Title Page

Protocol Title:		An Open-label Phase 2 Study of Carfilzomib Combinations (Carfilzomib Plus Dexamethasone, Carfilzomib Plus Lenalidomide and Dexamethasone, and Carfilzomib Plus Pomalidomide and Dexamethasone), To Assess Tolerability and Adherence in Subjects With Relapsed or Refractory Multiple Myeloma at US Community Oncology Centers
Short Protocol Title:		A Study of Carfilzomib Combinations in Subjects With Relapsed or Refractory Multiple Myeloma at US Community Oncology Centers
Protocol Number:		20170596
Investigational Product:		Carfilzomib
Trade Name:		Kyprolis®
Sponsor	**Name of Sponsor:**	Amgen, Inc.
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NCT Number:		NCT03512353
Protocol Date:		**Document Version** / **Date** Original / 04 January 2018 Superseding original / 26 January 2018 Protocol Amendment 1 / 06 March 2018 Protocol Amendment 2 / 05 October 2018 Protocol Amendment 3 / 29 March 2019 **Protocol Amendment 4 / 20 May 2019**
Version/Date:		**Data Element Standards Version** 5.0

Confidentiality Notice

Investigator's Agreement:

I have read the attached protocol entitled An Open-label Phase 2 Study of Carfilzomib Combinations (Carfilzomib Plus Dexamethasone, Carfilzomib Plus Lenalidomide and Dexamethasone, and Carfilzomib Plus Pomalidomide and Dexamethasone), To Assess Tolerability and Adherence in Subjects With Relapsed or Refractory Multiple Myeloma at US Community Oncology Centers, dated **20 May 2019**, 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 subinvestigators (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: An Open-label Phase 2 Study of Carfilzomib Combinations (Carfilzomib Plus Dexamethasone, Carfilzomib Plus Lenalidomide and Dexamethasone, and Carfilzomib Plus Pomalidomide and Dexamethasone), To Assess Tolerability and Adherence in Subjects With Relapsed or Refractory Multiple Myeloma at US Community Oncology Centers

Short Protocol Title: A Study of Carfilzomib Combinations in Subjects With Relapsed or Refractory Multiple Myeloma at US Community Oncology Centers

Study Phase: 2

Indication: relapsed or refractory multiple myeloma (RRMM)

Rationale

The ENDEAVOR study demonstrated the superiority of the combination of carfilzomib (Kyprolis®) with dexamethasone (Kd; 56 mg/m^2 twice weekly) over bortezomib with dexamethasone (Vd; 1.3 mg/m^2 twice weekly). Superiority of the Kd regimen was demonstrated in terms of both progression-free survival (PFS) (18.7 months vs 9.4 months, hazard ratio [HR] = 0.53) and overall survival (OS) (median 47.6 months vs 40.0 months, HR = 0.791, one-sided p = 0.010) (Dimopoulos et al, 2016; Dimopoulos et al, 2017). Despite the favorable benefit-risk profile of the Kd regimen, as demonstrated in the ENDEAVOR study, logistical challenges of the twice-weekly dosing have been reported within the United States (US) community practice setting. With the results from the A.R.R.O.W. study, the Kd 70mg/m^2 once weekly dosing schedule was approved in the US, providing the US practicing centers one more option to treat MM patients with relapse/refractory disease.

Triplet therapy combining a proteasome inhibitor (PI) with an immunomodulatory agent (IMiD) and steroid remains an important and commonly used option for many patients with RRMM. Patients refractory to PIs and IMiDs have extremely poor prognosis with median OS of approximately 13 months and PFS about 5 months (Kumar et al, 2017). Current treatment practices lead to a high prevalence of dual, lenalidomide-bortezomib refractory relapses in later lines of therapy.

The ASPIRE study demonstrated the superiority of the combination of carfilzomib with lenalidomide and dexamethasone (KRd; 27 mg/m^2 twice-weekly) over lenalidomide with dexamethasone. Superiority of the KRd regimen was demonstrated in terms of median PFS (26.3 vs 17.6 months, HR = 0.69), overall response rate (87.1% vs 66.7%,

odds ratio = 3.47) (Stewart et al, 2015), health-related quality-of-life (Stewart et al, 2016), as well as 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.

Pomalidomide and dexamethasone (Pd) has been approved for subjects with RRMM and has proven efficacy in subjects who were refractory to both bortezomib and lenalidomide. Several phase 2 studies have demonstrated improved efficacy and safety of adding carfilzomib to Pd (KPd) in advanced RRMM compared to historical outcomes with Pd. The key benefits of carfilzomib, pomalidomide, dexamethasone as a triplet-therapy for patients with relapsed and refractory multiple myeloma include increases in PFS, OS, and ORR (San Miguel et al, 2013).

The purpose of this study is to:

- Describe the safety profile of 3 different weekly carfilzomib based regimens:
  - carfilzomib plus dexamethasone regimen (Kd 56 mg/m^2 twice weekly in cycles 1-2 followed by Kd 70 mg/m^2 once weekly in cycles 3–12);
  - carfilzomib plus lenalidomide and dexamethasone regimen (KRd 27 mg/m^2 twice weekly in cycles 1-2 followed by KRd 56 mg/m^2 once weekly in cycles 3-12);
  - carfilzomib plus pomalidomide and dexamethasone regimen (KPd 27 mg/m^2 twice weekly in cycles 1-2 followed by KPd 56 mg/m^2 once weekly in cycles 3-12) in subjects with RRMM with 1–3 prior lines of therapy at study entry.
- Describe subjects' adherence these carfilzomib based regimens.

Objectives/Endpoints

Objectives	Endpoints
Primary	
Describe adherence and treatment safety across all 12 cycles of carfilzomib based regimens in subjects with relapsed or refractory multiple myeloma with 1-3 prior lines of therapy at study entry.	• proportion of subjects completing 12 cycles of treatment • proportion of actual cumulative dose received to the full intended cumulative dose in cycles 1-12 • relative dose intensity in cycles 1-12 • dose modifications and reasons in cycles 1-12 • treatment-emergent adverse events and serious adverse events
Secondary	
Assess subject health-related quality-of--life (HRQoL) with the Kd, KRd, and KPd regimens.	• European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire (EORTC QLQ) Core 30 (C30) and EORTC QLQ Multiple Myeloma Module (MY20) scores through cycle 12 or up to disease progression
Assess response to the Kd, KRd, and KPd regimens.	• response rate (stringent complete response [sCR], complete response [CR], very good partial response [VGPR], partial response [PR], minimal response [MR], stable disease [SD], progressive disease [PD], Not evaluable [NE]). • progression-free survival (PFS) at 1 year • response rate and PFS by line of prior therapy 1 vs $\geq$ 2

Hypotheses

Carfilzomib combinations (Kd, KRd, and KPd) have acceptable tolerability and adherence in subjects with RRMM in a community-based setting.

Overall Design

This is a phase 2, multicenter, open-label study in subjects with RRMM in US community oncology centers. Subjects with 1-3 prior lines of therapy at study entry are eligible to be screened for participation. Subjects refractory to their last line of treatment are eligible to participate as long as their last line of treatment did not include a proteasome inhibitor (PI). The study will consist of a screening period of up to 28 days for bone marrow aspirate, bone lesion assessment, and plasmacytoma assessment and up to 21 days for all other assessments, up to 12 cycles of treatment, and a 30-day safety follow-up period following the last dose of study drug.

During the treatment period, subjects in the Kd arm will be treated with Kd 20/56 mg/m^2 twice weekly for two 28-day cycles followed Kd 70 mg/m^2 once weekly for an additional ten 28-day cycles; subjects in the KRd arm will be treated with KRd 20/27 mg/m^2 twice weekly for two 28-day cycles followed by KRd 56 mg/m^2 once weekly for an additional ten 28-day cycles; and subjects in the KPd arm will be treated with KPd 20/27 mg/m^2 twice weekly for two 28-day cycles followed by KPd 56 mg/m^2 once weekly for an additional ten 28-day cycles.

After discontinuation of study drugs, subjects in all treatment arms will be followed for 30 days for safety.

Number of Subjects

A total of approximately 75 subjects will be enrolled in the study, with approximately 25 subjects in each arm.

Summary of Subject Eligibility Criteria

This study will enroll adults ≥ 18 years of age with RRMM. Subjects must have measurable disease, Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1, and at least 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 (MM).

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

Treatments

For all arms

Dexamethasone will be taken orally or by IV infusion at a dose of 20 mg once-daily on days 1, 2, 8, 9, 15, 16, 22, and 23 of cycles 1-2, and at a dose 40 mg once-daily on days 1, 8, 15 of cycles 3-12. All doses should be administered on the scheduled days ± 2 days but prior to carfilzomib infusion except for days 22 and 23 of cycles 1-2.

Dexamethasone will be administered at least 30 minutes (but no more than 4 hours) prior to carfilzomib. Subjects receiving dexamethasone IV on days 1, 2, 8, 9, 15, and 16, may receive the day 22 and day 23 dose orally.

Kd arm

Carfilzomib will be administered in the clinic by a qualified healthcare provider as an intravenous (IV) infusion.

Carfilzomib will be administered at 20 mg/m^2 on days 1 and 2 of the first cycle (see Table 7-1). After that, carfilzomib will be administered at 56 mg/m^2 on days 8, 9,

15, and 16 of the first cycle, and then on days 1, 2, 8, 9, 15, and 16 for cycle 2. Starting with cycle 3 through cycle 12, carfilzomib will be administered at 70 mg/m^2 on days 1, 8, and 15 of each 28-day cycle. All 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.

KRd arm

Carfilzomib will be administered in the clinic by a qualified healthcare provider as an IV infusion.

Carfilzomib will be administered at 20 mg/m^2 on days 1 and 2 of the first cycle (see Table 7-1). After that, carfilzomib will be administered at 27 mg/m^2 on days 8, 9, 15, and 16 of the first cycle, and then on days 1, 2, 8, 9, 15, and 16 for cycle 2. Starting with cycle 3 through cycle 12, carfilzomib will be administered at 56 mg/m^2 on days 1, 8, and 15 of each 28-day cycle. All 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.

Lenalidomide will be taken QD orally at a dose of 25 mg on days 1 to 21 of each cycle (cycles 1-12).

KPd arm

Carfilzomib will be administered in the clinic by a qualified healthcare provider as an IV infusion.

Carfilzomib will be administered at 20 mg/m^2 on days 1 and 2 of the first cycle (see Table 7-1). After that, carfilzomib will be administered at 27 mg/m^2 on days 8, 9, 15, and 16 of the first cycle, and then on days 1, 2, 8, 9, 15, and 16 for cycle 2. Starting with cycle 3 through cycle 12, carfilzomib will be administered at 56 mg/m^2 on days 1, 8, and 15 of each 28-day cycle. All 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.

Pomalidomide will be taken QD orally at a dose of 4 mg on days 1 to 21 of each cycle (cycles 1-12).

Procedures

Written informed consent must be obtained from all subjects before any study-specific screening procedures are performed.

Screening procedures will include:

- Collection of medical history; physical examination and measurements, electrocardiogram (ECG), vital signs, ECOG PS, echocardiogram, and pregnancy test for females of childbearing potential (FCBP).
- Multiple myeloma disease assessments to confirm measurable disease: serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), serum free light chain (SFLC), serum immunofixation (SIFE), urine immunofixation (UIFE), plasmacytoma evaluation, bone lesion assessment, and bone marrow aspirate with fluorescence in-situ hybridization (FISH).

At specified visits, outlined in the Schedule of Activities (Table 2-1), the following measurements will be collected: weight, vital signs, recording of concomitant medications, as well as review of adverse events and serious adverse events. Blood will be collected for local laboratory testing, including hematology and chemistry. Additionally, in FCBP a urine or serum pregnancy test will be performed locally.

Investigators are required to follow International Myeloma Working Group (IMWG) criteria for assessment of response and disease progression (see Section 12.8). Disease assessments based on local laboratory data will be performed per the Schedule of Activities (Table 2-1) and include: SPEP, UPEP, SFLC, SIFE, UIFE.

