	If ANC < 0.5 x 10^9/L	• hold dose • resume at 1 dose decrement when ANC ≥ 0.5 x 10^9/L

ANC = absolute neutrophil count.

7.4.1.1.2 Carfilzomib: Guidelines for Nonhematologic Toxicity

Guidelines for dose modification in the event of nonhematologic toxicities are summarized in Table 7-3.

Table 7-3. Dose Modification Guidelines for Nonhematologic Toxicities

Symptom/Sign/Investigation	Recommended Action
Renal Dysfunction[a]:	
CrCl ≥ 15 mL/min	Full dose
CrCl < 15 mL/min (NCI-CTCAE grade 4)	Hold dose and monitor renal function. If attributable to carfilzomib, resume when renal function has recovered to within 25% of baseline; restart at 1 dose level reduction. If not attributable to carfilzomib, dosing may be resumed at the discretion of the physician. If dialysis required use the maximal dose of 20 mg/m^2 and administer carfilzomib after dialysis.
Chronic dialysis stable for ≥ 30 days	Dose may be re-escalated up to full dose as clinically tolerated
Hepatic Dysfunction and Related Investigations	
Mild to moderate liver dysfunction: defined as 2 consecutive values, at least 28 days apart, of: (1) total bilirubin (> 33% direct) > 1x ULN to < 3x ULN OR (2) an elevation of AST and/or ALT with normal bilirubin	25% dose reduction. Dose may be re-escalated if liver function tests return to normal and drug-induced hepatotoxicity is excluded.
Grade 3 elevation in ALT and/or AST (> 5x ULN)	Hold carfilzomib until resolution to baseline. Monitor any abnormality weekly. Resume carfilzomib with a 25% dose reduction if drug-induced hepatotoxicity is excluded.
Grade 3 elevation in total bilirubin	Hold carfilzomib until resolution to baseline. Monitor total bilirubin and direct bilirubin weekly. Upon resolution of total bilirubin to normal, resume carfilzomib dosing with a 25% dose reduction if drug-induced hepatotoxicity is excluded.
Drug-induced hepatotoxicity (attributable to carfilzomib)	Discontinue carfilzomib
Other Nonhematologic Toxicities	
Tumor lysis syndrome: 3 or more of the following: • increase in creatinine of ≥ 50% • increase in uric acid, of ≥ 50% • increase in phosphate of ≥ 50% • increase in potassium of ≥ 30% • decrease in calcium OR • increase in LDH of ≥ 2-fold from baseline	Hold carfilzomib until all abnormalities in serum chemistries have resolved; resume at full dose.

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Footnotes defined on the last page of the table

Table 7-3. Dose Modification Guidelines for Nonhematologic Toxicities

Symptom/Sign/Investigation	Recommended Action
Congestive heart failure	Any subject with congestive heart failure, whether or not drug-related, must have the dose held until resolution or return to baseline. Appropriate medical management should be initiated and continued as clinically indicated. If no resolution after 4 weeks, carfilzomib will be permanently discontinued.
< Grade 3	Once congestive heart failure resolves or returns to baseline, resume at full dose.
≥ Grade 3	Once congestive heart failure resolves or returns to baseline, treatment may continue at 1 dose level reduction.
Infection (grade 3 or 4)	Hold carfilzomib. Once infection is controlled and the subject is without infection-related symptoms, and if ANC > 1.0×10^9/L, resume at full dose. If ANC < 1.0×10^9/L, follow hematologic toxicities dose reduction guidelines.
Hepatitis B reactivation	Hold carfilzomib until infection is adequately controlled (see Section 9.2.3.4.3).
Neuropathy (grade 2 with emergent pain, or grade 3)	Hold carfilzomib until resolved to ≤ grade 2 without pain; then resume at 1 dose decrement.
Neuropathy (grade 4)	Permanently discontinue carfilzomib.
Dyspnea (grade ≥ 2)	Hold carfilzomib until resolution to grade 1 or baseline, then resume at 1 dose decrement. Investigate cause and record findings. If caused by another adverse event listed in this table, follow recommendations for that adverse event.
Hypertension (SBP > 140 and/or DBP > 90, measured per Appendix 10 in Section 12.10)	
< grade 3	Continue at same dose and initiate appropriate treatment to control hypertension (see Section 12.10 for guidance)
Grade ≥ 3	Hold carfilzomib until resolution to normal or baseline. Initiate appropriate antihypertensive therapy prior to resuming carfilzomib at 1 dose decrement.
Pulmonary toxicity: Non-infectious interstitial lung disease, acute respiratory failure, ARDS (≥ grade 3)	Hold carfilzomib until resolution to grade 1 or baseline and restart at 1 dose decrement.
Pulmonary hypertension (grade ≥ 3)	Hold carfilzomib until resolution to grade 1 or baseline and restart at 1 dose decrement
Posterior reversible encephalopathy syndrome: Headaches, altered mental status, seizures, visual loss, and hypertension	If PRES is suspected, hold carfilzomib. Consider evaluation with neuroradiological imaging, specifically MRI, for onset of visual or neurological symptoms suggestive of PRES. If PRES is confirmed, permanently discontinue carfilzomib. If the diagnosis of PRES is excluded, carfilzomib administration may resume at same dose, if clinically appropriate.

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Footnotes defined on the last page of the table

Table 7-3. Dose Modification Guidelines for Nonhematologic Toxicities

Symptom/Sign/Investigation	Recommended Action
Thrombotic microangiopathy: Fever, microangiopathic hemolytic anemia, renal failure, thrombocytopenia, neurological manifestations	If the diagnosis is suspected, hold carfilzomib and manage per standard of care including plasma exchange as clinically appropriate. If TMA is confirmed, permanently discontinue carfilzomib. If the diagnosis is excluded, carfilzomib can be restarted
Venous thrombosis (≥ grade 3)	Hold carfilzomib and adjust anticoagulation regimen; resume at full dose once anticoagulation has been optimized per treating investigator's discretion.
Any other drug-related nonhematologic toxicity ≥ grade 3[b]	For carfilzomib attribution, hold dose. Resume at 1 dose decrement when toxicity has resolved to grade 1 or less or to baseline grade.

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ALT = alanine aminotransferase; ANC = absolute neutrophil count; ARDS = acute respiratory distress syndrome; AST = aspartate aminotransferase; CrCl = creatinine clearance; DBP = diastolic blood pressure; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; PRES = Posterior Reversible Encephalopathy Syndrome; SBP = systolic blood pressure; TMA = thrombotic microangiopathy; ULN = upper limit of normal.

[a] For a rapid fall from baseline in CrCl or an absolute fall of ≥ 60 mL/min, contact the medical monitor.

[b] In the event of a possible drug-related nonhematologic toxicity, the investigator should, to the best of his/her ability, assess its relationship to lenalidomide (R), carfilzomib (K), dexamethasone (d), or the combination of KRd to the extent possible. If both carfilzomib and lenalidomide are considered likely to be involved, then recommended actions for both should be instituted.

7.4.1.1.3 Conditions Not Requiring Carfilzomib Dose Reduction

Carfilzomib do not need to be held in the following cases:

- grade 3 nausea, vomiting, or diarrhea (that responds within 7 days to adequate treatment of antiemetics and/or antidiarrheal agents)
- grade 3 dexamethasone-related hyperglycemia
- isolated grade 3 γ-glutamyl transferase elevation
- grade 3 fatigue (unless persisting for > 7 days)
- alopecia

7.4.1.2 Non-Amgen Non-Investigational Product: Lenalidomide

Lenalidomide may be discontinued, temporarily delayed, or dosage temporarily reduced, in the event of a treatment-related toxicity that, in the opinion of the investigator, warrants the discontinuation, temporary delay or dose reduction.

Investigators are advised to consult the approved regional labeling for lenalidomide for additional details.

The reason for dose change of lenalidomide is to be recorded on each subject's eCRF.

7.4.1.3 Non-Amgen Non-Investigational Product: Dexamethasone

Dexamethasone may be discontinued, temporarily delayed, or dosage temporarily reduced, in the event of a treatment-related toxicity that, in the opinion of the investigator, warrants the discontinuation, temporary delay or dose reduction.

Investigators are advised to consult the approved regional labeling for dexamethasone for additional details.

The reason for dose change of dexamethasone is to be recorded on each subject's eCRF.

7.5 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product and/or other protocol-required therapies during the study are provided in the IPIM.

7.6 Treatment Compliance

Administration of IV medicinal products will occur at the study center. Oral medication may be dispensed for self-administration at home. Subjects are to document all administered doses and missed doses in a medication diary for all study-required medication taken at home.

7.7 Treatment of Overdose

None of the investigational products in this study have specific antidotes. Therapy for overdose involves monitoring and management of acute side effects until the subject is stable.

7.8 Prior and Concomitant Treatment

7.8.1 Prior Treatment

Prior therapies for non-multiple myeloma conditions that were being taken/used from 30 days prior to signing of the informed consent form (ICF) will be collected on the Concomitant Medications eCRF.

Collect therapy name, indication, dose, unit, frequency, start date and stop date.

Prior therapies for multiple myeloma must date back to the original diagnosis and will be collected on the Prior Multiple Myeloma Therapy eCRF. For subjects who are being referred to the research site, critical referral information will constitute multiple myeloma information from source notes. Prior lines of multiple myeloma treatment are defined as a planned course of therapy. Therefore, during initial treatment, the induction ±

autologous stem cell transplant ± consolidation and maintenance would be considered 1 line of therapy (see Section 12.8 for additional guidance on lines of therapy).

For prior antimyeloma therapies, collect transplant, best response, did subject relapse/progress on or after this regimen, date of relapse/progression, drug name, reason for therapy, start date, stop date, reason medication was stopped.

7.8.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 7.1.7.

Concomitant therapies are to be collected from informed consent through the 30 days after the last dose of all study drug(s).

For all concomitant therapies, collect therapy name, indication, dose, unit, frequency, start date and stop date and record on Concomitant Medications eCRF.

It is recommended to follow the Eighth Joint National Committee 2014 evidence-based guideline for the management of high blood pressure in adults (James et al, 2014Section). For elderly subjects, it is recommended to implement the 2018 ESH and ESC guidelines Section (Williams et al, 2018).

8. Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 8.1, 8.2.1, and 8.2.2.

8.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with

the subject the possibilities for continuation of the Schedule of Activities (see Table 2-1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on study to ensure safety surveillance and/or collection of outcome data.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.3.

Reasons for removal from protocol-required study drugs or procedural assessments include any of the following:

- Decision by Sponsor
- Lost to follow-up
- Death
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Adverse event
- Subject request
- Disease progression
- Pregnancy

8.2 Discontinuation From the Study

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 12.6 for further details). Refer to the Schedule of Activities (Table 2-1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.2.1 Reasons for Removal From Washout, Run-in or Invasive Procedures

Not applicable.

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Withdrawal of consent from study
- Death
- Lost to follow-up

8.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator can search publicly available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

9. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 2-1).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

9.1 General Study Periods

9.1.1 Screening, Enrollment and/or Randomization

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the ICF, the site will register the subject in the IxRS and screen the subject to assess eligibility for participation. The screening window is up to 28 days from date of consent until randomization.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure (see Section 6.4), as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for rescreening 1 time.