Clinical outcome assessments (COAs) will be measured using 3 questionnaires: HRQoL and [redacted]

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

With a sample size of 25 subjects in each treatment arm, assuming 50%, 75%, or 90% of subjects complete 12 cycles of treatment, the expected half-widths of the 95% confidence interval (CI) for estimating the proportion of subjects completing 12 cycles of treatment are provided below.

Sample Size	95% Confidence Interval Half-width (%)		
	50%	75%	90%
25	20.5	18.1	13.5

The full analysis set will be the same as the safety analysis set, which will include all enrolled subjects who received at least 1 dose of any study treatment (ie, carfilzomib, lenalidomide, pomalidomide, or dexamethasone). Unless otherwise specified, following analyses will be based on the safety analysis set.

For primary endpoints, the proportion of subjects completing 12 cycles of carfilzomib based regimens will be calculated. The proportion of actual cumulative dose received to the full intended cumulative dose in cycles 1-12 will be summarized descriptively. The full intended cumulative dose is defined as all therapy specified per Sections 7.1.1.2 and 7.1.2 without consideration for dose modification or skipped doses. Relative dose intensity in cycles 1-12 will be summarized descriptively. Dose modifications including dose reduction, dose withheld, and dose delay in cycles 1-12 will be summarized along with reasons including adverse events and non-adverse events. Treatment-emergent adverse events and serious adverse events in cycles 1-12 will be summarized descriptively following the methods specified in Section 10.3.2.3. The proportions of treatment discontinuations due to all adverse events, reasons for treatment discontinuation due to all adverse events, and dose reductions due to all adverse events will be summarized descriptively.

All EORTC QLQ-C30 and EORTC QLQ-MY20 subscale scores up to cycle 12 or disease progression will be summarized descriptively by cycle based on the safety analysis set. The rate of PFS at 1 year will be estimated using the Kaplan-Meier method and with CI estimated using the method by Kalbfleisch and Prentice, 1980 with log-log transformation. The response rate and 1-year PFS rate will be summarized descriptively by line of prior therapy 1 vs $\geq$ 2.

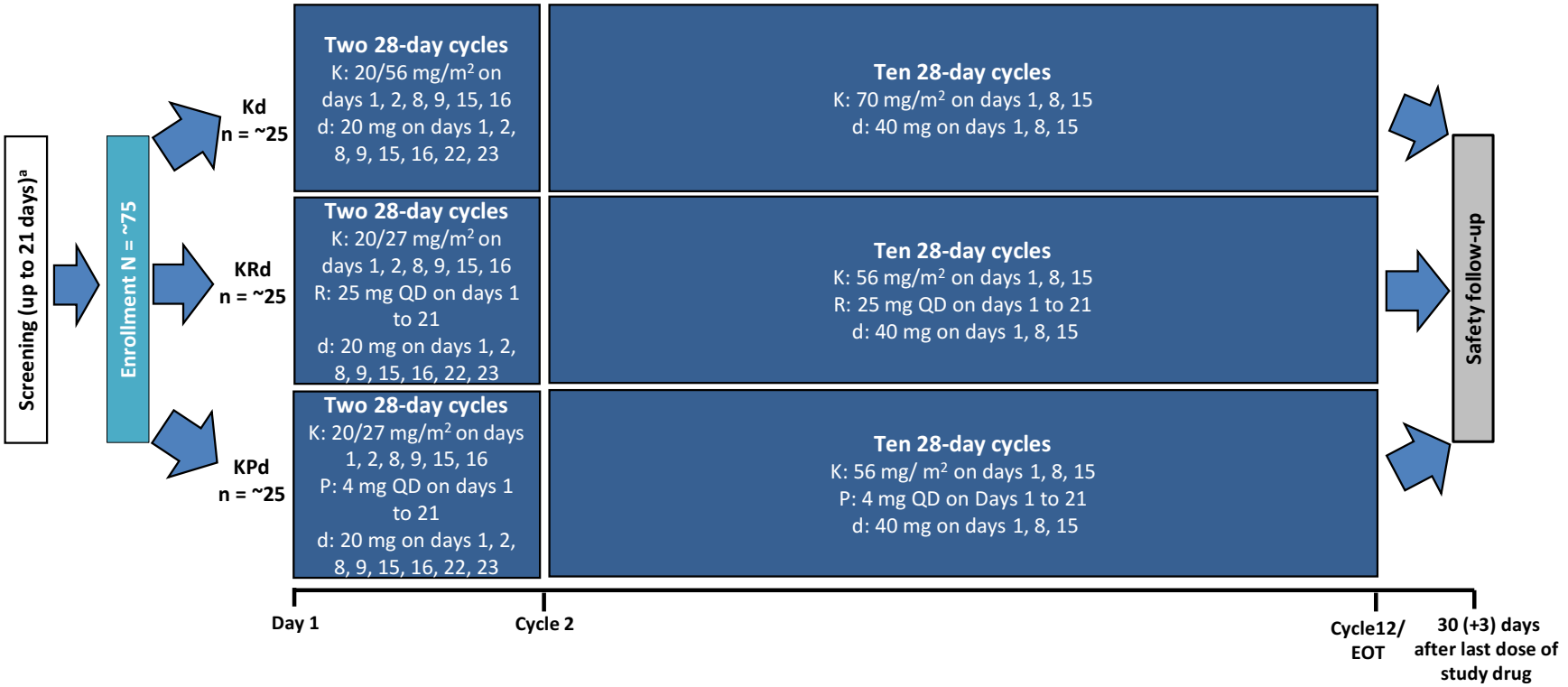
For a full description of statistical analysis methods, please refer to Section 10.

Sponsor Name: Amgen Inc.

2. Study Schema and Schedule of Activities

2.1 Study Schema

Figure 2-1. Study Schema



EOT = end of treatment; d = dexamethasone; K = Kyprolis (carfilzomib); P = pomalidomide; QD = once daily; R = lenalidomide

[a] All screening assessments except bone marrow aspirate, bone lesion assessment, and plasmacytoma assessment must be completed within 21 days before cycle 1 day 1. Bone marrow aspirate, bone lesion assessment, and plasmacytoma assessment must be completed within 28 days of cycle 1 day 1.

2.2 Schedule of Activities

Table 2-1. Schedule of Activities

PROCEDURE		Screening[a b] (up to 21 days before Day 1)	Treatment Period: Cycle 1-2 Day 1	2	8	9	15	16	22	23	Cycle 3-12 1	8	15	21	Safety FU[c] (30 [+3] days post last dose)	Notes
GENERAL AND SAFETY ASSESSMENTS																
Informed consent		X														
Inclusion and exclusion criteria		X														
Demographics		X														
Physical examination		X													X	
Physical measurements	Height, BMI	X														BSA should be calculated per Mosteller formula and utilized to calculate required study drug doses. BSA should be recalculated if weight changes by 20% or more (gain or loss)
	Weight	X	X								X					
	BSA	X	(X)													
Medical history		X														
Cardiac history		X														See Section 9.2.1.3
Substance use		X														
ECG		X														
Vital signs		X	X	X	X	X	X	X			X	X	X		X	Checked prior to administration of study drug(s) in all cycles.
ECOG performance status		X													X	
Echocardiogram		X														At screening and as clinically indicated (per Section 12.9)
Adverse events/serious adverse events		Continuous														Adverse events are to be captured during screening, starting with the signing of the informed consent. Recommended dyspnea evaluation per investigator's judgment per Section 12.9

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Table 2-1. Schedule of Activities

PROCEDURE			Screening[a] [b] (up to 21 days before Day 1)	Treatment Period: Cycle 1-2 Day 1	2	8	9	15	16	22	23	Cycle 3-12 1	8	15	21	Safety FU[c] (30 [+3] days post last dose)	Notes
Concomitant therapies review			Continuous														
LABORATORY ASSESSMENTS																	
Pregnancy test (FCBP only)[d]	Kd Arm	Urine or serum	X	X								X				X	
	KPd and KRd Arms	Serum	X													X	
		Urine or serum cycle 1 (predose)		X		X		X		X							Within 24 hours prior to dose of lenalidomide or pomalidomide for subjects in the KRd or KPd arms, respectively
		Urine or serum cycle 2 to 12 (predose; regular menses)		X								X					
		Urine or serum cycle 2 to 12 (predose; irregular menses)		X				X				X		X			
Hematology			X	X								X				X	Hematology and chemistry samples from screening may be used for C1D1 if taken within 3 days prior to C1D1. Lab results must be evaluated for potential dose modification assessment prior to dosing (see Section 7.4). Chemistry and hematology assessments, other than for C1D1, may be taken within 2 days prior to the scheduled assessment.
Chemistry			X	X								X				X	

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Table 2-1. Schedule of Activities

PROCEDURE	Screening[a] [b] (up to 21 days before Day 1)	Treatment Period												Safety FU[c] (30 [+3] days post last dose)	Notes
		Cycle 1-2								Cycle 3-12					
		Day 1	2	8	9	15	16	22	23	1	8	15	21		
Fasting lipid panel	X														Total cholesterol, HDL, LDL, triglycerides (fasting ≥ 12 hours)
NT-proBNP (or BNP)	X														At screening and as clinically indicated (see Section 12.9)
HbA1c	X														
Fasting glucose	X														Fasting ≥ 12 hours
Estimated GFR	X														Estimated GFR calculated using CKD-EPI equation (see Section 12.13)
Urinalysis	X														For calculation of albumin creatinine ratio per exclusion criteria 206, see Section 6.2
DISEASE-SPECIFIC ASSESSMENTS															
LDH	X														
Beta-2 microglobulin	X														
Corrected calcium	X														
SPEP/UPEP/SFLC/SIFE/UIFE[e]	X	X[f]								X					UPEP requires 24-hour urine collection. Evaluated by investigator based on IMWG criteria (see Section 12.8)
Myeloma Response Assessment[e]		(X)[g]												X	Disease assessment to be performed every 28 ± 7 days until confirmed PD regardless of cycle duration, including dose delays. Disease assessments at the safety follow-up visit are not required for subjects who discontinue early due to confirmed PD or if assessments were performed within 14 days prior to the safety follow-up visit.

Footnotes defined on last page of this table.

Table 2-1. Schedule of Activities

PROCEDURE	Screening[a b] (up to 21 days before Day 1)	Treatment Period												Safety FU[c] (30 [+3] days post last dose)	Notes
		Cycle 1-2								Cycle 3-12					
		Day 1	2	8	9	15	16	22	23	1	8	15	21		
Bone Lesion Assessment[b]	X														Screening and will be repeated if worsening clinical symptoms suggest PD, or as clinically indicated. (see Section 12.8 for IMWG criteria)
Plasmacytoma evaluation[b]	X														See Section 9.2.2.3. Only required at screening in subjects if clinically suspected and to confirm response (if performed at screening, see Section 12.8 for IMWG criteria)
Bone marrow aspirate with FISH[b]	X														Bone marrow aspirate is required at screening and to confirm a response of CR (see Section 12.8 for IMWG criteria). FISH is only required at screening.
CLINICAL OUTCOME ASSESSMENTS															
EORTC QLQ-C30		X								X				X	During treatment period, these questionnaires must be completed on day 1 of each cycle prior to dosing.
EORTC QLQ-MY20		X								X				X	
Amgen Satisfaction and Convenience Questionnaire		X								X				X	During treatment period, these questionnaires must be completed on day 1 of each cycle prior to dosing, starting with C2D1. Items 8-11 to be collected only once at end of treatment or at completion of the trial.

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Footnotes defined on last page of this table.

Table 2-1. Schedule of Activities

PROCEDURE	Screening[a] [b] (up to 21 days before Day 1)	Treatment Period												Safety FU[c] (30 [+3] days post last dose)	Notes
		Cycle 1-2								Cycle 3-12					
		Day 1	2	8	9	15	16	22	23	1	8	15	21		
STUDY TREATMENT															
Kd ARM															
Carfilzomib administration[h]		X	X	X	X	X	X			X	X	X			Cycle 1: 20 mg/m^2 on days 1 and 2; **56** mg/m^2 on days 8, 9, 15, and 16 Cycle 2: 56 mg/m^2 Cycles 3-12: 70 mg/m^2 For subjects with baseline hepatic function abnormalities (bilirubin or AST > ULN), see Section 7.1.1.2.1 for modification of the initial dose. For cycle 3, for subjects who were previously dose reduced, see Section 7.1.1.2 for starting dose.
Dexamethasone administration[h]		X	X	X	X	X	X	X[i]	X[i]	X	X	X			Cycles 1-2: 20 mg Cycles 3-12: 40 mg For subjects ≥ 75 years of age, see Section 7.4.1.2 for dose modification.