Rescreen subjects must first be registered as screen failures in IxRS and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 28-day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 28 days after the original signing of the ICF, all screening procedures, including informed consent, must be repeated.

9.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 2-1). Subjects assessed as eligible for the study will be randomized to a treatment arm and must start study treatment within 3 days of randomization. The date of the first dose of protocol-required therapies is

defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date (see Section 7.1.1.2 for additional details). Protocol-required therapies are to be administered last during each visit in which they are required, except for the ECGs required on cycle 1 day 8 and cycle 2 day 1 which should be performed at the end of carfilzomib infusion.

9.1.3 Safety Follow-up

Upon permanent discontinuation from the study treatment for any reason (including subjects who complete 12 cycles of treatment), a safety follow-up visit will be performed approximately 30 (+3) days after the last dose of all study drug(s) unless the subject is lost to follow-up, has withdrawn full consent, or has died. Subjects who discontinue treatment due to confirmed PD are also to complete the safety follow-up visit.

9.1.4 Long-term Follow-up

After discontinuation from study treatment, subjects who do not have confirmed PD are required to continue follow-up every 28 ± 7 days for survival, disease response assessments and reporting of new antimyeloma treatment until 12 months after randomization, first subsequent antimyeloma treatment, death, loss to follow-up, withdrawal of full consent, or confirmed PD, whichever comes first. For applicable study subjects, long-term follow-up will commence 28 days after the Safety Follow-up visit.

All subjects with confirmed PD before 12 months from randomization will be followed for survival every 28 ± 7 days until 12 months after randomization, death, loss to follow-up, or withdrawal of full consent, whichever comes first. For applicable study subjects, long term follow-up will commence 28 days after the Safety Follow-up visit.

Disease response assessments and survival information will be collected as indicated in the Schedule of Activities (Table 2-1).

9.1.5 End of Study

The end of study for each subject is the date they withdraw full consent from the study, completes the final safety follow-up visit (following 12 cycles of treatment) or final long-term follow-up visit (whichever is later), or death. This could be a safety follow-up visit 30 (+3) days after last dose of all study drug(s) or a final long-term follow-up response or survival assessment.

9.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

9.2.1 General Assessments

9.2.1.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC approved ICF before any study-specific procedures are performed.

9.2.1.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact on biomarker variability and PK of the protocol-required therapies.

9.2.1.3 Medical History

The Investigator or designee will collect a complete medical and surgical history that started within 30 days prior to signing of the ICF. In addition, medical history will include collecting information on the subject's significant medical conditions, prior surgeries, and neuropathy history, dating back to the original diagnosis. Record all findings on the medical history eCRF. The current toxicity grade will be collected for each condition that has not resolved. Cardiovascular risk factors, which include family history of cardiovascular disease and smoking history, will also be collected.

In addition to the medical history above, multiple myeloma history must date back to the original diagnosis. For subjects who are being referred to the research site, critical referral information will constitute multiple myeloma information from source notes. Prior lines of multiple myeloma treatment are defined as a planned course of therapy. Therefore, during initial treatment, the induction ± autologous stem cell transplant ± consolidation and maintenance would be considered 1 line of therapy (see Section 12.8 for additional guidance on lines of therapy).

9.2.1.4 Physical Examination

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate eCRF (eg, medical history, event).

9.2.1.5 Physical Measurements

Height (in centimeters) should be measured without shoes. Weight (in kilograms) should be measured without shoes.

Body Surface Area should be calculated using the Mosteller Formula (Mosteller, 1987):

BSA (m^2) = ([Height(cm) × Weight(kg)]/3600) ½.

9.2.1.6 Substance Abuse History

Obtain a detailed history of prior and/or concurrent use of tobacco.

9.2.1.7 Performance Status

The subject's performance status will be assessed using the ECOG PS (Section 12.9).

9.2.2 Efficacy Assessments

Disease assessments will be based on central laboratory data and local imaging obtained every 28 ± 7 days until confirmed PD (Section 9.2.2.5) irrespective of cycle duration including dose delays and treatment discontinuation.

Disease response and progression assessments include: serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), serum-free light chain (SFLC), serum and urine immunofixation (SIFE, UIFE, respectively) (Section 9.2.2.1), bone marrow sample evaluation (Section 9.2.2.2), serum calcium, bone lesion evaluation (Section 9.2.2.3) and plasmacytoma evaluation (Section 9.2.2.4).

9.2.2.1 SPEP, UPEP, SFLC, SIFE, and UIFE

Serum protein electrophoresis, UPEP, SIFE, UIFE, and SFLC will all be conducted at the central laboratory. Samples will be collected every 28 ± 7 days (starting from cycle 1 day 1) irrespective of cycle duration including dose delays and treatment discontinuation. Blood will be obtained for SFLC, SPEP, and SIFE. Twenty-four-hour urine samples will be obtained for UPEP and UIFE. A 24-hour urine sample obtained as standard of care may be used as the screening assessment, if obtained within 24-hours prior to signing consent and sent to central lab for analysis. Results for SPEP, UPEP, or SFLC must be available at screening and before randomization. Serum protein electrophoresis, UPEP, and SFLC will be repeated on cycle 1 day 1 (unless screening values are within 14 days of cycle 1 day 1).

Post cycle 1 day 1, UPEP and UIFE will be collected every 28 days as part of every myeloma disease assessment, along with SPEP, SIFE, and SFLC, and submitted to the central laboratory for processing.

Subjects will be evaluated for disease response and progression according to the IMWG response criteria in Section 12.11. Disease status categories include sCR, CR, VGPR, PR, SD, and PD. Investigator evaluation of disease response is to be based solely on the central laboratory results, not on local laboratory results for laboratory-based parameters.

The following confirmation assessments are required for all response categories (sCR, CR, VGPR, and PR; refer to definitions in Section 12.11):

- all response categories require 2 consecutive assessments before initiation of any new therapy
- all categories also require no known evidence of progression including new bone lesions if radiographic studies were performed
- confirmation of CR or better requires bone marrow assessment (aspirate or biopsy per IMWG-URC guidelines; sCR determination in this study requires a bone marrow biopsy or aspirate clot for immunohistochemistry)
- extramedullary plasmacytoma evaluation (if present at screening)

9.2.2.2 Bone Marrow Sample Evaluation Including FISH and MRD[-]CR Assessment

A baseline bone marrow aspirate sample will be collected during the 28-day screening period, or prior to dosing at cycle 1 day 1 and used to confirm the diagnosis and quantify the percent (%) of myeloma cell involvement. Where the screening platelet count is < **50** x 10^9/L, the site must allow sufficient time for the bone marrow sample to be processed and the percent (%) myeloma cell involvement reported before randomization.

The priority order of testing of the baseline bone marrow aspirate sample by the central laboratory, based on the volume and quality of sample obtained, will be

- for tumor specific sequence identification for MRD measurement by next-generation sequencing (NGS)
- cytomorphology analysis to confirm multiple myeloma diagnosis and to quantify the percent of myeloma cells in bone marrow
- fluorescent in situ hybridization (FISH).

Sites should also follow this guidance when collecting sample from the subject: if the bone marrow aspirate sample taken at baseline and received by the central lab are found to be of insufficient quantity or quality for testing at least 1 measure above, the site may be contacted to request provision of a suitable archival bone marrow aspirate or core sample to send to the central laboratory for analysis.

After screening, bone marrow samples are required at 2 subsequent time points:

- to confirm a response of CR or better, bone marrow samples should be collected within 35 days of the second consecutive laboratory disease assessment which shows CR. Samples to be collected at CR confirmation are:
  - Cytomorphology to assess percent (%) plasma cells: from a bone marrow aspirate
  - MRD: from a bone marrow aspirate, which should be frozen
  - Immunochemistry to confirm sCR: a bone marrow biopsy (trephine) or an aspirate clot
- At 12 months (± 4 weeks) from randomization (fixed landmark analysis), a sample is required for MRD assessment unless MRD analysis was done within the past 4 months, or if the subject has started new anti-myeloma therapy prior to 12-month landmark, or disease progression is recorded.

9.2.2.3 Bone Lesion Assessment (Skeletal Survey, CT, or PET/CT)

Skeletal survey will include lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. Low-dose whole body computed tomography or fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) may be used in place of skeletal survey. A standard of care bone lesion radiographic assessment performed within 45 days of Cycle 1 Day 1 may be used as the Screening assessment, and does not need to be repeated, unless standard of care method of assessment is different from as specified above, ie, MRI bone lesion assessment would not be allowed to substitute for the Screening bone lesion assessment.

It should be repeated if worsening clinical symptoms suggest PD or as clinically indicated. The same method of assessment used at baseline will be used throughout the study. These imaging studies will be read locally.

9.2.2.4 Extramedullary Plasmacytoma

Extramedullary plasmacytoma evaluation will be conducted at screening only if a lesion is suspected clinically. The evaluation may be done within 28 day screening window, if performed as a part of standard of care. If a measurable extramedullary plasmacytoma is detected during screening, evaluation will be repeated during treatment to confirm a response of PR or better, or to confirm PD or as clinically indicated. Clinical assessment of measurable sites of extramedullary disease will be performed and evaluated locally every 28 (± 7) days for subjects with a history of plasmacytoma or as clinically indicated during treatment for other subjects. If assessment can only be performed radiologically, then evaluation of extramedullary plasmacytomas may be done every 12 weeks. The

same technique, which may include clinical evaluation by palpation, ultrasound, CT scan, magnetic resonance imaging (MRI), or PET/CT should be employed for each measurement of plasmacytoma dimensions as clinically appropriate (refer to Section 12.11). Bidimensional lesion measurements must be performed and recorded in the designated eCRF.

9.2.2.5 Progressive Disease Assessment

Confirmation of PD requires 2 consecutive assessments made before the institution of any new therapy, as well as no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow, plasmacytoma, and skeletal survey assessments are not required to be confirmed by repeat testing.

Local laboratory evaluation will not be accepted. The assessments outlined in Section 12.11 are required for PD. Subjects will be considered to have PD if they meet the criteria for progression by a variable that was not considered measurable at baseline; however, for subjects who had a measurable serum or urine M-spike at baseline, progression cannot be defined by increases in SFLC alone (Kumar et al, 2016).

9.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Table 2-1).

9.2.3.1 Adverse Events

9.2.3.1.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

9.2.3.1.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) and is described in Section 12.4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after signing of the ICF through the 30 (+3) days after the last dose of all study drug(s) are reported using the Event eCRF.

9.2.3.1.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the ICF through 30 (+3) days after the last dose of all study drug(s) are reported using the Event eCRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours, as indicated in Section 12.4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

9.2.3.1.1.3 Serious Adverse Events After the Protocol-required Reporting Period

If the investigator becomes aware of serious adverse events suspected to be related to IP or fatal serious adverse events (regardless of causality) after completion of the protocol-required reporting period (as defined in Section 9.2.3.1.1.2), then these serious adverse events will be reported to Amgen within 24 hours following the investigator's awareness of the event on the Events CRF.

After End of Study, there is no requirement to actively monitor study subjects after the study has ended with regards to study subjects treated by the investigator. However, if the investigator becomes aware of serious adverse events suspected to be related to investigational product, then these serious adverse events will be reported to Amgen within 24 hours following the investigator's awareness of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

The method of recording, evaluating, and assessing causality of adverse events, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 12.4.

9.2.3.1.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

9.2.3.1.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Section 12.4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event eCRF.

9.2.3.1.4 Regulatory Reporting Requirements for Serious Adverse Events

If subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.3.1.5 Safety Monitoring Plan

Subject safety will be routinely monitored as defined in Amgen's safety surveillance and signal management process.

9.2.3.1.6 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and female partners of male subjects will be collected after the start of study treatment and until 30 days (for female subjects) and 90 days (for female partners of male subjects) after the last dose of all study drug(s).

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Section 12.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Section 12.5.

9.2.3.2 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature.

Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital signs eCRF. Take 3 blood pressure measurements spaced 1 to 2 minutes apart and additional measurements if the first 2 are more than 10 mmHg apart for either systolic or diastolic blood pressure (see Section 12.10).

The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs eCRF.

Additional Vital Sign Measurements

In cycles 1 and 6, an additional blood pressure measurement post-carfilzomib infusion will be collected (within 30 minutes of the end of infusion).

Record all measurements on the vital signs eCRF. For blood pressure, record the average blood pressure.

9.2.3.3 Electrocardiograms (ECGs)

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine

position, the subject should be in most recumbent position as possible. The ECG must include the following measurements: heart rate, QRS, QT, QTc, and PR intervals. The principal investigator or (eg, designated site physician, central reader) will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

Electrocardiograms will be required in all subjects at screening. Electrocardiogram monitoring is required on cycle 1 day 8 and cycle 2 day 1 at the end of the carfilzomib infusion, and as clinically indicated.

9.2.3.4 Other Safety

9.2.3.4.1 Echocardiogram

All subjects will have a baseline ECHO, including assessments of systolic and diastolic left ventricular function and right ventricular function. Screening ECHO may be done within 30 days prior to randomization, if performed as a part of standard of care. Echocardiogram is to be repeated approximately every 6 months (± 2 weeks) from cycle 1 day 1 until safety follow-up visit, and additionally, if clinically indicated. An ECHO must be performed within 72 hours of the onset of a cardiac failure event.

9.2.3.4.2 Pulmonary Function Tests (PFTs)

Baseline and surveillance pulmonary function tests are may be performed if clinically indicated at the discretion of the investigator.

9.2.3.4.3 Hepatitis B

All hepatitis testing will be performed locally. All subjects will be tested at screening for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and hepatitis B core antibody (anti-HBc), unless performed within 6 months of screening and there was no change in the subject’s risk factors within these 6 months.

Subjects with no history of HBV infection that are negative for hepatitis serologies at screening should be followed as clinically indicated.

Subjects with positive testing or who have a prior history of HBV infection should have consultation with a specialist in HBV and have HBV DNA testing and monitoring of HBV DNA every 12 weeks (± 2 weeks) or more frequently, if clinically indicated, through safety follow-up. Subjects that have received hepatitis B vaccination with only anti-HBs positivity and no clinical signs of hepatitis do not require HBV DNA monitoring.

Any subject who becomes HBV DNA positive or develops reactivation of HBV will have study treatment interrupted and receive appropriate antiviral treatment as per a specialist in hepatitis B. Resumption of clinical study therapy may be considered in subjects whose HBV reactivation is controlled and where the benefits of clinical study therapy outweigh the risks. After cessation of study therapy for any reason, any ongoing monitoring and antiviral treatment should be under the guidance of a specialist in HBV.

9.2.4 Clinical Laboratory Assessments

Refer to Section 12.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Table 2-1) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event eCRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

All protocol-required laboratory assessments, as defined in Section 12.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Table 2-1).

9.2.4.1 Pregnancy Testing

A serum pregnancy test must be completed at screening (10 to 14 days prior to cycle 1 day 1). A serum or urine pregnancy test must be completed within 24 hours of initiation of lenalidomide for FCBP. Additional pregnancy testing must also be performed during treatment, as per Schedule of Activities (Table 2-1) and at the safety follow-up visit.

Note: Females who have undergone a bilateral tubal ligation/occlusion do not require pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Form, see Figure 12-2). Refer to Section 12.5 for contraceptive requirements.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

9.2.4.2 Prespecified Biomarker Assessments

Minimal residual disease in bone marrow is a mandatory measurement in this study. Minimal residual disease will be measured by a NGS-based assay. Bone marrow aspirate sample will be collected as per Schedule of Activities (Table 2-1). The bone marrow aspirate sample will be processed and stored according to a protocol that is provided by the central lab. The samples will be analyzed centrally by the NGS-based MRD assay. See Section 9.2.2.2 for details on priority of samples for bone marrow aspirate testing.

9.2.5 Pharmacokinetic Assessments

All subjects enrolled will have pharmacokinetic (PK) samples assessed. Approximately 15 subjects in each arm will be invited to participate in the intensive PK/PDn substudy at select sites (see Section 9.2.9). Sparse PK samples will be collected from the rest of the subjects, eg, subjects who do not consent to participate in the optional intensive PK/PDn substudy.

Venous samples of approximately 2.5 mL will be collected for measurement of plasma concentrations of carfilzomib as specified in the Schedule of Activities (Table 2-1). Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be collected within ± 5-minute time windows around the nominal time points (except for the time point immediately prior to the end of infusion, for which the PK collection needs to occur prior to the end of infusion).

9.2.6 Pharmacodynamic Assessments (Only for Subjects Participating in the Optional Intensive PK/PDn Substudy)

Venous blood samples of approximately 2 mL will be collected for measurement of carfilzomib PDn as per Schedule of Activities (Table 2-1). Blood samples will only be collected from approximately 15 subjects in each arm who consent to participate in optional intensive PK/PDn substudy (see Section 9.2.9).

9.2.7 Clinical Outcome Assessments

All COAs will be completed via electronic tablet at the site prior to any other assessments or procedures.

9.2.7.1 EORTC QLQ-C30

The EORTC QLQ-C30 is a self-reported 30-item generic instrument for use in cancer subjects across tumor types. It assesses 15 domains consisting of 5 functional domains

(physical, role, emotional, cognitive, social), 9 symptom domains (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties), and a GHS or QOL scale (Aaronson et al, 1993).

[redacted]

9.2.7.3 Patient-reported Convenience With Carfilzomib-dosing Schedule Question

This is a carfilzomib-specific convenience single-item/question. This item was modified from a question used in the A.R.R.O.W. study ("neutral" option was removed). This item is not psychometrically validated (see Section 12.12 for more details).

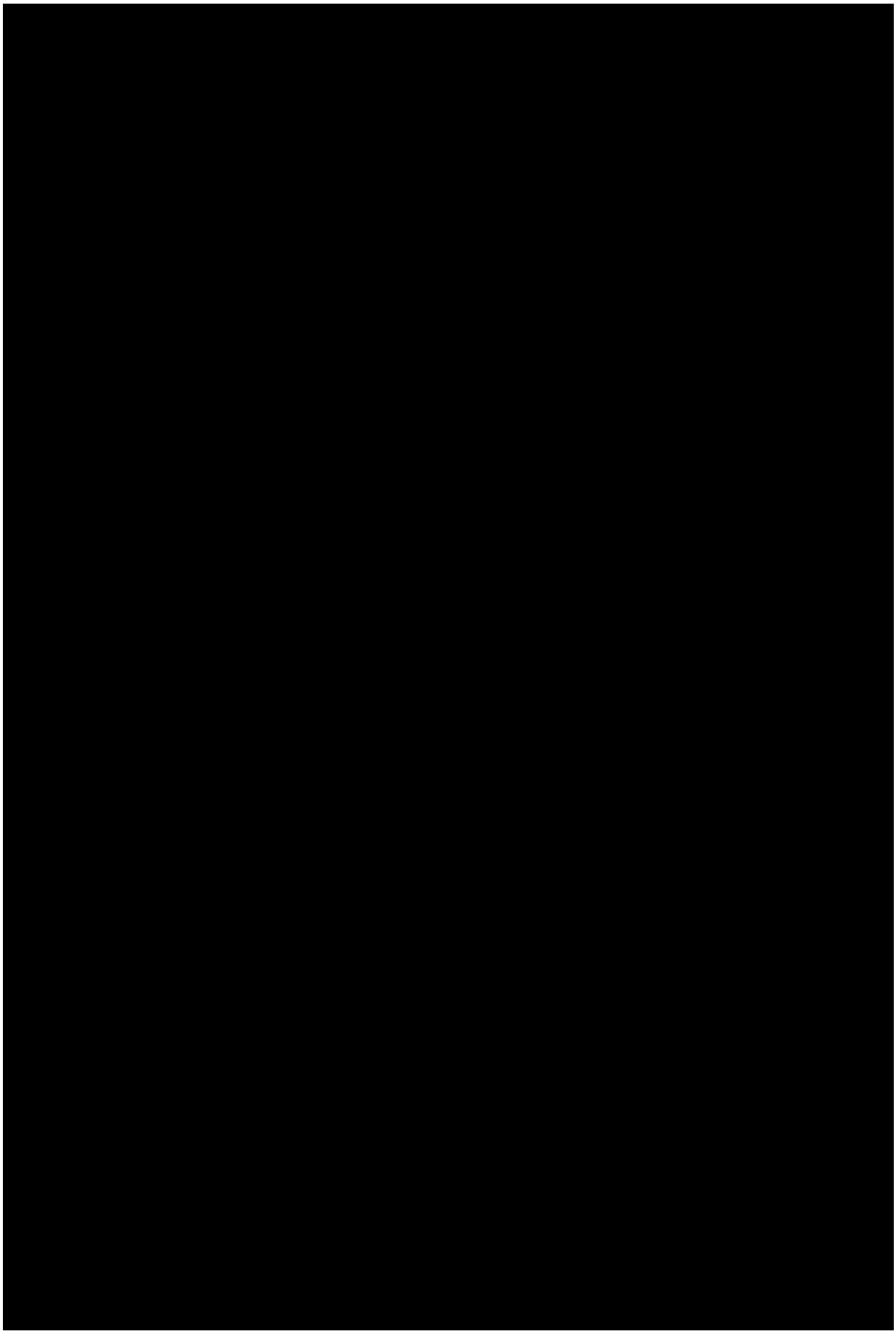
[redacted]

9.2.7.5 Cancer Therapy Satisfaction Questionnaire (CTSQ)

The CTSQ measures treatment satisfaction in individuals with cancer (Trask et al, 2008). The CTSQ contains 3 domains covering 16 items (Cheung et al, 2016):

- Expectations of Therapy
- Feelings about side effects
- Satisfaction with therapy

[redacted]



[redacted]

9.2.9 Optional Substudies

9.2.9.1 Intensive Pharmacokinetic/Pharmacodynamic Substudy

Approximately 15 subjects in each arm will be invited to participate in the intensive PK/PDn substudy at select sites. See Sections 9.2.5 and 9.2.6 for more details on the assessments.

Documentation of informed consent for the optional intensive PK/PDn substudy must be confirmed prior to performing intensive PK/PDn procedures.

9.2.10 Other Assessments

Not applicable.