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Table 2-1. Schedule of Activities

PROCEDURE	Screening[a] [b] (up to 21 days before Day 1)	Treatment Period												Safety FU[c] (30 [+3] days post last dose)	Notes
		Cycle 1-2								Cycle 3-12					
		Day 1	2	8	9	15	16	22	23	1	8	15	21		
KRd ARM															
Carfilzomib administration[h]		X	X	X	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 Cycle 2: 27 mg/m^2 Cycles 3-12: 56 mg/m^2 For subjects with baseline hepatic function abnormalities (bilirubin or AST > ULN), see Section 7.1.1.2.1 for modification of the initial dose. For cycle 3, for subjects who were previously dose reduced, see Section 7.1.1.2 for starting dose.
Lenalidomide administration		Days 1 to 21 of each cycle													25 mg
Dexamethasone administration[h]		X	X	X	X	X	X	X[i]	X[i]	X	X	X			Cycles 1-2: 20 mg Cycles 3-12: 40 mg For subjects ≥ 75 years of age, see Section 7.4.1.2 for dose modification.

Footnotes defined on last page of this table.

Table 2-1. Schedule of Activities

PROCEDURE	Screening[a b] (up to 21 days before Day 1)	Treatment Period												Safety FU[c] (30 [+3] days post last dose)	Notes
		Cycle 1-2								Cycle 3-12					
		Day 1	2	8	9	15	16	22	23	1	8	15	21		
KPd ARM															
Carfilzomib administration[h]		X	X	X	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 Cycle 2: 27 mg/m^2 Cycles 3-12: 56 mg/m^2 For subjects with baseline hepatic function abnormalities (bilirubin or AST > ULN), see Section 7.1.1.2.1 for modification of the initial dose. For cycle 3, for subjects who were previously dose reduced, see Section 7.1.1.2 for starting dose.
Pomalidomide		Days 1 to 21 of each cycle													4 mg
Dexamethasone administration[h]		X	X	X	X	X	X	X[i]	X[i]	X	X	X			Cycles 1-2: 20 mg Cycles 3-12: 40 mg For subjects ≥ 75 years of age, see Section 7.4.1.2 for dose modification.

Footnotes defined on next page of this table.

AST = aspartate aminotransferase; BMI = body mass index; BNP = brain natriuretic peptide; BSA = body surface area; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CR = complete response; C = cycle; d = dexamethasone; 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; EORTC QLQ-MY20 = EORTC Quality-of-life Questionnaire Multiple Myeloma Module; FCBP = females of childbearing potential; FISH = fluorescence in-situ hybridization; FU = follow-up; HbA1c = hemoglobin A1c; GFR = Glomerular Filtration Rate; HDL = high-density lipoprotein; IMWG = International Myeloma Working Group; K = Kyprolis (carfilzomib); LDH = lactate dehydrogenase; LDL = low-density lipoprotein; NT-proBNP = N terminal of the prohormone brain natriuretic peptide; P = pomalidomide; PD = progressive disease; R = lenalidomide; SFLC = serum free light chain; SIFE = serum immunofixation; SPEP = serum protein electrophoresis; UIFE = urine immunofixation; ULN = upper limit of normal; UPEP = urine protein electrophoresis
(X) = Parentheses indicate that the particular test is situational at that time point, as specified in the respective notes.

[a] All screening assessments except bone marrow aspirate, bone lesion assessment, and plasmacytoma assessment must be completed within 21 days before cycle 1 day 1. Bone marrow aspirate, bone lesion assessment, and plasmacytoma assessment must be completed within 28 days of cycle 1 day 1.

[b] If performed as part of standard of care within 28 days of cycle 1 day 1, then do not repeat at screening unless clinically indicated.

[c] Once a subject discontinues from the study drug (see Section 8.1), he/she will have a safety follow-up visit 30 (+3) days after the last dose of study drug(s), unless the subject is lost to follow-up, has withdrawn consent, or has died. After the safety follow-up, subjects who remain on study are required to complete disease response assessments and will be followed for subsequent antimyeloma treatment every 28 ± 7 days until up to 12 months from enrollment, death, loss to follow-up, withdrawal of consent or PD, whichever occurs first.

[d] Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.

[e] Disease assessment should be performed every 28 ± 7 days until confirmed PD regardless of cycle duration, including dose delays. Cycle 1 disease assessment is conducted 28 (± 7) days post cycle 1, day 1. Subjects who discontinue treatment prior to confirmed PD should continue to complete disease assessments each cycle until up to 12 months from enrollment, death, loss to follow-up, withdrawal of consent or PD, whichever occurs first.

[f] Unless screening values are within 14 days of cycle 1 day 1, SPEP, UPEP, and SFLC will be repeated on cycle 1 day 1.

[g] Cycle 12 disease assessment is conducted 28 (± 7) days post cycle 12, day 1.

[h] All 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 (see Section 7.1.1.2 for additional details).

[i] Dexamethasone (if administered orally) may be self-administered at home by the subject on non-clinic days (days 22 and 23 of cycles 1-2). See Section 7.6 for additional details.

3. Introduction

3.1 Study Rationale

Carfilzomib (Kyprolis®) with dexamethasone (Kd) and the combination of carfilzomib with the immunomodulatory agent (IMiD) lenalidomide and dexamethasone (KRd) twice-weekly dose regimens have demonstrated favorable benefit risk profiles as in the ENDEAVOR and ASPIRE studies, respectively, and preliminary data for the KPd twice-weekly regimen also indicated the favorable benefit risk profile; however, logistical challenges of the twice weekly dosing have been reported within the United States (US) community practice setting. Therefore, there is the need to explore a more convenient dosing schedule which may lead to better adherence to the treatment, especially in the community setting.

The ENDEAVOR study demonstrated the superiority of the Kd regimen (56 mg/m^2 twice weekly) over bortezomib with dexamethasone (Vd; 1.3 mg/m^2 twice weekly). Superiority of the Kd regimen was demonstrated in terms of both progression-free survival (PFS) (18.7 months vs 9.4 months, hazard ratio [HR] = 0.53) and overall survival (OS) (median 47.6 months vs 40.0 months, HR = 0.791, one-sided p = 0.010) (Dimopoulos et al, 2016; Dimopoulos et al, 2017).

Subsequently, the A.R.R.O.W. study results demonstrated that treatment with once weekly Kd at the dose of 70 mg/m^2 (30 minute infusion) resulted in superior PFS and overall response rate (ORR), compared to the twice weekly administration of Kd 27 mg/m^2 in patients with relapsed and refractory multiple myeloma (RRMM). The safety profile was comparable in the 2 arms. Based on A.R.R.O.W. data, the Kd once weekly dose of 70 mg/m^2 was included in the US label.

Meanwhile, the treatment for RRMM is evolving towards triplet therapies, and triplets containing a proteasome inhibitor (PI) and IMiD are among the most efficacious therapies.

The ASPIRE study demonstrated the superiority of the KRd regimen (27 mg/m^2) twice-weekly) over lenalidomide with dexamethasone. Superiority of the KRd regimen was demonstrated in terms of median PFS (26.3 vs 17.6 months, HR = 0.69), ORR (87.1% vs 66.7%, odds ratio = 3.47) (Stewart et al, 2015), health-related quality-of-life (Stewart et al, 2016), as well as 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.

In addition to the twice weekly triplet dosing regimen (KRd), the once weekly KRd dosing regimen has been tested. The ongoing Study CFZ013 evaluates once-weekly KRd in patients with relapsed or relapsed and refractory multiple myeloma who have been treated with 1 to 3 prior lines of therapy. As of data cut-off 18 July 2018, efficacy results from 56 subjects treated with weekly KRd 56 mg/m^2 (n = 10) or KRd 70 mg/m^2 (n = 46) has shown similar efficacy, as determined by ORR (90.0% versus 89.1%, respectively) and similar ORR as previously reported for twice-weekly KRd (27 mg/m^2) in the ASPIRE study, 87.1% (Biran et al, 2018). These results complement the significant efficacy results of carfilzomib as a triplet therapy.

The IMiD pomalidomide and dexamethasone (Pd) has been approved for subjects with RRMM and has proven efficacy in subjects who were refractory to both bortezomib and lenalidomide. Several phase 2 studies have demonstrated improved efficacy and safety of adding carfilzomib twice weekly to Pd (KPd) in advanced RRMM compared to historical outcomes with Pd. The key benefits of carfilzomib, pomalidomide, dexamethasone as a triplet-therapy for patients with relapsed and refractory multiple myeloma include increases in PFS, OS, and ORR. The safety profile shows that the adverse events observed with the combination KPd are consistent with the product labels for carfilzomib and pomalidomide (Sonneveld et al, 2018; Shah et al, 2015).

These data from the twice weekly KPd regimen provided the rationale to explore a once weekly KPd regimen, which may deliver a comparable clinical benefit /risk profile with more convenience.

This study will assess the tolerability and adherence in RRMM subjects at US community oncology centers with 3 carfilzomib combinations: Kd, KRd and KPd. The 3 regimens will be given for 2 cycles as a twice weekly dosing schedule followed by 10 cycles of a once weekly dosing schedule. The twice weekly schedule of these 3 carfilzomib combinations is the originally approved schedule and familiar to the treating physicians. The approval of the once weekly dosing schedule for Kd is relatively new to the clinical practice. To provide a consistent dosing schedule among the different arms, in context of this variable carfilzomib dosing, each carfilzomib combination begins with a twice weekly schedule and transitions to a once weekly schedule.

The purpose of this study is to:

- Describe the safety profile of 3 different weekly carfilzomib based regimens:
  - carfilzomib plus dexamethasone regimen (Kd 56 mg/m^2 twice weekly in cycles 1-2 followed by Kd 70 mg/m^2 once weekly in cycles 3-12));
  - carfilzomib plus lenalidomide and dexamethasone regimen (KRd 27 mg/m^2 twice weekly in cycles 1-2 followed by KRd 56 mg/m^2 once weekly in cycles 3-12);
  - carfilzomib plus pomalidomide and dexamethasone regimen (KPd 27 mg/m^2 twice weekly in cycles 1-2 followed by KPd 56 mg/m^2 once weekly in cycles 3-12) in subjects with relapsed or refractory multiple myeloma (RRMM) with 1-3 prior lines of therapy at study entry.
- Describe subjects' adherence to these carfilzomib based regimens.

3.2 Background

3.2.1 Disease

Multiple myeloma (MM) is a plasma cell disorder representing 1.5% of all cancers and up to 13% of all hematological malignancies worldwide (Katzel et al, 2007). According to the American Cancer Society, approximately 30 000 new cases of MM are expected to be diagnosed in 2016 (SEER Cancer Statistic Review). Multiple myeloma is a disease of older adults, with a median age at diagnosis of 70 years (Howlader et al, 2013). Although MM is usually responsive to cytotoxic therapy, responses are often brief, highlighting the need for new therapeutic targets and more successful combination therapies. Over the 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). The 5-year survival rates have almost doubled, increasing from 27% to 47% between 1989 and 2010 (Pulte et al, 2014). Despite improvements in the management of the disease, MM still remains a serious illness and most patients eventually develop treatment resistance (Barlogie et al, 2006). In addition, response time generally decreases with subsequent number of treatment lines (Kumar et al, 2004).

Treatment of RRMM presents a special therapeutic challenge, due to the heterogeneity of disease at relapse and the absence of clear biological based treatment recommendations at various time points of disease progression. The treatment landscape is evolving rapidly with increasing recognition of the inherent clonal heterogeneity and genomic instability of the plasma cells influencing both inherent and acquired therapeutic resistance, the identification of the optimal choice and sequence of therapies has become critical. Several new agents and targets are currently under development and show considerable promise. Besides PI and IMiD, other newer treatment approaches have been approved since 2015, including monoclonal antibodies

targeting SLAMF7 (ie, elotuzumab) or CD38 (ie, daratuzumab) (O'Donnell and Raje, 2017); and more innovative agents are in clinical development.