10. Statistical Considerations

10.1 Sample Size Determination

The sample size was determined so that the primary objective could be tested via synthesis method at 1-sided 2.5% significance level with 80% power, including an interim analysis for futility when the first 230 subjects have been randomized and had the best overall response assessed by the date when treatment was completed, disease progression/death occurred, patient dropped out or started new therapy, whichever occurred first.

A sample size of 460 subjects is needed to achieve 80% power for demonstrating that once-weekly KRd 56 mg/m^2 preserves at least 60% of twice-weekly KRd 27 mg/m^2 effect in terms of ORR at a 1-sided 2.5% significance level by the synthesis method. The stratified relative risk (RR) of ORR during the first 12 cycles of treatment in ASPIRE study (twice-weekly Rd vs KRd 27 mg/m^2 RR and 95% CI: 0.755 [0.696, 0.818]) will be used as the historical reference for the test of non-inferiority. This calculation assumes a true RR of 1 with ORR = 86.6% for both arms (once-weekly KRd 56 mg/m^2 vs twice-weekly KRd 27 mg/m^2), and an interim analysis for futility at 50% information fraction using O'Brien-Fleming beta-spending function. The reference ORR = 86.6% was determined based on the BOR observed by the end of 12 cycles of treatment in ASPIRE study (Amgen data on file).

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

The analysis and reporting of the data from this study will be performed using the following analysis populations:

10.2.1.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population constitutes all randomized subjects and will be the basis for the analyses of efficacy in this study. Subjects in the analyses based on the ITT population will be analyzed according to the treatment group to which they were randomized.

10.2.1.2 Safety Population

The safety population includes all randomized subjects who receive at least 1 dose of any study treatment (carfilzomib, lenalidomide, or dexamethasone), and will be the basis for the analyses of safety. Subjects in the analyses based on the safety population will be analyzed according to the treatment group corresponding to the actual treatment received. Any subject who received at least 1 weekly dose of carfilzomib 56 mg/m^2 will be included in arm 1 (once-weekly KRd 56 mg/m^2). Otherwise, subjects will be included in arm 2 (twice-weekly KRd 27 mg/m^2).

10.2.1.3 Per-Protocol Population

The per-protocol population will include all randomized subjects who do not have any major protocol deviations that might affect the interpretation of the analyses of the efficacy endpoints. The major protocol deviations include:

- Major inclusion criteria not met
- Major exclusion criteria not met
- Major treatment non-compliance
  - Treatment received different from treatment randomized
  - Concomitant use of protocol prohibited medications.

10.2.2 Covariates

In addition to the stratification factors for randomization (original ISS stage at study entry, prior lenalidomide treatment, prior PI treatment, prior anti-CD38 exposure), other baseline covariates may be considered to examine primary and selected secondary endpoints in subgroups or in sensitivity analyses, as appropriate. More details will be described in the statistical analysis plan (SAP).

10.2.3 Subgroups

The ORR will be estimated for selected subgroups if appropriate:

- original ISS stage at baseline (stage 1 or 2 vs stage 3)
- prior lenalidomide treatment (yes vs no)
- prior PI treatment (yes vs no)
- prior anti-CD38 exposure (yes vs no)
- prior bortezomib treatment (yes, no)
- age (< 65, ≥ 65; 18 to < 65, 65 to < 75, ≥ 75)
- number of prior therapies (1 vs > 1; 1 vs 2 vs > 2)
- cytogenetic risk measured by FISH (high-risk vs standard risk)
- bortezomib refractory status (yes vs no)
- lenalidomide refractory status (yes vs no)
- prior transplant (yes vs no)

10.2.4 Handling of Missing and Incomplete Data

Subjects may have missing data points for various reasons and the impact on the analysis might differ from 1 endpoint to another. The general rules for accommodating the missing or incomplete data may be refined during the blind review of the data, and they will be described in detail in SAP. Sensitivity analyses might be needed to evaluate the robustness of the primary analysis and/ or key secondary analyses results in case of significant missing data.

Incomplete dates for the start of adverse event, concomitant medications, and death will be imputed and the detailed rules will be specified in SAP.

The calculation of scores and methods to deal with missing data will be handled according to the EORTC QLQ-C30 questionnaire's standard scoring guidelines.

No imputation will be done for the analysis of the primary and key secondary endpoints. The frequency of missing disease assessments and deviation of the actual disease assessment times from the scheduled assessment times will be summarized by treatment arms. Sensitivity analyses will be performed to assess the impact of missing any disease or response assessment on the analysis of ORR and PFS. Similar analysis will be performed for QOL endpoints.

Details of missing data analysis and imputation rules will be described in SAP.

10.3 Statistical Analyses

The SAP will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 5.3.1.

10.3.1 Planned Analyses

10.3.1.1 Interim Analysis and Early Stopping Guidelines

An interim futility analysis will be performed to limit the number of patients exposed to treatment in case of low activity.

The primary purpose of this interim analysis is to assess the likelihood that the treatment effect of the once-weekly KRd 56 mg/m^2 will preserve at least 60% of twice-weekly KRd 27 mg/m^2 effect in terms of ORR. The date of the analysis will be set up by Amgen based on the date when the first 230 subjects have been randomized and had a BOR assessed by the date when treatment was completed, confirmed PD or death occurred, subject was lost to follow-up, withdrew consent, or started new therapy, whichever occurred first.

This interim data analysis will address the primary and key secondary study objectives for the selected subjects. This analysis will be performed by an independent contract research organization, and the sponsor will be blinded to the results. An independent DMC will review the unblinded results and may suggest early termination of the trial. Using an O'Brien-Fleming beta-spending function, the stopping boundary for futility in p-value scale is 0.289. This stopping boundary corresponds to an approximate RR of 0.930, meaning that the study is futile if the observed ORR in the once-weekly KRd 56 mg/m^2 arm is < 80.8%, when the observed ORR in the twice-weekly KRd 27 mg/m^2 arm is 86.6%. With such a stopping boundary, the trial has over 70% probability to stop for futility when the null hypothesis of inferiority is true.

Based on this stopping criteria and clinical evaluation of the benefit/risk ratio, the DMC may recommend the continuation of study for the final analysis including all subjects enrolled in the study.

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

10.3.1.2 Primary Analysis

The primary analysis corresponds to the final analysis.

10.3.1.3 Final Analysis

Amgen will set a final analysis data cut-off date for efficacy and safety analysis in anticipation of the date when all subjects have completed the study. Final analysis will address all the study objectives. Data will be subject to ongoing checks for integrity, completeness, and accuracy in accordance with the Data Management Plan with the expectation that all outstanding data issues are resolved ahead of the snapshot. The data will be locked to prevent further changes, and a snapshot of the locked database will be used in the analysis.

The hypotheses for the primary and key secondary objectives (ORR, PFS, and convenience after cycle 4 of treatment) will be tested using a fixed sequence hierarchical testing procedure to control the family-wise type I error rate at 1-sided 0.025 level. The testing is ordered as follows: non-inferiority of ORR, non-inferiority of PFS, and superiority of patient-reported convenience after cycle 4 of treatment.

Starting with the hypothesis of ORR, if any hypothesis in the sequence is rejected at a 1-sided significance level of 0.025, then the subsequent hypothesis will be tested. Otherwise, if any hypothesis failed to be rejected, then the subsequent hypotheses will not be tested.

For the primary endpoint, the stopping boundary (0.025 in p-value scale) corresponds to an approximate RR = 0.975, meaning that the study meets the primary objective if the observed ORR for the once-weekly KRd 56 mg/m^2 arm is at least 84.3%, when the observed ORR in the twice-weekly KRd 27 mg/m^2 arm is 86.6%.

The final analysis of efficacy endpoints will be based on the ITT population, while the final analysis of safety endpoints will be based on the safety population.

10.3.2 Methods of Analyses

10.3.2.1 General Considerations

The analyses of efficacy and safety endpoints will be based on the analysis sets defined in Section 10.2.1. The primary and final analyses of the efficacy endpoints will use the ITT population, while the per-protocol population will be used for sensitivity analyses, if applicable. The final analysis of the safety endpoint will use the safety population.

10.3.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Overall response over the duration of the study: Clopper-Pearson method for by treatment overall response rate (ORR) estimate and CI. Mantel-Haenszel stratified RR for the inference of treatment effect. The synthesis approach will be used to show that once-weekly KRd 56 mg/m^2 preserves at least 60% of twice-weekly KRd 27 mg/m^2 effect vs Rd.
Secondary	PFS over the duration of the study: Kaplan-Meier (KM) estimates for PFS distribution by treatment and PFS rates and CI at 6 and 12 months, stratified Cox proportional hazards (PH) model for HR and CI estimate, and the synthesis approach will be used to show that once-weekly KRd 56 mg/m^2 preserves at least 50% of twice-weekly KRd 27 mg/m^2 effect vs Rd. The stratified HR of PFS observed during the first 12 months of treatment in ASPIRE study (twice-weekly Rd vs KRd 27 mg/m^2 RR 1.81; 95% CI: 1.39, 2.38) will be used as the historical reference for the test of non-inferiority. Patient-reported convenience after cycle 4 of treatment: Cochran-Mantel-Haenszel method will be used to evaluate the treatment effect (OR) for whether carfilzomib dosing is reported as convenient or inconvenient; a logistic regression model including the randomization stratification factors and treatment group will be considered for sensitivity analysis. TTR: mean, SD, median, minimum and maximum among responders. DOR: KM method among responders. TTP: KM method and stratified Cox PH model OS over the duration of the study: KM estimates for OS distribution by treatment and OS rates and CI at 6 and 12 months, stratified Cox PH model for HR and CI estimate. MRD[-]CR: proportion of MRD[-]CR will be reported with CI calculated using Clopper-Pearson method. MRD[-] status at 12 months from randomization: proportion of MRD[-] will be reported with CI calculated using Clopper-Pearson method. Physical functioning and role functioning (EORTC QLQ-C30) over time: a repeated measures analysis of covariance adjusting for the baseline covariates. A restricted maximum likelihood-based mixed model for repeated measures (MMRM) will be considered as sensitivity analysis. Patient-reported treatment satisfaction (CTSQ) after cycle 4 of treatment: analysis of covariance at the corresponding fixed time point.
Exploratory	Will be described in the statistical analysis plan finalized before database lock

10.3.2.3 Safety Analyses

10.3.2.3.1 Adverse Events

Incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and adverse events of interest will also be provided. More details will be included in the SAP.

10.3.2.3.2 Laboratory Test Results

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

10.3.2.3.3 Vital Signs

The vital signs and their change from baseline will be summarized by cycle.

10.3.2.3.4 Physical Measurements

The physical measurements and their change from baseline will be summarized by cycle.

10.3.2.3.5 Electrocardiogram

The 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 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 studies.

10.3.2.3.6 Exposure to Investigational Product

The extent of exposure to all study treatments (carfilzomib, lenalidomide, and dexamethasone) will be evaluated for each arm with respect to treatment duration number of cycles started, total dose received, number of doses administered, dose intensity. The reasons for dose modifications, or discontinuation from any study treatment will be summarized separately. More details will be included in the SAP.

10.3.2.3.7 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.

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12. Appendices

12.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
AST	aspartate aminotransferase
BOR	best overall response
BSA	body surface area
CFR	US Code of Federal Regulations
COA	Clinical Outcome Assessment
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CT	computed tomography
CTSQ	Cancer Therapy Satisfaction Questionnaire
DMC	data monitoring committee
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30
[redacted]	
FACIT	Functional Assessment of Chronic Illness Therapy
[redacted]	
FCBP	females of childbearing potential
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
GHS	global health status
HBsAg	hepatitis B surface antigen

Abbreviation or Term	Definition/Explanation
HBV	hepatitis B virus
HR	hazard ratio
HRQOL	health-related quality-of-life
HRT	hormone-replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IMiD	immunomodulatory drug
IMWG-URC	International Myeloma Working Group Uniform Response Criteria
Interactive Voice/Web Response System (IxRS)	telecommunication/web-based technology that is linked to a central computer in real time as an interface to collect and process information
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Boards
IRC	Independent Review Committee
ISS	International Staging System
IV	intravenous
KM	Kaplan-Meier
KRd	carfilzomib in combination with lenalidomide and dexamethasone
MM	multiple myeloma
MMRM	mixed model for repeated measures
MRD	minimal residual disease
MRD[-]	minimal residual disease negative
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NDMM	newly diagnosed multiple myeloma
NGS	next-generation sequencing
OR	odds ratio
ORR	overall response rate
OS	overall survival
PD	progressive disease
PDn	pharmacodynamics
PET/CT	positron emission tomography/computed tomography
PFS	progression-free survival

Abbreviation or Term	Definition/Explanation
PH	proportional hazard
PI	proteasome inhibitor
PK	pharmacokinetics
PR	partial response
RBC	red blood cell
Rd	lenalidomide with dexamethasone
REMS	Risk Evaluation and Mitigation Strategy
RR	relative risk
RRMM	relapsed or refractory multiple myeloma
SAP	Statistical Analysis Plan
sCR	stringent complete response
[redacted]	
SFLC	serum-free light chain
SIFE	serum immunofixation
SmPC	Summary of Product Characteristics
Source Data	Information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
SPD	maximal perpendicular diameter
SPEP	serum protein electrophoresis
SWT	Satisfaction With Therapy
TLS	tumor lysis syndrome
TTP	time to progression
TTR	time to response
UIFE	urine immunofixation
UPEP	urine protein electrophoresis
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
VGPR	very good partial response

12.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 12-1 will be performed by the central laboratory and by the local laboratory.

Local laboratory results may be used in the event that the central laboratory results are not available for the purpose of a time sensitive study treatment decision, including laboratories for efficacy assessment. A sample for central analysis is to be obtained at the same time for each laboratory assessment in Table 12-1. Any local laboratory result used to make a study treatment decision must be entered into the electronic case report form (eCRF) with the exception of the myeloma response assessment where only the central laboratory results are to be entered.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 6.1 to 6.2 of the protocol.

Subjects must fast for at least 9 hours before screening hematology and serum chemistries. If central laboratory results for lactate dehydrogenase, bilirubin, aspartate aminotransferase, and potassium are not reported/available at screening, local laboratory results may be utilized if completed within the screening window and must be reported on the eCRF. Screening coagulation, pregnancy, and hepatitis B serology tests will be done at local laboratories. Post-enrollment, laboratory samples may be collected and analyzed by local laboratories if immediate results are necessary for management of treatment-emergent adverse events or dosing determination. Evaluation of lab results for dose determination as required per Schedule of Assessments must be documented prior to dosing in each cycle. Any local lab values that lead to dose modification decisions must be recorded in the eCRF. Any local lab results that fulfill ≥ grade 3 values per Common Terminology Criteria for Adverse Events (CTCAE) must be recorded in the eCRF.

For cycle 1 day 1, hematology and serum chemistry panel from screening may be used if within 3 days of day 1 and within 48 hours of D1 of a cycle from C2 onwards.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 12-1. Analyte Listing

Central Laboratory			
Chemistry	**Hematology**	**Disease Assessments**	**Other Labs**
Sodium Potassium Chloride Bicarbonate Albumin Calcium Corrected calcium Glucose BUN or Urea Creatinine Total bilirubin Direct bilirubin Alk phosphatase AST (SGOT) ALT (SGPT) Phosphate Magnesium	RBC Hemoglobin Hematocrit Platelets WBC Differential Neutrophils Bands/stabs Segs Eosinophils Basophils Lymphocytes Monocytes Plasma cell count: • plasma cell percent	MRD assessment by NGS (bone marrow aspirate) FISH (bone marrow aspirate) SPEP Serum Immunofixation UPEP Urine immunofixation SFLC	Pharmacokinetics Pharmacodynamics
Central Laboratory Screening Only			
Screening only: *LDH* *Uric acid* *Amylase* *Lipase* *Fasting lipid panel:* • *Total cholesterol* • *HDL* • *LDL* • *Triglycerides*	*Screening only:* *HbA1c*		*Screening only:* *NT-proBNP* *Screening only unless clinically indicated:* *Quantitative immunoglobulins (serum): IgA, IgD, IgE, IgG, IgM* *beta2-microglobulin (serum)*
Local Laboratory			
	Screening only - Coagulation: *PT/INR* *PTT*		*Screening and as required by protocol:* *Other:* Serum pregnancy Urine pregnancy HBV serologies • Hepatitis B surface antigen (HBsAg) • Hepatitis B surface antibody (anti-HBs) • Hepatitis B core antibody (anti-HBc) HBV DNA testing

ALT = alanine aminotransferase; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; AST = aspartate aminotransferase; BUN = blood urea nitrogen; FISH = fluorescent in situ hybridization; HbA1c = hemoglobin A1c; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HDL = high density lipoprotein; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MRD = minimal residual disease; NGS = next-generation sequencing; NT-proBNP = N terminal of the prohormone brain natriuretic peptide; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell count; SFLC = serum-free light chain; SGOT = serum glutamic-oxaloacetic transaminase; SGPT - serum glutamic-pyruvic transaminase; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; WBC = white blood cell count.

12.3 Appendix 3. Study Governance Considerations

Data Monitoring Committees and Independent Review Committee

Data Monitoring Committee

An independent data monitoring committee (DMC) will be convened for this study and will act in an advisory capacity to the sponsor with respect to safeguarding the interests of study subjects, assessing interim data, monitoring the overall conduct of the study, and providing with recommendations relating to continuing, modifying, or stopping the study based on these findings (International Council for Harmonisation Good Clinical Practice [ICH GCP 5.5.2]). Details of the DMC will be described in the DMC Charter. The initial assessment from this committee will be planned after 30 subjects (approximately 15 for the experimental arm and 15 for the control arm) have been enrolled and have finished the first cycle of treatment to ensure safety of all arms. A provision will be made allowing an early follow-up DMC meeting to be decided at the time of the initial assessment. The DMC will meet approximately every 6 months to review safety data on a regular basis, and once to review the efficacy data for futility. The interim analysis for futility is planned to occur when the first 230 subjects have been randomized and had a best overall response (BOR) assessed by the date when treatment was completed, confirmed progressive disease or death occurred, subject was lost to follow-up, withdrew full consent, or started new therapy, whichever occurred first.

Records of all meetings will be maintained by the DMC for the duration of the study. Records of all meetings will be transferred and stored in the trial master folder at the conclusion of the study. Further details are provided in the DMC charter.

Independent Review Committee

The individual subject disease response and disease progression for this study will be independently assessed by an Independent Review Committee (IRC) in accordance with the International Myeloma Working Group Uniform Response Criteria (IMWG-URC) (Section 12.11). The membership criteria and operational details of the IRC will be described in the IRC Charter. The IRC will centrally review the disease-related tests and assessments (Section 9.2.2) to evaluate disease progressions and responses without the knowledge of randomization assignments or Investigator's disease assessments. The IRC assessment will be used for the primary analysis of efficacy endpoints except for minimal residual disease (MRD) rate and clinical outcome assessments (COA) endpoints.

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

- The investigator will be responsible for the following:
- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the US Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Recruitment Procedures

Site staff will identify potential subjects from their existing patient population or may seek referral patients through existing professional networks or other community sources such as patient advocacy groups. All patient-facing materials must be reviewed/approved by the sponsor and the local IRB/IEC.

Informed Consent Process

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the

subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 8.

Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another informed consent form if the rescreening occurs within 28 days from the previous informed consent form signature date.

The informed consent form (ICF) will contain a separate section that addresses the use of remaining mandatory samples for optional future research. The investigator or authorized designee will explain to each subject the objectives of the future research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for future research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the Case Report Form (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- A recognized expert in the therapeutic area
- An Investigator who provided significant contributions to either the design or interpretation of the study
- An Investigator contributing a high number of eligible subjects

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or

adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research and Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Retention of study documents will be governed by the Clinical Trial Agreement.

Case report forms must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

Source Documents

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the Interactive Voice Response System/Interactive Web Response System (IxRS) system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a COA).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen

- Investigational product-related correspondence including (Proof of Receipts, Investigational Product Accountability Record[s], Return of Investigational Product for Destruction Form[s], Final Investigational Product Reconciliation Statement, as applicable)
- Non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable

Retention of study documents will be governed by the Clinical Trial Agreement.

Study and Site Closure

Amgen or its designee may stop the study or study center participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

12.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure. • Note: Treatment-emergent adverse events will be defined in the statistical analysis plan (SAP)

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • For situations when an adverse event or serious adverse event is due to multiple myeloma report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, multiple myeloma). Note: The term “disease progression” should not be used to describe the disease-related event or adverse event. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:

Other medically important serious event

Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event/serious adverse event information in the Event case report form (CRF).
  - Additionally, the investigator is required to report a fatal disease-related event on the Event CRF.
- The investigator must assign the following adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Severity (or toxicity defined below);
  - Assessment of relatedness to investigational product, other protocol-required therapies, and/or study-mandated activity and/or procedures
  - Action taken and
  - Outcome of event
- If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Event CRF.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to Amgen in lieu of completion of the Event CRF page.

Adverse Event and Serious Adverse Event Recording
• If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen. • The investigator will record the adverse event by the diagnostic term for that adverse event (not the individual signs/symptoms). Only in the event that no diagnosis can be made should the individual signs/symptoms be documented as an adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity
The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on: The Common Terminology Criteria for Adverse Events, version 5.0 which is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Assessment of Causality
• The investigator is obligated to assess the relationship between investigational product, protocol-required therapies, and/or study-mandated activity and/or procedure(s) and each occurrence of each adverse event/serious adverse event. • Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality. • There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.

Assessment of Causality
• The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. • The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed Event CRF. • The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system via the **Events form**. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using a paper-based Serious Adverse Event Contingency Report Form (also referred to as the electronic Serious Adverse Event [eSAE] Contingency Report Form) (see Figure 12-1) within 24 hours of the investigator's knowledge of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on the paper-based Serious Adverse Event Contingency Report Form (see Figure 12-1). • Once the study has ended, serious adverse event(s) suspected to be related to investigational product will be reported to Amgen if the investigator becomes aware

of a serious adverse event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Report Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to IP)**

1. **Site Information**

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. **Subject Information**

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the serious adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

   Serious Adverse Event Diagnosis or Syndrome* –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria)rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

   Is event serious?* – Indicate Yes or No. This is a mandatory field.