The choice of salvage therapy for RRMM patients depends on various factors including disease biology, patient's general condition, as well as the prior treatment and the response and long-term toxicity of prior treatment. The other considerations are tolerability and adherence to salvage therapy which will impact the treatment exposure hence impact the treatment effects. Given the various considerations around treatment decision, it's critical to evaluate multiple salvage therapies to provide options meeting the different needs of RRMM patients.

3.2.2 Amgen Investigational Product Background: Carfilzomib

Carfilzomib is a tetrapeptide epoxyketone 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 ($t_{1/2}$ = 15-30 minutes); < 1% is excreted intact (Kortuem and Stewart, 2013).

Carfilzomib entered clinical studies in September 2005. On 20 July 2012, Kyprolis® was granted accelerated approval by the US Food and Drug Administration (FDA) for the treatment of patients with MM who have received at least 2 prior therapies, including bortezomib and an 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 trials: 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. With the results from the A.R.R.O.W. study, the Kd 70 mg/m^2 once weekly dosing schedule was approved in the US to treat MM. Carfilzomib for Injection has been approved in 34 countries/regions worldwide.

As of 19 July 2018, approximately 8210 subjects have been enrolled in 116 actively enrolling or completed/closed single-group or randomized carfilzomib clinical trials. It is estimated that approximately 88964 patients have been exposed to carfilzomib in the post-marketing setting.

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

3.2.3 Benefits of Once-weekly Dosing

Carfilzomib is FDA approved as a weekly administration in combination with dexamethasone (Kyprolis USPI); however, triplet therapies are emerging as SOC for RRMM. Evidence suggests that the convenience afforded by a once-weekly dosing schedule can help improve patient adherence to treatment with antimyeloma IV agents. The ongoing Study CFZ013 evaluating once-weekly KRd in patients with relapsed or relapsed and refractory multiple myeloma has shown similar efficacy as previously reported for twice-weekly KRd (27 mg/m^2) in the ASPIRE study (Biran et al, 2018). Two studies of a once-weekly versus twice-weekly schedule of bortezomib as combination therapy showed consistent findings that patients with multiple myeloma treated with a once-weekly dose regimen were more adherent, received higher doses, had fewer dose reductions, and were treated for longer durations compared with patients treated with a twice-weekly dose regimen (Bringhen et al, 2010; Reeder et al, 2010). Reducing the burden of treatment with once-weekly dosing is also expected to improve quality of life in patients with relapsed multiple myeloma, which has been shown to be dependent on the ability to maintain a social role and meaningful activities (Mortensen and Salomo, 2016).

A once-weekly dose regimen would substantially reduce the time burden on patients and caregivers over twice-weekly dosing. The total time for a patient to receive IV treatment includes transportation time to and from the clinic, wait time, pre-infusion preparation time, infusion and post-infusion time, and lost work or leisure time for family members or friends who accompany patients to the clinic. Travel time to the medical facility was < 30 minutes for most patients, with 40% of patients traveling over 1 hour, based on a study in the United Kingdom and an average of 30 to 35 minutes based on a survey in the US (Barrett-Lee et al, 2007; data on file). Thus, a once-weekly dose regimen would represent substantial time-savings for patients and their caregivers.

In summary, in the setting of RRMM, the ENDEAVOR study demonstrated that the labelled dose of twice weekly carfilzomib (56 mg/m^2) significantly improved survival.

However, real world data discussed above indicates that it is difficult to sustain this level of therapy for a prolonged period of time and that once weekly dosing may improve treatment adherence and clinical benefit. Once weekly data from the A.R.R.O.W. and CHAMPION 1 trials demonstrated the efficacy and safety of a once weekly dose of 70 mg/m^2 and cross trial comparison between ENDEAVOR and CHAMPION 1 indicate there may be no loss of efficacy with weekly dosing (Berenson et al, 2016). The A.R.R.O.W. study results demonstrated that treatment with once weekly Kyprolis and dexamethasone at the dose of 70 mg/m^2 (30 min infusion) resulted in superior PFS and ORR, compared to the twice weekly administration of Kd 27 mg/m^2 in patients with RRMM. The safety profile was comparable in the two arms. Based on A.R.R.O.W. data, the Kd once weekly dose of 70 mg/m^2 was included in the US label. Meanwhile, other once weekly dosing combination regimens including carfilzomib based triplets are being explored and this study is expected to add the data evidence generated from the multi-center community setting. The goal of the study is to demonstrate feasibility and adherence of weekly combinations of carfilzomib. The initial treatment with 2 cycles of twice weekly therapy is designed to provide the more familiar labelled treatment for subjects with RRMM.

3.3 Benefit/Risk Assessment

The following benefit risk assessment supports the conduct of this clinical trial. Reference should be made to the Carfilzomib Investigator's Brochure for further data on carfilzomib.

3.3.1 Therapeutic Context

Multiple myeloma is a clonal neoplastic proliferation of plasma cells, the second most common hematologic malignancy, and is responsible for approximately 80 000 annual deaths worldwide (1% of cancer deaths). The 5-year prevalence of MM worldwide was estimated at 229 000 persons. Multiple myeloma is a disease of older adults, with a median age at diagnosis of 70 years (Howlader et al, 2013). While treatment for MM will typically induce remission, the disease eventually relapses in most patients. As patients go through cycles of relapse and remission, the duration of remission becomes shorter with each successive line of therapy, and eventually becomes nonresponsive to therapy (Richardson et al, 2007; Kumar et al, 2004).

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 health-related quality of life, and to provide relief of pain and other disease-related symptoms.

3.3.2 Key Benefits

Therapy for RRMM has evolved rapidly in the last several years. Doublet therapy combining a PI and steroid remains an important and commonly used option for many patients. The ENDEAVOR trial was a phase 3 head-to-head comparison of Vd and Kd in RRMM. Patients treated with Kd in the ENDEAVOR study had improved PFS compared with those treated with Vd: median PFS 18.7 vs 9.4 months (HR = 0.53; 95% CI 0.44-0.65; $p < 0.0001$) (Dimopoulos et al, 2016) and improved OS in subjects followed for a minimum of 3 years, median OS 47.6 vs 40 months (HR = 0.79, 95% CI, 0.648-0.964; one-sided $p = 0.01$) (Dimopoulos et al, 2017). All patient subgroups demonstrated clinical benefit from Kd compared with Vd (Moreau et al, 2015; Chng et al, 2017). The ENDEAVOR study led to expanded approval of carfilzomib in patients who had received 1 to 3 lines of prior therapy. Based on these findings, Kd is the only doublet regimen on the NCCN recommended preferred list for RRMM (NCCN Multiple Myeloma, 2018).

The CHAMPION -1 study was conducted to determine the maximum tolerated dose (MTD) of carfilzomib administered once weekly in combination with dexamethasone to subjects with RRMM. The MTD was determined to be 70 mg/m^2. The efficacy and safety of 70 mg/m^2 once-weekly dosing regimen was evaluated in 104 subjects. Among this cohort, 52% of subjects were refractory to bortezomib. For the overall population, the overall response rate (ORR) at 70 mg/m^2 was 77% (71% in patients refractory to bortezomib) with 13% achieving complete response (CR). The median PFS was 12.6 months (Berenson et al, 2016). The median PFS for the ENDEAVOR (56 mg/m^2 twice weekly) and CHAMPION-1 (70 mg/m^2 once weekly) trials were 18.7 and 12.6 months, respectively. However, bortezomib-refractory subjects were not eligible in the ENDEAVOR trial. Among the 50 subjects who were not refractory to bortezomib in the CHAMPION-1 trial, the Kaplan-Meier median PFS were 21.0 months (no prior bortezomib exposure) and 19.4 months (prior bortezomib exposure but not refractory), which compared favorably to the results in the ENDEAVOR study (Amgen data on file).

The MTD defined in the CHAMPION-1 trial was used in the phase 3 A.R.R.O.W. trial, in which subjects with RRMM were treated with Kd with carfilzomib dosed either at

27 mg/m^2 twice-weekly or 70 mg/m^2 once-weekly. The study included 478 subjects with RRMM who received 2 or 3 prior lines of therapy, including a PI and an IMiD. Subjects treated with the once-weekly Kd regimen achieved a statistically significant superior PFS with a median of 11.2 months compared with 7.6 months for those treated with the twice-weekly Kd regimen (HR = 0.69, 95% CI, 0.54-0.88) (A.R.R.O.W. Press release, 2017). The safety profile was comparable in the two arms. Based on A.R.R.O.W. data, the Kd once weekly dose of 70 mg/m^2 was included in the US label. These results provide additional evidence supporting the efficacy and tolerability of the once-weekly Kd regimen.

Other once weekly dosing combination regimens of carfilzomib are being explored.

Triplet therapies are emerging as the SOC for RRMM. The combination of a proteasome inhibitor (PI) with an immunomodulatory agent (IMiD) and steroid is a commonly used and guideline recommended option for patients with RRMM. Patients refractory to PIs and IMiDs have extremely poor prognosis with median OS of approximately 13 months and PFS about 5 months (Kumar et al, 2017). Current treatment practices lead to a high prevalence of dual, lenalidomide-bortezomib refractory relapses in later lines of therapy.

The ASPIRE study demonstrated the superiority of the combination of carfilzomib with lenalidomide and dexamethasone (KRd; 27 mg/m^2 twice-weekly) over lenalidomide with dexamethasone. Superiority of the KRd regimen was demonstrated in terms of median PFS (26.3 vs 17.6 months, HR = 0.69), overall response rate (87.1% vs 66.7%, odds ratio = 3.47) (Stewart et al, 2015), health-related quality-of-life (Stewart et al, 2016), as well as 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.

Pomalidomide and dexamethasone (Pd) has been approved for subjects with RRMM and has proven efficacy in subjects who were refractory to both bortezomib and lenalidomide. Several phase 2 studies have demonstrated improved efficacy and safety of adding carfilzomib to Pd (KPd) in advanced RRMM compared to historical outcomes with Pd. The key benefits of carfilzomib, pomalidomide, dexamethasone as a

triplet-therapy for patients with relapsed and refractory multiple myeloma include increases in PFS, OS, and ORR.

3.3.3 Key Risks

Multiple important identified and potential risks for carfilzomib were identified in the pooled safety data from 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. Where applicable, risk minimization measures specific to a particular risk are also provided.

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

Embryo-fetal toxicity is associated with 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 USPI and REVLIMID Summary of Product Characteristics (SmPC) or local prescribing information.

Embryo-fetal toxicity is associated with pomalidomide treatment. Investigators and subjects must comply with the requirements of restricted distribution programs if one is present in the local region; (eg, POMALYST REMS program in the United States). Additional information regarding risks for pomalidomide are described in Pomalyst USPI or local prescribing information.

3.3.3.1 Risks

3.3.3.1.1 Cardiac Toxicity

In the pooled data set (n = 2944), the subject incidence of cardiac failure and myocardial infarction was 7.2% and 2.0%, respectively. The subject incidence of serious cardiac failure and serious myocardial infarction was 4.1% and 1.3%, respectively. Fatal outcomes have been observed with cardiac failure, myocardial infarction, and cardiac arrest. The risk of cardiac failure is increased in elderly patients (≥ 75 years). Subjects with New York Heart Association (NYHA) Class III and IV heart failure, recent myocardial infarction, and conduction abnormalities uncontrolled by medications were not eligible for clinical trial 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 Pulmonary Toxicities

The subject incidence of serious respiratory failure and serious interstitial lung disease was < 0.1% and 0.8%, respectively. Fatal outcomes have been observed with respiratory failure and interstitial lung disease.

3.3.3.1.3 Pulmonary Hypertension

The subject incidence of pulmonary hypertension was 1.4% with a subject incidence of 0.3% for serious events. Some events have been fatal.

3.3.3.1.4 Dyspnea

The subject incidence of dyspnea was 31.0% with a subject incidence of 2.3% for serious events. The cause of the dyspnea should be investigated promptly and treated accordingly (see Section 12.9 for more details).

3.3.3.1.5 Hypertension

The subject incidence of hypertension was 20.3% with a subject incidence of 1% for serious events. Blood pressure is monitored while on study and hypertension should be treated as needed. If the 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.

3.3.3.1.6 Acute Renal Failure

The subject incidence of acute renal failure was 10.8% with a subject incidence of 5.3% for serious events. Some events have been fatal. 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 glomerular filtration rate (GFR). Reduce or stop dose as described in the dose modification Section 7.4.

3.3.3.1.7 Tumor Lysis Syndrome

The subject incidence of tumor lysis syndrome (TLS) was 0.7% with a subject incidence of 0.5% for serious events. Subjects with a high tumor burden should be considered to be at greater risk for TLS. Instructions for ensuring proper hydration prior to cycle 1 and in subsequent cycles as needed are provided in Section 7.1.4.3. Serial monitoring of serum electrolytes to monitor for TLS are included in the protocol. Uric acid lowering drugs should be considered in patients at high risk for TLS. If TLS occurs, the subject should be treated promptly, and carfilzomib should be interrupted until the TLS is resolved.

3.3.3.1.8 Infusion-related Reactions

The subject incidence of infusion-related reactions was 1.8% with a subject incidence of 0.3% for serious events. The dexamethasone that is administered as part of the regimen is expected to decrease the incidence and severity of infusion-related reactions.

3.3.3.1.9 Hemorrhage and Thrombocytopenia

The subject incidence of hemorrhage and thrombocytopenia was 19.5% and 33.8%, respectively. The subject incidence of serious hemorrhage and serious thrombocytopenia was 2.2% and 1.5%, respectively. Thrombocytopenia is a significant risk factor for hemorrhage events. Fatal outcomes have been reported for these events. Carfilzomib causes thrombocytopenia with platelet nadirs observed between day 8 and 15 of each 28-day cycle with recovery to baseline platelet count by the start of the next cycle. Serial monitoring of platelets will be performed every 28 days throughout treatment period (see Schedule of Activities, Table 2-1). Dose modification guidance for thrombocytopenia (including stopping carfilzomib) is provided in Section 7.4.

3.3.3.1.10 Venous Thromboembolism

The subject incidence of venous thromboembolism was 7.0% with a subject incidence of 2.4% for serious events. Fatal outcomes have been reported with deep venous thrombosis and pulmonary embolism events. As described in Section 7.1.4.2, thromboprophylaxis should be considered based on an individual benefit-risk assessment.

3.3.3.1.11 Hepatic Toxicity

The subject incidence of hepatic toxicity was 1.9% with a subject incidence of 0.7% for serious events. Cases of hepatic failure, including fatal cases, have been reported in < 1% of subjects in clinical studies with carfilzomib. Serial monitoring of liver enzymes is conducted every 28 days throughout treatment period (see Schedule of Activities,

Table 2-1). Dose modification guidance for hepatic toxicity (including stopping carfilzomib) is provided in Section 7.4.

3.3.3.1.12 Thrombotic Microangiopathy

The subject incidence of thrombotic microangiopathy (TMA) was 0.2% and all events were serious. Fatal outcomes have been reported with TMA. As described in the dose modification Section 7.4, carfilzomib should be held if the diagnosis is suspected. If the diagnosis is excluded, carfilzomib may be restarted based on an individual benefit-risk assessment. The safety of reinitiating carfilzomib in subjects previously experiencing TMA (including thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome) is unknown.

3.3.3.1.13 Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) is a neurological disorder, which can present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension; the diagnosis is confirmed by neuro-radiological imaging. The subject incidence of PRES was 0.1% and all events were serious. As described in the dose modification Section 7.4, carfilzomib should be held if the diagnosis is suspected. The safety of reinitiating carfilzomib in subjects previously experiencing PRES is unknown.

3.3.3.1.14 Herpes Zoster Infections

Herpes zoster infections is an important potential risk for carfilzomib. The subject incidence of herpes zoster infection was 2.9% but < 0.1% were serious events. Antiviral prophylaxis should be considered in subjects treated with carfilzomib to decrease the risk of herpes zoster reactivation.

4. Objectives, Endpoints and Hypotheses

4.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
Describe adherence and treatment safety across all 12 cycles of carfilzomib based regimens in subjects with relapsed or refractory multiple myeloma with 1-3 prior lines of therapy at study entry.	• proportion of subjects completing 12 cycles of treatment • proportion of actual cumulative dose received to the full intended cumulative dose in cycles 1-12 • relative dose intensity in cycles 1-12 • dose modifications and reasons in cycles 1-12 • treatment-emergent adverse events and serious adverse events
Secondary	
Assess subject health-related quality-of--life (HRQoL) with the Kd, KRd, and KPd regimens.	• European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire (EORTC QLQ) Core 30 (C30) and EORTC QLQ Multiple Myeloma Module (MY20) scores through cycle 12 or up to disease progression
Assess response to the Kd, KRd, and KPd regimens.	• response rate (stringent complete response [sCR], complete response [CR], very good partial response [VGPR], partial response [PR], minimal response [MR], stable disease [SD], progressive disease [PD], Not evaluable [NE]). • progression-free survival (PFS) at 1 year • response rate and PFS by line of prior therapy 1 vs ≥ 2

Objectives	Endpoints
Exploratory	
[redacted]	

4.2 Hypotheses

Carfilzomib plus dexamethasone twice weekly with or without daily lenalidomide or pomalidomide, followed by carfilzomib plus dexamethasone once weekly with or without daily lenalidomide or pomalidomide, is tolerable in subjects with RRMM in a community-based setting.

5. Study Design

5.1 Overall Design

This is a phase 2, multicenter, open-label study in subjects with RRMM in US community oncology centers. Subjects with 1-3 prior lines of therapy at study entry are eligible to be screened for participation. Subjects refractory to their last line of treatment are eligible to participate as long as their last line of treatment did not include a PI. The study will consist of a screening period of up to 28 days for bone marrow aspirate, bone lesion assessment, and plasmacytoma assessment and up to 21 days for all other assessments, up to 12 cycles of treatment, and a 30-day safety follow-up period following the last dose of study drug.

During the treatment period, subjects in the Kd arm will be treated with Kd 20/56 mg/m^2 twice weekly for up to two 28-day cycles followed by Kd 70 mg/m^2 once weekly for another ten 28-day cycles; subjects in the KRd arm will be treated with KRd 20/27 mg/m^2 twice weekly for up to two 28-day cycles followed by Kd 56 mg/m^2 once weekly for another ten 28-day cycles; subjects in the KPd arm will be treated with KPd 20/27 mg/m^2 twice weekly for up to two 28-day cycles followed by KPd 56 mg/m^2 once weekly for another ten 28-day cycles. After discontinuation of study drugs, subjects will be followed for 30 days for safety.

The overall study design is described by a study schema in Section 2.1. The endpoints are defined in Section 4.1.

5.2 Number of Subjects

A total of approximately 75 subjects will be enrolled in the study with approximately 25 subjects in each arm.

Subjects in this clinical investigation shall be referred to as “subjects”. A sample size of approximately 75 subjects will provide for descriptive statistics to be generated for patient safety and treatment adherence. 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 40 investigative sites in the United States will be included in the study. Sites that do not enroll subjects within 5 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 is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

The primary completion date is the date when the last subject has completed the assessments for the safety follow-up visit.

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 study will consist of a screening period (up to 28 days for bone marrow aspirate, bone lesion assessment, and plasmacytoma assessment and up to 21 days for all other assessments), approximately 12-month treatment period, and a 30 (+3)-day safety follow-up. Therefore, the total study duration for an individual subject is estimated to be approximately 14 months.

5.4 Justification for Investigational Product Dose

The dose and dosing frequency of carfilzomib regimens used in this study were selected based on data from phase 1/2 and phase 3 studies.

5.4.1 Justification for Investigational Product Dose for Kd Arm

The safety and efficacy of 20/56 mg/m^2 twice weekly carfilzomib combined with dexamethasone has been defined in a randomized phase 3 trial (ENDEAVOR; Dimopoulos et al, 2016). ENDEAVOR compared carfilzomib administered at 56 mg/m^2 over a 30-min infusion twice per week with dexamethasone against Vd in subjects with RRMM who had received between 1 and 3 previous treatments, a similar subject population to what is being proposed in this phase 2 trial. The carfilzomib arm proved superior at the first interim analysis for efficacy reducing the risk of progression or death by 47% (median PFS [Kd vs Vd]: 18.7 months vs 9.4 months), and at the second interim

OS analysis reducing the risk of death by 21% compared to Vd (median OS 47.6 months vs 40.0 months, HR = 0.791, one-sided p = 0.010). Grade 3 or worse adverse events were reported in 81% of subjects in the Kd group and 71% of subjects in the Vd group. The most frequent grade 3 cardiopulmonary events of interest reported in the Kd and Vd groups, respectively, included hypertension 15% vs 3%, pneumonia 9% vs 9%, dyspnea 6% vs 2%, and congestive heart failure in 6% vs 2%.

Based on the results of the ENDEAVOR study, the FDA approved carfilzomib in combination with dexamethasone for the treatment of patients with RRMM who have received 1 to 3 lines of therapy. The dose of carfilzomib to be used in combination with dexamethasone is 56 mg/m^2 twice weekly following an initial treatment with 20 mg/m^2 on the first 2 days of treatment (Kyprolis USPI).

The safety and efficacy of the 70 mg/m^2 dose has been evaluated in the phase 2 (CHAMPION-1) and phase 3 (A.R.R.O.W.) studies. Carfilzomib pharmacokinetics in the CHAMPION-1 study with the 70 mg/m^2 once weekly dose showed higher maximum concentration than that with the 56 mg/m^2 twice-weekly dose (2390 ng/mL vs 2079 ng/mL, respectively). However, the area under the curve was higher with 56 mg/m^2 twice a week (1896 ng•hr/mL vs 1030 ng•hr/mL per week).

The CHAMPION-1 study, a phase 1/2 trial, provided additional safety data for the 70 mg/m^2 weekly dosing of carfilzomib in combination with dexamethasone. In that study, 104 subjects were treated for a median of 7.7 months at the MTD of 70 mg/m^2 weekly in combination with dexamethasone 40 mg weekly in a similar patient population as the proposed study. At 70 mg/m^2, the most common grade $\geq$ 3 adverse events were fatigue (11%) and hypertension (7%). For specific adverse events of interest, the rates of grade $\geq$ 3 hypertension, dyspnea, cardiac failure, and peripheral neuropathy were 7%, 5%, 2%, and 1%, respectively. Discontinuations due to adverse events were reported to occur in 12% of subjects. Discontinuations due to adverse events and the incidence of specific cardiovascular events of interest were all lower than that reported in the phase 3 ENDEAVOR trial (Berenson et al, 2016).

The MTD defined in the CHAMPION-1 trial was used in the phase 3 A.R.R.O.W. trial, in which subjects with RRMM were treated with Kd with carfilzomib dosed either at 27 mg/m^2 twice-weekly or 70 mg/m^2 once-weekly. The study included 478 subjects with RRMM who received 2 or 3 prior lines of therapy, including a PI and an IMiD. Subjects treated with the once-weekly Kd regimen achieved a statistically significant superior PFS with a median of 11.2 months compared to 7.6 months for those treated with the

twice-weekly Kd regimen (HR = 0.69, 95% CI, 0.54-0.88). The overall safety profile of the once-weekly Kd regimen was comparable to that of the twice-weekly regimen. The most frequently reported treatment-emergent adverse events (greater than or equal to 20%) in either treatment arm were anemia, diarrhea, fatigue, hypertension, insomnia and pyrexia (A.R.R.O.W. Press release, 2017). With the results from the A.R.R.O.W. study, the Kd 70 mg/m^2 once weekly dosing schedule was approved in the US, providing the US practicing centers one more option to treat MM patients with relapse/refractory disease.

5.4.2 Justification for Investigational Product Dose for KRd and KPd Arms

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).