   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   Relationship to IP – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

   Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

   If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**

   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

FORM-056006 *Instructions Page 1 of 2* *Version 7.0 Effective Date: 1 February 2016*

Completion Instructions - Electronic Adverse Event Contingency Report Form (for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

5. **IP Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.
6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. **Case Description**
    Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

AMGEN
Study # 20180015
carfilzomib

Electronic Serious Adverse Event Contingency Report Form

For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day ____ Month ____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP?								Outcome of Event 1-Resolved 2-Not resolved 3-Fatal 4-Unknown	Check only if event is related to study procedure eg, biopsy
						carfilzomib		<Device>		<Device>		<Device>			
						No✓	Yes✓	No✓	Yes✓	No✓	Yes✓	No✓	Yes✓		
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											

Serious Criteria: **01** Fatal; **02** Immediately life-threatening; **03** Required/prolonged hospitalization; **04** Persistent or significant disability /incapacity; **05** Congenital anomaly / birth defect; **06** Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
carfilzomib	☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN Study # 20180015 carfilzomib	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Test / Unit											
	Test											
	Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20180015 carfilzomib	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee -	Title	Date
I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.		

12.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

For the region-specific guidance regarding the use of lenalidomide, please refer to the regional label.

Study-specific contraception requirements for males and females of childbearing potential are outlined in Section 6.2.

12.5.1 Risks Associated With Pregnancy

Male and female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant or father a child during treatment and for 30 days (for female subjects) and 90 days (for male subjects) after the last dose of protocol-required therapies.

12.5.2 Counseling

12.5.2.1 Female Subjects of Childbearing Potential

For a female of childbearing potential, lenalidomide is contraindicated unless all of the following are met (ie, all females of childbearing potential [FCBP] must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- She understands the potential teratogenic risk to the unborn child.
- She understands the need for effective contraception, without interruption, 28 days before starting study treatment, throughout the entire duration of study treatment, during treatment interruptions, and for an additional 30 days after the last dose of all study drug(s)
- She should be capable of complying with effective contraceptive measures.
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy.
- She understands the need to commence the study treatment as soon as study drug is dispensed after a negative pregnancy test.
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol.
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide.

<u>The investigator must ensure that for FCBP:</u>

- Complies with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding.
- Acknowledge the aforementioned requirements.

12.5.2.2 Female Subjects Not of Childbearing Potential

For a female NOT of childbearing potential, lenalidomide is contraindicated unless all of the following are met (ie, all females NOT of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

12.5.2.3 Male Subjects:

- Traces of lenalidomide have been found in blood, sperm, and semen. Male subjects taking lenalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):
  - Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential
  - Understand the need for the use of a condom with spermicide even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.
  - Counseling about the requirement for latex condom with spermicide use during sexual contact with FCBP and the potential risks of fetal exposure must be conducted at a minimum of every 28 days and at the time that lenalidomide treatment is discontinued. During counseling, subjects must be reminded to not share study drug and to not donate blood, sperm, or semen.

12.5.3 Definition of Females of Childbearing Potential

A female is considered fertile after menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

<u>Females in the following categories are not considered female of childbearing potential</u>:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

  Note: Site personnel documentation from the following sources is acceptable:
  1) review of subject's medical records; 2) subject's medical examination; or
  3) subject's medical history interview.

- Premenarchal female

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 consecutive months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment

12.5.4 Contraception Methods

12.5.4.1 Contraception Methods for Female Subjects

Females of childbearing potential should be advised to avoid becoming pregnant while being treated with carfilzomib or lenalidomide. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryo-fetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

Carfilzomib was clastogenic in the in vitro chromosomal aberration test in peripheral blood lymphocytes.

Therefore, as a precaution, FCBP and/or their male partners must agree to use 2 methods of contraception as described below or abstain from sexual activity 28 days before treatment, during treatment, during treatment interruptions, and for an additional 30 days after the last dose of all study drug(s).

Female subjects of childbearing potential must agree to use 2 methods of contraception simultaneously (1 highly effective form of contraception as described below, and 1 additional effective contraceptive method [male latex or synthetic condom with spermicide for male partners of FCBP, or a diaphragm or cervical cap]).

Highly Effective Contraceptive Methods

Note: Failure rate of < 1% per year when used consistently and correctly.

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- intrauterine device
- intrauterine hormonal-releasing system
- bilateral tubal ligation/occlusion
- vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject)

12.5.4.2 Contraception Methods for Male Subjects

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with protocol-required therapies; the reliability of sexual abstinence must be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject).
- Use a condom with spermicide during treatment and for an additional 90 days after the last dose of protocol-required therapies even if he has undergone a successful vasectomy.

The female partner should consider using an acceptable method of effective contraception such as: hormonal, intrauterine device, intrauterine hormonal-releasing system, female barrier method (diaphragm, cap, sponge [a female condom is not an option because there is a risk of tearing when both partners use a condom]).

Male subjects with a pregnant partner must practice sexual abstinence or wear a condom with spermicide to prevent exposure of the unborn child to carfilzomib or lenalidomide through semen.

Male subjects will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure.

Note: If the male's sole female partner is of non-childbearing potential or has had a bilateral tubal ligation/occlusion, he is not required to use additional forms of contraception during the study.

12.5.4.3 Unacceptable Methods of Birth Control for Male and Female Subjects

Birth control methods that are considered unacceptable in clinical studies include:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method

12.5.5 Pregnancy Testing

12.5.5.1 Female Subjects

Medically supervised pregnancy tests with a minimum sensitivity of 50 mIU/mL must be performed for FCBP, including FCBP who commit to complete abstinence, as outlined below.

Before starting lenalidomide:

Female Subjects:

- FCBP must have 2 negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the first dose of study drugs and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the Investigator has verified that the results of these pregnancy tests are negative.
- Will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure.
- Must agree to abstain from donating blood during study participation and for at least 90 days after the last dose of all study drug(s).

During study participation and for 30 days after discontinuation from the study:

Female Subjects:

- FCBP with regular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, and 30 [+3] days after the last dose of all study drug(s). If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, 30 [+3] days after the last dose of all study drug(s).
- In addition to the required pregnancy testing, the Investigator must confirm with FCBP that she is continuing to use 2 reliable methods of birth control at each visit.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days and at the time that lenalidomide treatment is discontinued. During counseling, subjects must be reminded to not share study drug and to not donate blood.

- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 30 days after the last dose of all study drug(s).
- If pregnancy or a positive pregnancy test does occur in a study patient, study drug must be immediately discontinued.

12.5.5.2 Male Subjects:

If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

12.5.6 Additional Precautions

- Subjects should be instructed never to give lenalidomide to another person and to return any unused lenalidomide to the study doctor at the end of treatment.
- Only enough lenalidomide for 1 cycle of therapy may be dispensed with each cycle of therapy.
- Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in subjects with neutropenia.
- Carfilzomib could decrease the effectiveness of oral contraceptives. The investigator should notify subjects of this risk when choosing the methods of birth control. Additional medications given during the study may alter the contraceptive. The investigator must discuss these contraceptive changes with the subject.
- Female subjects should not donate blood during therapy and for at least 90 days after the last dose of all study drug(s).
- Male subjects should not donate blood, semen, or sperm during therapy and for at least 90 days after the last dose of all study drug(s).
- Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use different method of highly effective methods of contraception and/or for an increased length of time. The investigator must discuss these contraceptive changes with the subject.

12.5.7 Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 30-days after the last dose of protocol-required therapies.
- Information will be recorded on the Pregnancy Notification **Form** (see Figure 12-2). The **form** must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification **Form** that violates the country or regions local privacy laws).

- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 30 days after the last dose of all study drugs. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an adverse event or serious adverse event. Abnormal pregnancy outcomes (eg, spontaneous abortions, stillbirth, fetal death, congenital anomalies) will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject has a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a poststudy pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 12.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 8.1 for details).

Male Subjects With Partners Who Become Pregnant

- In the event a male subject fathers a child during treatment, and for an additional 90 days after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 12-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.

- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

12.5.8 Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 30 days after the last dose of protocol-required therapies.
- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 235.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 30 days after discontinuing protocol-required therapies.

Figure 12-2. Pregnancy and Lactation Notification Forms

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20180015

Study Design: ☒ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐ N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd__/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20180015

Study Design: ☒ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

12.6 Appendix 6. Sample Storage and Destruction

Any blood or bone marrow sample collected according to the Schedule of Activities (Table 2-1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand multiple myeloma, the dose response and/or prediction of response to carfilzomib, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, biomarker development, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. After the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood or bone marrow samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no

longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 12.3 for subject confidentiality.

12.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Hepatotoxicity stopping rules are described in Section 7.4.1.1.2.

12.8 Appendix 8. Guidelines for Documenting Prior Treatment

Subjects must have documented relapse after at least 1, but no more than 3 prior treatment regimens or lines of therapy for multiple myeloma including relapse after the last line of therapy prior to enrollment. When documenting prior treatments for multiple myeloma, the following guidelines should be used:

- A new line of therapy is considered to start when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of lack of adequate response, progressive disease (PD) (even if the level of progression has not yet met International Myeloma Working Group-Uniform Response Criteria [IMWG-URC] for PD), relapse, or toxicity.
- An increase in dose of therapy, with the intention of recapturing response in a subject who has evidence of progression on that therapy, is considered a new therapy.
- A new line of therapy is also considered to start when a planned period of observation of therapy is interrupted by a need for additional treatment for the disease.
- Examples of 1 line of therapy include:
  - Induction therapy and stem cell transplant followed by planned maintenance therapy (provided there is no intervening PD)
  - Induction therapy followed by maintenance therapy (provided there is no intervening PD)
- Documentation of at least partial response (PR) to at least 1 prior therapy
- For patients with prior carfilzomib therapy, documentation of response (≥ PR) must be available for the most recent previous carfilzomib therapy as well as stop date. Documentation that the subject was not removed from carfilzomib therapy due to toxicity must also be available. For patients with prior therapy with either carfilzomib, the start of the 6-month treatment-free interval is when either carfilzomib is discontinued even if other portions of the regimen are continued.

12.9 Appendix 9. ECOG Performance Status

Grade	Description
0	Normal activity, fully active, able to carry on all predisease performance without restriction.
1	Symptoms, but fully ambulatory, restricted in physically strenuous but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

ECOG = Eastern Cooperative Oncology Group.
Source: Oken et al, 1982.

12.10 Appendix 10. 2018 ESH/ESC Office Blood Pressure Measurement

For more information, please see American Medical Association, 2019 (https://www.ama-assn.org/delivering-care/hypertension/one-graphic-you-need-accurate-blood-pressure-reading).