Based on evidence from phase 2 studies of KPd, weekly doses up to 70 mg/m^2 in subjects with first relapse and up to 54 mg/m^2 in subjects with advanced myeloma using a twice-weekly schedule of carfilzomib have been tolerated (Sonneveld et al, 2018;

Shah et al, 2015). Consistent with the observation from the A.R.R.O.W. study, that adjustment from a twice-weekly to a once-weekly schedule was demonstrated to have a favorable benefit/risk profile with no new safety issues identified, the CFZ013 trial identified 56 to 70 mg/m^2 weekly carfilzomib combined with Rd to have an acceptable safety profile. Given these data, this phase 2 study will evaluate the 56 mg/m^2 once-weekly dose schedule for KRd and KPd triplet therapies.

5.5 Patient Input on Study Design

Not applicable.

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). This log may be completed and updated via the Interactive Voice/Web Response System (IXRS).

Eligibility criteria will be evaluated during screening.

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

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

101 Subject has provided informed consent prior to initiation of any study specific activities/procedures.

102 Males or females ≥ 18 years of age.

103 Relapsed MM after last treatment or refractory while receiving non-proteasome inhibitor therapy.

104 Measurable disease with at least 1 of the following assessed within 21 days prior to enrollment:

- immunoglobulin G (IgG)MM: 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.

105 Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1 (Section 12.10)

106 Subjects must have at least partial response (PR) to at least 1 line of prior therapy.

107 Subjects must have received at least 1 but not more than 3 prior lines of therapy for MM (induction therapy followed by stem cell transplant and consolidation/maintenance therapy will be considered as 1 line of therapy; see Section 12.11).

109 Measured creatinine clearance (radionucleotide or 24-hour urine) or calculated creatinine clearance per the Chronic Kidney Disease Epidemiology Collaboration formula, of ≥ 30mL/min/1.73 m^2 within 21 days of enrollment (see Section 12.13).

Kd Arm

110 Prior therapy with a PI is allowed as long as the subject was not removed due to toxicity (except for neuropathy, see criterion 213), and if received carfilzomib must have achieved at least a PR and have at least a 6-month carfilzomib treatment-free interval from last dose received until enrollment.

KRd Arm

111 Prior therapy with a PI or lenalidomide is allowed as long as the subject had at least a PR to most recent therapy with PI or lenalidomide, was not removed due to toxicity (except for neuropathy, see criterion 213), and if received carfilzomib must have at least a 6-month carfilzomib treatment-free interval from last dose received until enrollment.

KPd Arm

112 Prior therapy with a PI is allowed as long as the subject had at least a PR to most recent therapy with PI, was not removed due to toxicity (except for neuropathy, see criterion 213), and if received carfilzomib must have at least a 6-month carfilzomib treatment-free interval from last dose received until enrollment.

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 History of plasma cell leukemia.

206 Subjects with nephrotic range proteinuria (≥ 3 g albumin for 24 hours urine OR ≥ 2 g albumin/1 g of creatinine on a random urine specimen).

207 Myelodysplastic syndrome.

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

Other Medical Conditions

208 History of other malignancy within the past 3 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% five-year disease-free survival

209 Known HIV infection, hepatitis C infection (subjects with hepatitis C that achieve a sustained virologic response following 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 directed at hepatitis B are allowed).

210 Active acute or chronic graft-versus-host disease (any grade).

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

212 Known cirrhosis.

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

214 Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 14 days prior to enrollment.

Cardiopulmonary Conditions

215 Uncontrolled hypertension, defined as an average systolic blood pressure ≥ 160 mmHg or diastolic ≥ 100 mmHg (see Section 12.12 for more details). Subjects with controlled hypertension are eligible.

216 Active congestive heart failure with or without reduced ejection fraction (NYHA Class III to IV), symptomatic ischemia, uncontrolled arrhythmias, clinically significant electrocardiogram (ECG) abnormalities, screening ECG with corrected QT interval (QTc) of > 470 msec, pericardial disease, myocardial infarction within 4 months prior to enrollment.

217 Known chronic obstructive pulmonary disease.

218 Known interstitial pneumonitis.

Prior/Concomitant Therapy

219 Immunotherapy within 21 days prior to enrollment.

220 Chemotherapy with approved anticancer therapeutic within 21 days prior to enrollment.

221 Glucocorticoid therapy (prednisone > 30 mg/day or equivalent) within 14 days prior to enrollment.

222 Focal radiation therapy within 7 days prior to enrollment. Radiation therapy to an extended field involving a significant volume of bone marrow within 21 days prior to enrollment (ie, prior radiation must have been to less than 30% of the bone marrow).

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

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

225 Contraindication to dexamethasone, lenalidomide, or pomalidomide.

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

227 Intolerance to intravenous (IV) hydration.

Prior/Concurrent Clinical Study Experience

228 Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

Organ Function Assessments

229 Hepatic dysfunction within 21 days prior to enrollment (see Section 7.1.1.2.1):

- bilirubin ≥ 1.5 times the upper limit of normal (ULN)
- aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 times the ULN

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

231 Severe valvular disease assessed by transthoracic echocardiogram.

232 Severe right-ventricular dysfunction assessed by transthoracic echocardiogram.

233 Right-ventricular systolic pressure > 40 mm Hg assessed by transthoracic echocardiogram.

235 Absolute neutrophil count (ANC) < 1 x 10^9/L within 21 days prior to enrollment. Screening ANC should be independent of growth factor support for ≥ 1 week.

236 Hemoglobin < 80 g/L within 21 days prior to enrollment. Use of erythropoietic stimulating factors and red blood cell (RBC) transfusions per institutional guidelines is allowed, however most recent RBC transfusion may not have been done within 7 days prior to obtaining screening hemoglobin.

237 Platelet count < 50 x 10^9/L (≤ 30 x 10^9/L if myeloma involvement in the bone marrow is > 50%) within 21 days prior to enrollment. Subjects should not have received platelet transfusions for at least 1 week prior to obtaining the screening platelet count.

Other Exclusions

242 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 study drug(s). Refer to Section 12.5 for additional contraceptive information.

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

244 Male subjects unwilling to abstain from donating sperm during treatment and for an additional 90 days after the last dose of study drug(s).

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

246 Subject likely to not be available to complete all protocol required study visits or procedures, and/or to comply with all required study procedures (eg, Clinical Outcome Assessments [COAs]) to the best of the subject and investigator's knowledge.

247 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.

Kd Arm

249 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 study drug(s).

250 Female subjects of childbearing potential unwilling to use 1 highly effective method of contraception during treatment and for an additional 30 days after the last dose of study drug(s). Refer to Section 12.5 for additional contraceptive information.

251 Female subjects of childbearing potential with a positive pregnancy test assessed at screening and/or ay 1 by a serum pregnancy test and/or urine pregnancy test.

KRd and KPd Arms

252 Female subjects of childbearing potential unwilling to use 2 methods of contraception (1 of which must be highly effective; see Section 12.5) during the study and for an additional 30 days after the last dose of study drug. Additionally, subjects must be using contraception at least 28 days prior to initiating treatment. Refer to Section 12.5 for additional contraceptive information.

253 Female subjects of childbearing potential with a positive serum pregnancy test assessed within 14 days prior to first dose of study drug or a positive urine pregnancy test within 24 hours prior to first dose. In addition, females of childbearing potential must agree to pregnancy testing weekly during the first 4 weeks of pomalidomide or lenalidomide use followed by a pregnancy test every 4 weeks in females with regular menses or every 2 weeks in females with irregular menstrual cycles.

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 (IRB) 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 must personally sign and date the IRB 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 case report form (CRF).

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 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.

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 demography, screen failure details, eligibility

criteria, and any serious adverse events. In the event a screen-failure subject experiences a serious adverse event, medical history and prior therapies 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 for more detail.

7. Treatments

Study treatment is defined as any investigational product(s), non-investigational product(s), placebo, 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 in below.

7.1 Treatment Procedures

7.1.1 Investigational Products

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

For all treatment arms, carfilzomib will be administered at 20 mg/m^2 on days 1 and 2 of the first cycle (see Table 7-1). For subjects in the Kd arm, carfilzomib will be administered at 56 mg/m^2 on days 8, 9, 15, and 16 of the first cycle, and then on days 1, 2, 8, 9, 15, and 16 in cycle 2. Starting with cycle 3 through cycle 12, carfilzomib will be administered at 70 mg/m^2 on days 1, 8, and 15 of each 28-day cycle. For subjects in the KRd and KPd arms, carfilzomib will be administered at 27 mg/m^2 on days 8, 9, 15, and 16 of the first cycle, and then on days 1, 2, 8, 9, 15, and 16 in cycle 2. Starting with cycle 3 through cycle 12, carfilzomib will be administered at 56 mg/m^2 on days 1, 8, and 15 of each 28-day cycle.

At the time of implementation of protocol amendment 3, subjects previously enrolled may have completed more than 2 but less than 6 cycles of twice weekly carfilzomib dosing on the Kd arm as per protocol amendment 2. These subjects should complete the dosing regimen as per protocol amendment 2, (ie, 6 cycles of twice weekly dosing for carfilzomib [Kd 56 mg/m^2] transitioning to once weekly dosing for carfilzomib [Kd 70 mg/m^2], starting with cycle 7). For these subjects, the schedule of activities outlined per Table 2-1 for cycles 1 and 2 will continue for cycles 1 through 6. At the start of cycle 7, these subjects will then follow the schedule of activities as outlined per Table 2-1 cycles 3 through 12. In addition, the starting nominal dose of carfilzomib on day 1 cycle 7 (which is the initiation of the once weekly carfilzomib dosing for these subjects) should be reduced by the same number of dose levels and same percentage dose reduction as it was reduced to during cycle 6 (which is the twice weekly carfilzomib dosing). Dexamethasone will be administered at a dose of 20 mg once daily on days 1, 2, 8, 9, 15, 16, 22, and 23 cycles 1 through 6 and at a dose of 40 mg once daily on days 1, 8, 15 for the Kd arm for cycles 7 through 12 for these subjects.

All 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. The starting dose should be modified for chronic mild hepatic insufficiency per Section 7.1.1.2.1.

Table 7-1. Carfilzomib Dosage

Cycle 1	Cycle 2	Cycles 3-12
Kd Arm		
D1, 2: 20 mg/m^2 D8, 9, 15, 16: 56 mg/m^2	D 1, 2, 8, 9, 15, 16: 56 mg/m^2	D1, 8, 15: 70 mg/m^2
KRd Arm		
D1, 2: 20 mg/m^2 D8, 9, 15, 16: 27 mg/m^2	D 1, 2, 8, 9, 15, 16: 27 mg/m^2	D1, 8, 15: 56 mg/m^2
KPd Arm		
D1, 2: 20 mg/m^2 D8, 9, 15, 16: 27 mg/m^2	D 1, 2, 8, 9, 15, 16: 27 mg/m^2	D1, 8, 15: 56 mg/m^2

D = day

Subjects receiving carfilzomib at doses less than the protocol planned dose (56 mg/m^2 or 27 mg/m^2 based on treatment arm) during cycle 2 may have been reduced by 1 or more dose levels and/or by 25% for hepatic function abnormalities. Subjects should have the starting nominal dose of carfilzomib (70 mg/m^2 or 56 mg/m^2 based on treatment arm) on day 1 cycle 3 reduced by the same number of dose levels and the same

percentage dose reduction as they were reduced during cycle 2, see Table 7-2 for dose level reductions.

Carfilzomib is to be administered as an IV infusion over 30 (± 5) minutes. Subjects should receive 250 mL of normal saline or equivalent IV fluid prior to and after each dose during cycle 1. After cycle 1, at the discretion of treating physician, subjects may receive up to but no more than 250 mL of normal saline or equivalent fluid prior to each dose of carfilzomib. For subjects at risk of TLS, see Section 7.1.4.3.

Mechanical infusion pumps are recommended, but gravity-dependent infusions are permitted if the 30-minute infusion duration can be reliably maintained. Carfilzomib infusion must occur at a facility capable of managing hypersensitivity reactions.

Each subject's first dose will be calculated based upon baseline BSA per the Mosteller formula. In subjects with BSA of greater than 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 experiences a change in body weight of ≥ 20% compared to baseline or last calculation of BSA, in which case the BSA and dose should be recalculated. The dose can also be modified in response to toxicity following the dose modification guideline tables (see Section 7.4).

The planned dose, dose administered, start date/time, stop date/time, reason for change in planned dose or schedule, and package lot number of carfilzomib are to be recorded on each subject's CRF.