12.11 Appendix 11. Summary of International Myeloma Working Group - Uniform Response Criteria

Response Subcategory	Multiple Myeloma Response Criteria
sCR	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow aspirate and • Normal SFLC ratio and • Absence of clonal cells in bone marrow biopsy by immunohistochemistry or 2- to 4-color flow cytometry[a]
CR	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow • In subjects with baseline measurable disease only by SFLC, normal SFLC ratio
VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-protein with urine M-protein < 100 mg per 24 hours • In subjects with baseline measurable disease only by SFLC, a decrease ≥ 90% in the difference between involved and uninvolved FLC levels • In subjects achieving a VGPR by other criteria, a soft tissue plasmacytoma must decrease by more than 90% in the SPD compared with baseline
PR	• ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours • In subjects with measurable disease only by SFLC, a decrease ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • In addition to these criteria, if present at baseline, a ≥ 50% reduction in the size (SPD) of soft tissue plasmacytomas is also required
SD	• Not meeting criteria for CR, VGPR, PR, or PD
PD	• Increase of 25% from lowest confirmed response value in 1 or more of the following: – Serum M-component (absolute increase must be ≥ 0.5 g/dL if the lowest M-component was < 5 g/dL – Urine M-component (absolute increase must be ≥ 200 mg per 24 hours) – Only in subjects without measurable serum and urine M protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) • Increase of serum M-component of ≥ 1 g/dL if the lowest M-component was ≥ 5 g/dL) • Appearance of new lesion(s), ≥ 50% increase from nadir in SPD of > 1 lesion, or ≥ 50% increase in longest diameter of a previous lesion > 1 cm in short axis • ≥ 50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

CR = complete response; FC = flow cytometry; FLC = free light chain; PD = progressive disease; PR = partial response; sCR = stringent complete response; SFLC = serum-free light chain; SPD = maximal perpendicular diameter; VGPR = very good partial response

[a] In this study, only immunohistochemistry is used for response assessment.

All response categories (complete response [CR], stringent complete response [sCR], very good partial response [VGPR], partial response [PR]) require 2 consecutive assessments before the initiation of any new therapy, as well as no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow, plasmacytoma, and skeletal survey assessments are not required to be confirmed by repeat testing.

Subjects will continue in the last confirmed response category until there is confirmation of progression or improvement to a higher response status; subjects cannot move to a lower response category.

For sCR: presence/absence of clonal cells is based upon the kappa/lambda (κ/λ) ratio. An abnormal kappa lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis.

Response criteria for all categories and subcategories of response, except CR, sCR, and PD are applicable only to patients that have measurable disease, defined by at least 1 of:

- Immunoglobulin (Ig) G multiple myeloma: serum monoclonal paraprotein (M-protein) level ≥ 1.0 g/dL,
- IgA, IgD, IgE multiple myeloma: serum M-protein level ≥ 0.5 g/dL,
- urine M-protein ≥ 200 mg/24 hours,
- in subjects without measurable serum or urine M-protein, serum-free light chain (SFLC) ≥ 100 mg/L (involved light chain) and an abnormal serum kappa lambda ratio

Determination of PD while on study requires 2 consecutive assessments (to confirm response or PD, 2 discrete samples are required; samples may be drawn on the same day) before classification of PD and/or the institution of new therapy. Confirmative samples for PD after new therapy can be used. Serum M-component increases of ≥ 1 g/dL from nadir are sufficient to define progression if nadir M-component is ≥ 5 g/dL.

Plasmacytomas: A plasmacytoma is considered measurable if the longest diameter is at least 1 cm and the product of the cross diameters is at least 1 cm^2. Progression is defined as appearance of a new lesion(s), ≥ 50% increase from nadir of the sum of the products of the maximal perpendicular diameter (SPD) of the measurable lesion as measured serially, or a ≥ 50% increase in the longest diameter of a previous lesion > 1 cm short axis; ≥ 50% increase in plasma cells if this is the only measure of disease.

For defining nadir, in the case where a value is felt to be a spurious result per physician/Independent Review Committee (IRC) discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

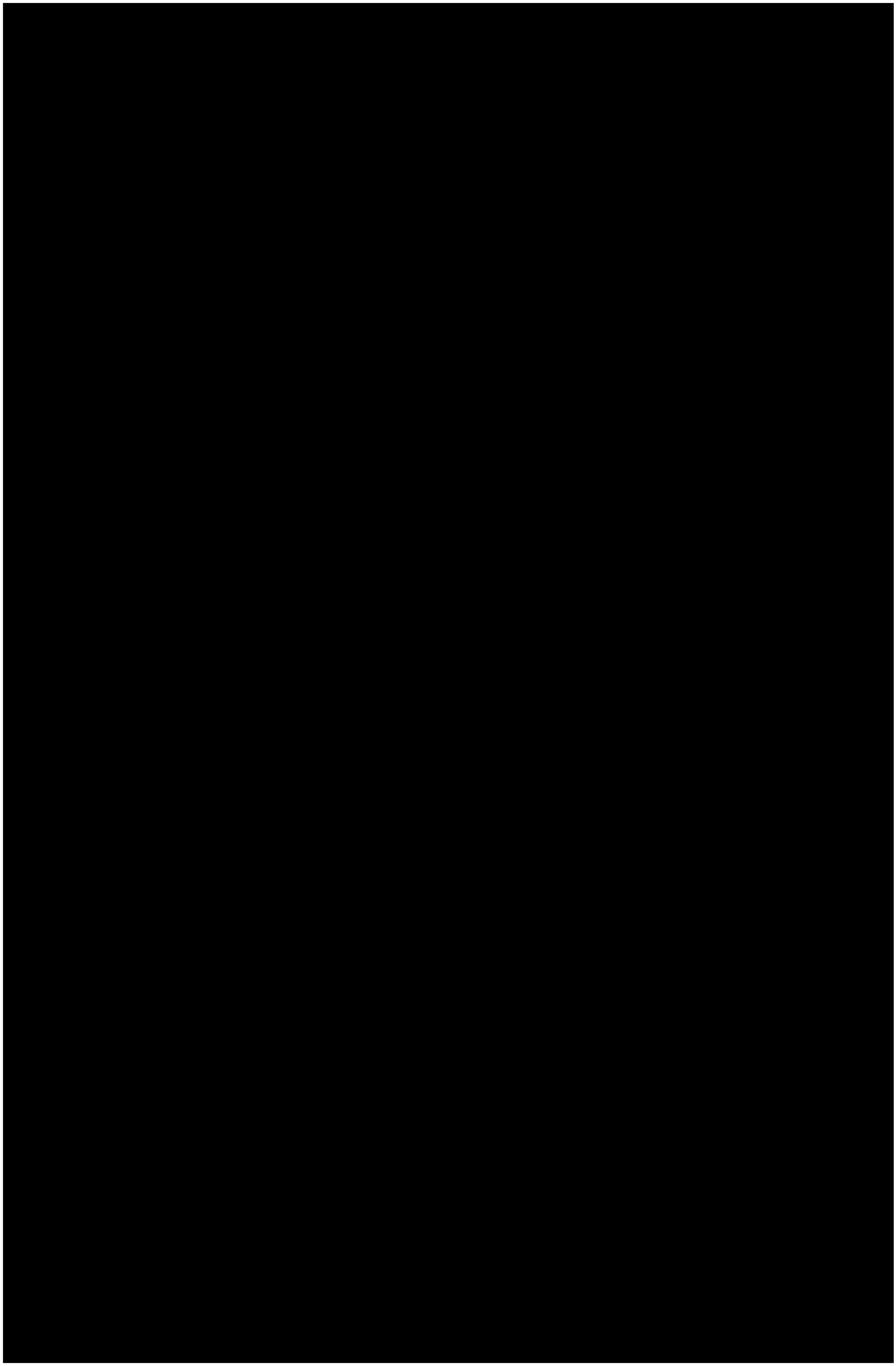
Sources: Kumar et al, 2016; Rajkumar et al, 2011; Durie et al, 2006.

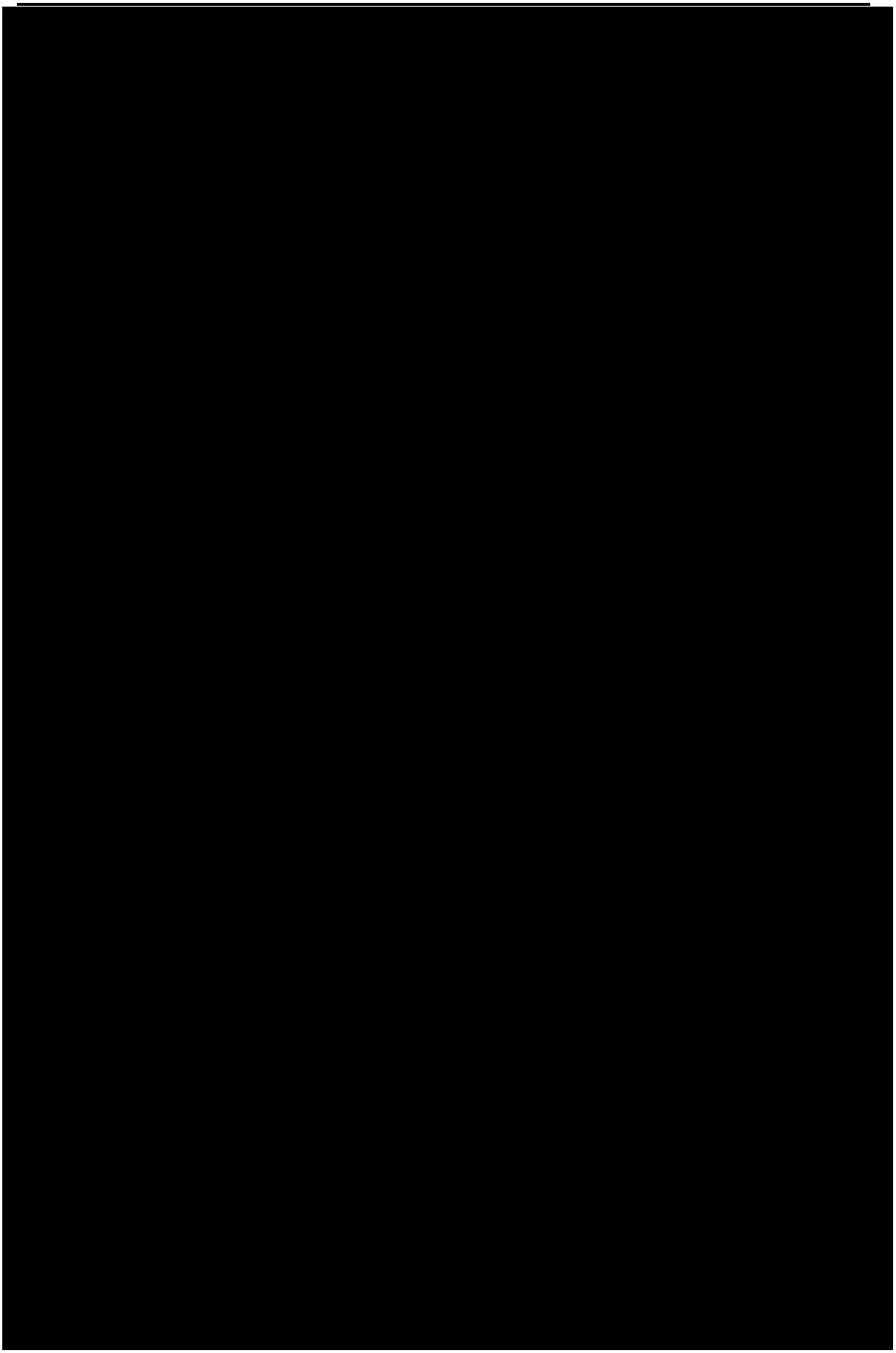
12.12 Appendix 12. Patient-reported Convenience With Carfilzomib-dosing Schedule Question

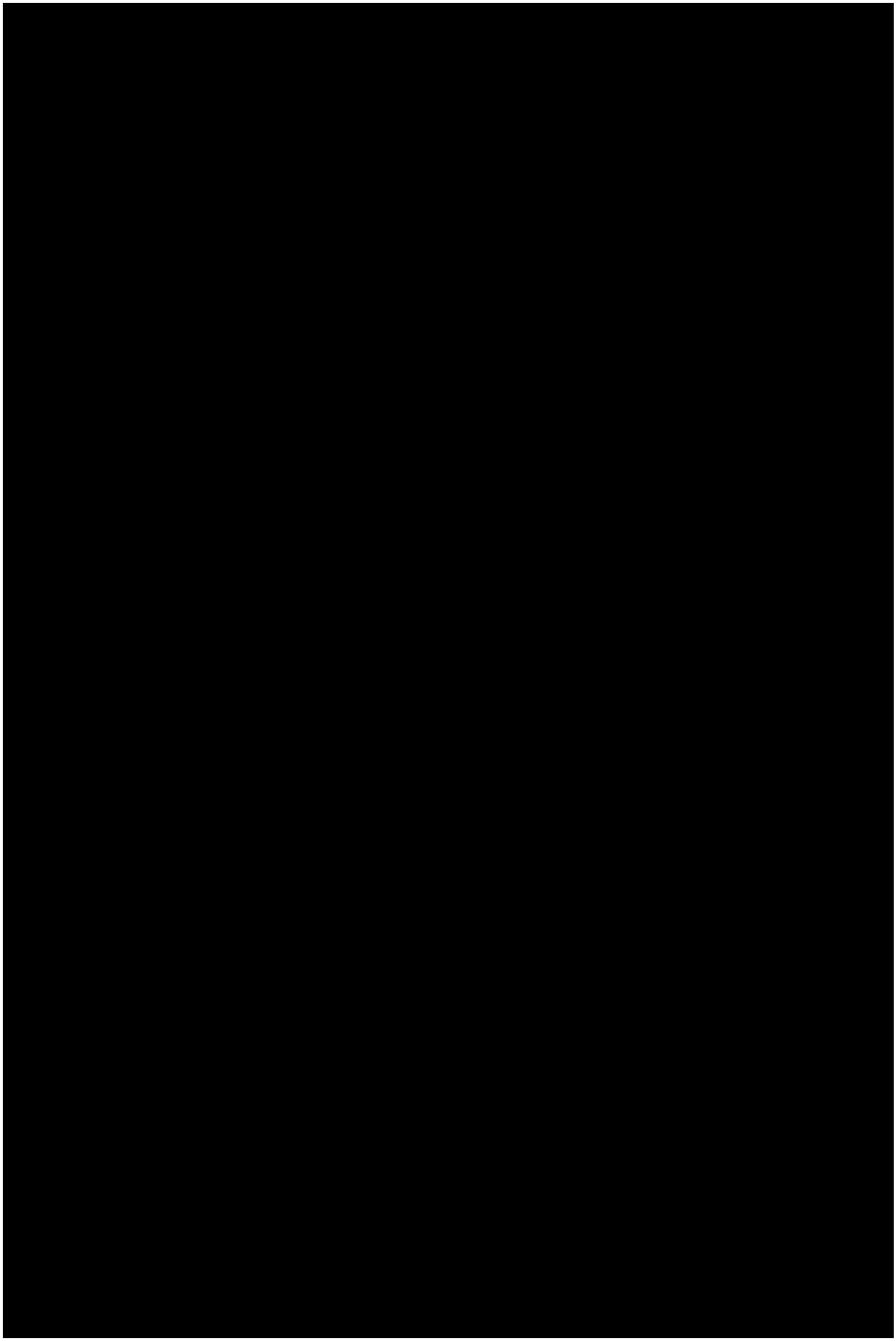
Instructions: We want to ask you a question about the convenience of the carfilzomib-dosing schedule you are receiving in this clinical study. Please provide 1 response.

I find the carfilzomib-dosing schedule

☐$_1$ Very Inconvenient ☐$_2$ Inconvenient ☐$_3$ Convenient ☐$_4$ Very Convenient







Superseding Amendment 3

Protocol Title: A Randomized, Open-label, Phase 3 Study Comparing Once-weekly vs Twice-weekly Carfilzomib in Combination With Lenalidomide and Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma (A.R.R.O.W.2)

Amgen Protocol Number Carfilzomib 20180015

EudraCT Number: 2018-000665-36

NCT Number: 03859427

Amendment Date: 02 September 2021

Rationale:

The protocol amendment dated 02 September 2021 is being amended to:

- revise exclusion criterion 214 from 'exceeds' to 'greater than or equal to' in order to retain consistency with Protocol Amendment 2 on the exact cutoff blood pressure for exclusion.
- correct an error in Section 9.2.2.2 to clarify that the percent myeloma cell involvement must be reported before randomization for subjects with a screening platelet count $< 50 \times 10^9$/L.
- update the protocol on typographical, formatting, and editorial changes.

Amendment 3

Protocol Title: A Randomized, Open-label, Phase 3 Study Comparing Once-weekly vs Twice-weekly Carfilzomib in Combination With Lenalidomide and Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma (A.R.R.O.W.2)

Amgen Protocol Number Carfilzomib 20180015

EudraCT Number: 2018-000665-36

NCT Number: 03859427

Amendment Date: 12 August 2021

Rationale:

The protocol amendment dated 12 August 2021 is being amended to:

- to remove the word “rate” from overall response rate of the primary endpoint
- update the Schedule of Activities to align with language updates
- clarify study duration for subjects (Section 5.3.2)
- clarify inclusion criterion 103
- replace inclusion criteria 106 and 107 with 110 and 111, respectively
- clarify exclusion criterion 214 and replace exclusion criterion 234 with 244
- clarify administration of Dexamethasone (Section 7.1.2.1)
- update the section 7.1.2.2.2. Dosage, Administration, and Schedule to clarify the dosage of Lenalidomide that investigator should refer to the regional product label for dose adjustments in patients with renal impairment
- update other protocol-required therapies include thromboprophylaxis (Section 7.1.4.3) and bisphosphonate or monoclonal antibody therapy (Section 7.1.4.6)
- clarify that the study treatment with lenalidomide and dexamethasone will be discontinued upon confirmation of disease progression (Section 7.4.1.2 and 7.4.1.3)
- update Section 9.1.4 to clarify long-term follow-up will commence 28-days after the safety follow-up visit
- update SPEP, UPEP, SFLC, SIFE, and UIFE (Section 9.2.2.1)
- update bone marrow sample assessment at baseline (remove permission to use archival material) (Section 9.2.2.2)
- update Bone Lesion Assessment (Section 9.2.2.3)

- update language in the SAE safety reporting sections to align with the alternative protocol language provided in the Memorandum sent out on 16Jul2021
- update Pulmonary Function Tests (Section 9.2.3.4.2) to clarify that the Baseline and surveillance pulmonary function tests are optional; may be performed if clinically indicated at the discretion of the investigator.
- update Planned Analysis (Section 10.3.1) and Methods of Analysis (Section 10.3.2)
- update Appendix 4 to align to eSAE Timed Transmission process
- update Appendix 11 to align with IMWG guidance
- aligned the protocol with current Amgen protocol template and safety reporting language
- typographical, formatting, and editorial changes were done throughout the protocol

Amendment 2

Protocol Title: A Randomized, Open-label, Phase 3 Study Comparing Once-weekly vs Twice-weekly Carfilzomib in Combination With Lenalidomide and Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma (A.R.R.O.W.2)

Amgen Protocol Number (Carfilzomib) 20180015

EudraCT number 2018-000665-36

Amendment Date: 24 August 2020

Rationale:

- To amend the secondary objective to collect progression free survival and overall survival over the duration of the study
- Overall study design language amended to assess subjects with multiple myeloma disease response until first subsequent antimyeloma treatment
- Updated language for randomization with regard to the staging system to be used
- Updated language for data monitoring committee to meet approximately every 6 months to review safety and efficacy data for futility planned to occur when the first 230 subjects are randomized
- Added information of dose infusion using an infusion pumps
- Study procedures section amended to remove conduct of interviews with subjects to validate questionnaires for multiple myeloma module
- Deleted early success for efficacy from interim analysis

Amendment 1

Protocol Title: A Randomized, Open-label, Phase 3 Study Comparing Once-weekly vs Twice-weekly Carfilzomib in Combination with Lenalidomide and Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma (A.R.R.O.W.2)

Amgen Protocol Number (carfilzomib) 20180015

Amendment Date: 10 October 2019

Rationale:

This protocol is amended to:

- Hepatitis B testing (hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody) has been added at screening for all subjects who have not had testing within 6 months of screening. In addition, guidance has been provided regarding hepatitis B virus (HBV) DNA testing and monitoring for subjects with positive hepatitis B serology or a prior history of HBV.
- Overall survival at 1 year has been added as a secondary endpoint to satisfy requests to collect information on overall survival.
- A long-term follow-up (LTFU) period with a duration of 12 months after randomization was added to separate this period from the safety follow-up period after cessation of treatment. The LTFU period outlines the collection of overall survival data for all subjects up to 12 months from randomization. In addition, clarifications were made regarding the collection of disease response assessments and subsequent antimyeloma therapy every 28 $\pm$ 7 days until end of study for subjects who discontinued study treatment and do not have confirmed progressive disease. End of study for each subject was clarified to account for the long-term follow-up period.
- Dexamethasone is to be administered 40 mg weekly. Clarifications were made to the treatment descriptions and the study schema to specify the weekly dose regimen for dexamethasone.
- For disease response assessments, a bone marrow sample is to be collected and for confirmation of stringent complete response (sCR) a bone biopsy or aspirate clot is required for immunohistochemistry. Clarifications were made to the notes of the Schedule of Activities to specify the type of bone marrow sample required for specific assessments. Additionally, clarifications on sample requirements, timing of assessments, and response categories/subcategories were made to descriptions of the efficacy assessments and the IMWG summary in the protocol appendix.
- Dose modification guidelines for non-hematological toxicities were revised for renal dysfunction to align with the product labeling. The guidelines for congestive heart failure were clarified for events < grade 3 and $\geq$ grade 3. Guidelines were added for hepatitis B reactivation.

- The planned interim analysis will be for futility and early success for efficacy. Additionally, clarifications were made on the disposition of the database for the respective planned analyses.
- [redacted]
- The analyte listing was formatted to better clarify which assessments should be performed by central laboratory and those which could be handled by a local laboratory. New analytes were listed and clarifications were made to which analytes were required at screening only.
- Recording the severity of an adverse event was clarified for when the severity changes from the date of onset to the date of resolution.
- Inclusion criteria for prior therapy was clarified with the addition of bullets. No changes were made to the requirements.
- Administration, typographical and formatting changes were made throughout the protocol. Updates have been implemented to align with the current template.