7.1.1.2.1 Starting Dose in Hepatic Insufficiency

For subjects with mild hepatic insufficiency during screening, the initial dose of carfilzomib on days 1 and 2 of cycle 1 should be reduced by 25% to 15 mg/m^2. For subjects in the Kd arm, starting on day 8 and for all subsequent doses of carfilzomib during cycles 1 and 2, the dose should be 42 mg/m^2 (Brown et al, 2017); the dose in cycle 3 through 12 should be 5**3** mg/m^2. For subjects in the KRd and KPd arms, starting on day 8 and for all subsequent doses of carfilzomib during cycles 1 and 2, the dose should be 20 mg/m^2 as per the protocol and doses in cycles 3 through 12 should be 42 mg/m^2.

If hepatic function returns to normal, the dose in following cycles may be re-escalated to the full dose per the protocol. For dose modification due to subsequent changes in hepatic function, refer to Section 7.4.1.1.3 (Table 7-4).

Mild and moderate hepatic dysfunction is defined as:

- Mild: bilirubin > 1.0-1.5 x ULN, or AST > ULN with bilirubin ≤ ULN
- Moderate: bilirubin > 1.5-3.0 x ULN with any AST
  - Grade 3 elevation in ALT and/or AST (> 5x ULN)

7.1.2 Non-investigational Products

7.1.2.1 Dexamethasone: Dosage, Administration, and Schedule

For all treatment arms, dexamethasone will be taken orally or by IV infusion at a dose of 20 mg once-daily on days 1, 2, 8, 9, 15, 16, 22, and 23 of Kd cycles 1-2, and at a dose 40 mg once-daily on days 1, 8, 15 of Kd cycles 3-12. All doses should be administered on the scheduled days ± 2 days but prior to carfilzomib infusion except for days 22 and 23 of cycles 1-2.

Dexamethasone will be administered at least 30 minutes (but no more than 4 hours) prior to carfilzomib. Subjects receiving dexamethasone IV on days 1, 2, 8, 9, 15, and 16, may receive the day 22 and day 23 dose orally.

For subjects ≥ 75 years of age, see Section 7.4.1.2 for dose modification.

The dose, date, time, and reason for dose change are to be recorded on each subject's CRF.

Dexamethasone will not be provided or reimbursed by Amgen. The investigator will be responsible for obtaining supplies of dexamethasone.

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 for the KRd treatment arm. 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 assigned to the KRd arm of this study, and all research subjects enrolled on this study who are assigned to the KRd arm, 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.

7.1.2.2.2 Dosage, Administration, and Schedule

Lenalidomide will be taken once-daily orally at a dose of 25 mg on days 1-21 of each 28-day cycle. 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 on schedule with the next cycle. Dose modifications are permitted in response to toxicity following the dose modification guideline tables.

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

7.1.2.3 Pomalidomide

7.1.2.3.1 Prescribing Requirements

Pomalidomide, a non-Amgen non-investigational product, will also be used in this study for the KPd treatment arm. Pomalidomide should be administered in accordance with the POMALYST REMS® program of Celgene Corporation (http://www.pomalystrems.com/.) All physicians who prescribe pomalidomide for research subjects assigned to the KPd arm of this study, and all research subjects enrolled on this study who are assigned to the KPd arm, must be registered in and comply with all requirements of the POMALYST 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 pomalidomide.

7.1.2.3.2 Dosage, Administration, and Schedule

Pomalidomide will be taken once-daily orally at a dose of 4 mg on days 1-21 of each 28-day cycle. Pomalidomide should be taken at home by the subject at about the same time each day. Pomalidomide 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 on schedule with the next cycle. Dose modifications are permitted in response to toxicity following the dose modification guideline tables.

The planned dose, quantity administered, start date, start time, 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 in this study.

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

Protocol-required, suggested, or permitted supportive therapies listed below are commercially available and will not be provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies.

Additional details regarding these protocol-required therapies are provided in the IPIM.

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 for 3 days, 2 times a day, or per institutional standards), or valacyclovir (eg, 500 mg orally 2 times a day, or per institutional standards), dose adjustments for renal function where appropriate, initiated within 1 week of the first dose should continue for the duration of treatment with carfilzomib.

7.1.4.2 Thromboprophylaxis

It is strongly suggested that all subjects receive an anticoagulant (eg, enteric-coated aspirin at standard prophylactic dose or other anticoagulant or antiplatelet medication, such as clopidogrel bisulfate, low molecular weight heparin, or warfarin). In addition, a second thromboprophylaxis medication is strongly recommended in subjects with elevated risk of thrombosis, based on an individual benefit/risk assessment (Li et al, 2017); see Section 12.14 for more details.

7.1.4.3 Tumor Lysis Syndrome Prophylaxis

An approved uric acid-lowering agent (eg, allopurinol) in subjects at high risk for TLS due to high tumor burden may be prescribed at the investigator's discretion, according to the Kyprolis USPI. Risk factors for TLS include but are not limited to: elevated lactate dehydrogenase, beta-2 microglobulin > 5.5 mg/L, elevated uric acid, elevated circulating plasma cells, elevated serum creatinine, presence of soft tissue plasmacytomas, or international stage III disease.

Subjects at elevated risk of TLS should be hydrated with 500 mL of normal saline or equivalent IV fluid prior to and 250 mL after the first dose of carfilzomib and each subsequent dose until the investigator determines that the risk of TLS has resolved or up to the end of the first cycle.

7.1.4.4 Proton-pump Inhibitor

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

7.1.4.5 Other Permitted Therapies

The following medications and supportive therapies are examples of support therapies that may be used during the study:

- Antifungal prophylaxis: Fluconazole 200 mg/day (minimum) or equivalent therapy is recommended, especially for patients living (coming from) areas known to have high incidence of environmental mycoses.
- Prophylaxis for Pneumocystosis jirovenci: Pneumocystis jirovenci pneumonia prophylaxis should be considered, as per institutional guidelines while on dexamethasone.
- Bone-preserving therapy: bone preserving therapy (bisphosphonate or other bone preserving therapy) is strongly recommended for all subjects with evidence of lytic destruction of bone or with osteopenia (Gralow et al, 2013; Terpos et al, 2013). Commercially available IV bisphosphonates (pamidronate and zoledronic acid) or monoclonal antibodies are preferred when available, used according to the manufacturer's recommendations, as described in the prescribing information, for subjects with osteolytic or osteopenic myelomatous bone disease. Oral bisphosphonates may be used as alternatives if IV bisphosphonates are not available at the study site. It is preferred that investigators use the same route of bisphosphonate therapy for all subjects at their sites.
- Subjects who are using bone preserving 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 bone preserving therapy at the time of enrollment should start as soon as possible during cycle 1 or 2 of treatment. Investigators should not start bone-preserving therapy during the study, unless it has been agreed with the sponsor that there is no sign of disease progression.
- Antivirals, antihypertensives, statins, and antibiotics.
- Hyperglycemia medical management.

- Prevention of constipation (eg, adequate hydration, high-fiber diet, and stool softeners, if needed)
- Prophylactic antiemetics, with the exception of corticosteroids.
- Colony-stimulating factors, erythropoietin, and transfusion of platelets and RBC.
- Loperamide is recommended for the treatment of diarrhea, starting at the time of the first watery stool. The loperamide dose and regimen is according to institutional guidelines. Prophylactic loperamide is not recommended.
- Adequate hydration is recommended for prevention of myeloma-related kidney disease.

7.1.5 Other Treatment Procedures

No other treatment procedures are required. Patients may receive surgery or radiation therapy as clinically indicated.

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(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any investigational/non-investigational product(s) provisioned and/or repackaged/modified by Amgen.

Any product complaint(s) associated with an investigational product(s), non-investigational product(s), or device(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

Concurrent therapy with a marketed or investigational anticancer therapeutic for either a palliative or therapeutic intent is excluded. 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 (other than as indicated in this protocol). Higher steroid doses given short term for exacerbations of nonmalignant conditions (eg, asthma flare) if medically indicated are permitted. Investigational agents are not to be used during the study. 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.

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 who meet eligibility criteria will be assigned by the investigator to treatment with either Kd, KRd, or KPd; no cross-over will be allowed.

Investigators are advised to consider the following guidelines when assigning subjects to treatment:

- Kd arm: it is recommended that subjects who are suitable for an IMid free doublet regimen are assigned to the Kd arm.
- KRd arm: it is recommended that subjects who are not refractory to lenalidomide (lenalidomide sensitive or naïve) and who are suitable for triplet therapy are assigned to the KRd arm.
- KPd arm: it is recommended that subjects who are refractory to lenalidomide (progressed on or within 60 days of completing this therapy) and who are suitable for a triplet therapy are assigned to the KPd arm.

The treatment assignment date is to be documented in the subject's medical record and on the enrollment CRF.

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

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

Carfilzomib 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. Carfilzomib dose must be modified based on specified toxicities, as indicated in Table 7-3 and Table 7-4. The subject will be considered on protocol treatment while receiving carfilzomib. Carfilzomib (both twice-weekly and once-weekly regimen) must be discontinued permanently if a delay of more than 6 weeks is required due to unresolved toxicity.

If day 1 of a cycle is delayed, 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.

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

If either carfilzomib or dexamethasone are held for the remainder of the previous cycle or the new cycle is delayed due to residual toxicity on the planned day 1 of the next cycle, then the new cycle will be started at 1 dose decrement for the drug(s) causing the delay.

For conditions that do not require carfilzomib dose reduction, refer to Section 7.4.1.3.

7.4.1.1.1 Dose Reduction Levels

Dose reduction levels of carfilzomib for toxicity management of individual subjects are provided in Table 7-2. Subjects that require dose reduction may have the dose escalated according to specific rules, see Section 7.4.1.1.4. Subjects should have the starting nominal dose of carfilzomib (56 mg/m^2 or 70 mg/m^2 based on treatment arm) on day 1 cycle 3 reduced by the same number of dose levels and the same percentage dose reduction as they were reduced during cycle 2, see Table 7-2 for dose level reductions. Subjects who require fifth dose reductions should discontinue carfilzomib.

Table 7-2. Dose Decrements for Carfilzomib

Nominal Dose[a, b] (mg/m^2)	First Dose Reduction Dose -1 (mg/m^2)	Second Dose Reduction Dose -2 (mg/m^2)	Third Dose Reduction Dose -3 (mg/m^2)	Fourth Dose Reduction Dose -4 (mg/m^2)
20	15	11	Discontinue	
27	20	15	11	Discontinue
56	45	36	27	20
70	56	45	36	27

[a] If dose reduction of carfilzomib is required on Cycle 1 Day 1 or Cycle 1 Day 2 for any reason other than mild hepatic insufficiency, the investigator should contact the medical monitor to discuss the situation, before any additional doses of carfilzomib are administered.
[b] For patients with baseline chronic hepatic impairment (mild), reduce the starting and subsequent doses of carfilzomib by 25% (ie, 15 mg/m^2 day 1 and 2 of cycle 1 and 42 mg/m^2 day 8 cycle 1 and thereafter).

7.4.1.1.2 Guidelines for Hematologic Toxicity

Guidelines for carfilzomib dose modification in the event of thrombocytopenia and neutropenia are summarized in Table 7-3.

Table 7-3. 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.

7.4.1.1.3 Guidelines of Nonhematologic Toxicity

Guidelines for dose modification in the event of nonhematologic toxicities are summarized in Table 7-4.

Table 7-4. Dose Modification Guidelines for Nonhematologic Toxicities

For grading criteria, see CTCAE grading scale in Section 12.4.	
Symptom/Sign/Investigation	Recommended Action
Renal Dysfunction[a]:	
Estimated GFR ≥ 15 mL/min/1.73 m^2	Full dose. For acute deterioration requiring dialysis, see below.
Estimated GFR < 15 mL/min/1.73 m^2 (NCI-CTCAE grade 4)	Hold dose until estimated GFR returns to ≥ 15 mL/min/1.73 m^2, then resume same dose. If dialysis is required (regardless of estimated GFR levels), 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 (see Section 7.4.1.1.4. for dose re-escalation). Carfilzomib must be administered after dialysis.
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 bilirubin (> 3x ULN), ALT and/or AST (> 5x ULN)	Hold carfilzomib until resolution to baseline or normal. Monitor any abnormality weekly. Resume carfilzomib with a 25% dose reduction for 1 full cycle if drug-induced hepatotoxicity is excluded. If no worsening in the total bilirubin, AST or ALT on the reduced dose for 1 full cycle, dose may be re-escalated, if drug induced hepatotoxicity is excluded (see Section 7.4.1.1.4 for dose re-escalation instructions).
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 last page of this table.

Table 7-4. Dose Modification Guidelines for Nonhematologic Toxicities

For grading criteria, see CTCAE grading scale in Section 12.4.	
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. Once congestive heart failure resolves or returns to baseline, treatment may continue at 1 dose level reduction. If no resolution after 4 weeks, the subject will be withdrawn from all study treatment.
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.
Neuropathy (grade 2 with 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 ≥ 3)	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 Section 12.15)	
< Grade 3	Continue at same dose if initiation of appropriate treatment controls hypertension (see Section 12.12 for guidance)
Grade ≥ 3	Hold carfilzomib until resolution to normal or baseline. Initiate appropriate anti-hypertensive therapy prior to resuming carfilzomib at 1 dose decrement (see Section 12.12 for guidance).
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.
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 at prior dose

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Footnotes defined on last page of this table.

Table 7-4. Dose Modification Guidelines for Nonhematologic Toxicities

For grading criteria, see CTCAE grading scale in Section 12.4.	
Symptom/Sign/Investigation	Recommended Action
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; CTCAE = Common Terminology Criteria for Adverse Events; DBP = diastolic blood pressure; GFR = Glomerular Filtration Rate; 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 estimated GFR or an absolute fall of ≥ 60 mL/min/1.73 m^2, 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 carfilzomib (K), dexamethasone (d), or the combination of Kd to the extent possible. If both carfilzomib and dexamethasone are considered likely to be involved, then recommended actions for both should be instituted.

7.4.1.1.4 Rules for Re-escalation of Carfilzomib Dose Following Toxicity

Conditions of carfilzomib-related toxicity that are not permitted for dose re-escalation:

- Pulmonary hypertension
- Non-infectious pulmonary toxicities (per Table 7-4)
- Congestive heart failure (≥ grade 3)

A reduction in dose level required for any of the adverse events listed above may not be re-escalated. For all other carfilzomib-related toxicities that require dose level reduction, if the reduced dose level is tolerated for 1 full cycle, carfilzomib may be re-escalated at the treating physician's discretion up to the maximum dose planned in that cycle (56 mg/m^2 twice weekly or 70 mg/m^2 once weekly).

7.4.1.2 Non-Amgen/Amgen Non-investigational Product: Dexamethasone

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

For conditions that do not require dexamethasone dose reduction, refer to Section 7.4.1.1.3.

For subjects ≥ 75 years of age, the starting dose of dexamethasone should be 20 mg weekly, 10 mg administered on days 1, 2, 8, 9, 15, 16, 22, and 23 during cycles 1-2, and 20 mg administered on the days 1, 8, 15 during cycles 3-12.

7.4.1.2.1 Dose Reduction Levels

Two dose reduction levels are defined for dexamethasone, as shown in Table 7-5. Dose reductions are permanent and dose must not be increased following a dose reduction.

Table 7-5. Dose Decrements for Dexamethasone

	Reduced Weekly Dexamethasone Doses (mg)	
Nominal Dose (mg)	Dose -1	Dose -2
40	20	12[a]
20	12	8

[a] If the dose needs to be divided over 2 days, administer 8 mg on the first day and 4 mg on the second day.

7.4.1.2.2 Guidelines for Dexamethasone-related Toxicity

Dexamethasone will be permanently discontinued after 2 dose reductions in the event of additional dexamethasone-related toxicities. At the investigator's discretion, dexamethasone may be tapered prior to complete discontinuation according to institutional practice. The subject may continue on treatment with the other protocol-specified drug(s).

Guidelines for dexamethasone-related toxicities are summarized in Table 7-6.

Table 7-6. Treatment Guidelines for Dexamethasone-related Toxicity

Symptom	Findings	Recommended Action
Cardiovascular	Edema > grade 3 (anasarca or limiting function and unresponsive to therapy)	Diuretics as needed, and restart dexamethasone at 1 dose decrement; if edema persists despite above measures, decrease dose by another dose decrement. Discontinue dexamethasone permanently if symptoms persist despite second reduction.
Gastrointestinal Toxicity	Dyspepsia, gastric or duodenal ulcer, or gastritis grade 1 or 2 (requiring medical management)	Continue dexamethasone at same dose and treat with therapeutic doses of histamine 2 (H2) blockers, or proton pump inhibitor. Consider adding sucralfate or other antiulcer treatment as clinically indicated. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
	Dyspepsia, gastric or duodenal ulcer, or gastritis ≥ grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms return to baseline. Restart dexamethasone at 1 dose decrement along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone permanently.
	Acute pancreatitis	Discontinue dexamethasone permanently.
General Disorders	Limb edema > grade 3 (> 30% limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self-care activities of daily living)	Hold dexamethasone until symptoms return to baseline. Diuretics as needed, and restart dexamethasone at 1 dose decrement; if edema persists despite above measures, decrease dose by another dose decrement. Discontinue dexamethasone permanently if symptoms persist despite second reduction.
Psychiatric Disorders	Confusion or mood alteration ≥ grade 2 (interfering with function ± interfering with activities of daily living)	Hold dexamethasone until symptoms return to baseline. Restart dexamethasone at 1 dose decrement. If symptoms persist despite above measures, reduce by another dose decrement.

Table 7-6. Treatment Guidelines for Dexamethasone-related Toxicity

Symptom	Findings	Recommended Action
Musculoskeletal	Muscle weakness ≥ grade 2 (symptomatic and interfering with function ± interfering with activities of daily living)	Decrease dexamethasone by 1 dose decrement. If weakness persists, decrease dose by another dose decrement. Discontinue dexamethasone permanently if symptoms persist.
Metabolism and Nutrition Disorders	Hyperglycemia ≥ grade 3 (fasting glucose > 250 mg/dL)	Treat with insulin or other hypoglycemic agents as needed until glucose is ≤ grade 2 (< 250 mg/dL) then resume dexamethasone. If uncontrolled despite above measures, decrease dose by 1 dose decrement until ≤ grade 2 (< 250 mg/dL).
All Other	Other toxicity ≥ grade 3 felt related to dexamethasone	Hold dexamethasone dose. Resume at 1 dose decrement when toxicity has resolved to ≤ grade 2. If toxicity recurs, hold dexamethasone dose until toxicity has resolved to ≤ grade 2 and resume dexamethasone dose by another dose decrement. If toxicity recurs despite 2 dose decrements, discontinue dexamethasone permanently.

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7.4.1.3 Conditions Not Requiring Dose Reduction

Carfilzomib and dexamethasone 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-gamma-glutamyl transferase elevation
- grade 3 fatigue (unless persisting for > 7 days)
- alopecia

7.4.1.4 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.

7.4.1.5 Non-Amgen Non-investigational Product: Pomalidomide

Pomalidomide 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 pomalidomide for additional details.

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

7.4.2 Hepatotoxicity Stopping and Rechallenge Rules

Hepatotoxicity stopping rules are described in Section 7.4.1.1.3.

7.5 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product 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 site. Oral medicinal products 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

All therapy administered for treatment of MM prior to screening must be captured on the appropriate CRF, regardless of duration of time between prior therapy and screening.

For prior therapies being taken for MM (eg, chemotherapy), collect therapy name, dose, best response, start date and stop date. Prior lines of MM treatment are defined in Section 12.11.

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 30 days prior to enrollment through the end of study.

For concomitant therapies, collect therapy name, indication, dose, unit, frequency, start date and stop date.

Concomitant medications used prophylactically should be described as such on the designated eCRF. Blood and blood products are not considered concomitant medications and must be recorded on the appropriate eCRF.

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 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 investigational product(s) 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
- Requirement for alternative therapy
- 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.

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
- Disease progression (NOTE: safety follow-up visit is required, and will occur 30 (+3) days after the last dose of study drug[s])

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 site.

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 and Enrollment

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 informed consent form, the site will register the subject in the IXRS and screen the subject in order to assess eligibility for participation. The screening window is up to 28 days for bone marrow aspirate, bone lesion assessment, and plasmacytoma assessment and up to 21 days for all other assessments.

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 (for bone marrow aspirate, bone lesion assessment, and plasmacytoma assessment) or a new 21-day (for all other assessments) 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 (for bone marrow aspirate, bone lesion assessment, and plasmacytoma assessment) or more than 21 days (for all other assessments) 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). The date of the first dose of carfilzomib is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. All 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 (see Section 7.1.1.2 for additional details). Administration of protocol-required therapies is to be administered last during each visit that it is required.

9.1.3 Safety Follow-up

Once a subject discontinues from the study drug (see Section 8.1), he/she will have a safety follow-up visit 30 (+3) days after the last dose of study drug(s) unless the subject is lost to follow-up, has withdrawn consent, or has died. After the safety follow-up, subjects who remain on study are required to complete disease response assessments and will be followed for subsequent antimyeloma treatment every 28 ± 7 days until up to 12 months from enrollment, death, loss to follow-up, withdrawal of consent or progressive disease (PD), whichever occurs first.

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 must sign and personally date the IRB-approved informed consent before any study-specific procedures are performed.

9.2.1.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.

9.2.1.3 Medical History

The investigator or designee will collect a complete medical and surgical history that started within 5 years prior to enrollment through signing of the ICF. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF. The current toxicity grade will be collected for each condition that has not resolved. Cardiovascular risk factors are to be recorded for the subject including history of cardiovascular disease (heart attack, stroke, peripheral vascular disease), arrhythmias and previous abnormal ECG findings (eg, ventricular hypertrophy and/or ischemic changes), hypertension (include treatment history), thromboembolism, hyperlipidemia (include statin use), and diabetes. Family history of coronary artery disease in first degree relatives with onset < 65 years of age for female relative or < 55 years of age for male relative should also be recorded.

In addition to the medical history above, multiple myeloma history must date back to the original diagnosis. For subjects who were previously referred to a research site, critical referral information will constitute multiple myeloma information from source notes.

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 CRF (eg, medical history, event). A complete physical examination includes examination of cardiovascular and respiratory systems, abdominal examination, and general neurologic examination. Clinically significant abnormal physical examination findings identified prior to the signing of the ICF should be reported as part of medical history, not as adverse events.

9.2.1.5 Physical Measurements

9.2.1.5.1 Height and Weight

Height in centimeters is to be measured without shoes. Weight in kilograms is to be measured without shoes.

9.2.1.5.2 Body Mass Index

Body Mass Index (BMI) is to be calculated using the following formula:

$BMI\ (kg/m^2) = weight\ (kg)/(height\ [cm]/100)^2$

9.2.1.5.3 Body Surface Area

Body Surface Area (BSA) is to be calculated using the Mosteller formula:

$BSA\ (m^2) = ([Height(cm) \times Weight(kg)] / 3600)^{½}$

9.2.1.6 Substance Abuse History

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

9.2.1.7 Performance Status

The subject's performance status will be assessed using the ECOG PS (Section 12.10).

9.2.2 Efficacy Assessments

Investigators are required to follow International Myeloma Working Group (IMWG) criteria for assessment of response and disease progression (see Section 12.8).

Disease assessments are required during screening to confirm eligibility and for determination of disease response (per the Schedule of Activities, Table 2-1). Per IMWG, determination of disease response requires: serum free light chain (SFLC), serum and urine protein electrophoresis (SPEP, UPEP, respectively), serum and urine immunofixation (SIFE, UIFE, respectively), bone marrow aspirate (for CR confirmation; Section 9.2.2.1), corrected calcium, and plasmacytoma evaluation, if present at screening (Section 9.2.2.3).

Investigators are responsible for the determination of response and disease progression. Disease assessments based on local laboratory data will start on day 1 of cycle 1 and are performed every 28 (± 7) days regardless of cycle duration, including dose delays until confirmed PD or cycle 12. The cycle 12 disease assessment is conducted 28 (± 7) days post cycle 12, day 1.

Subjects who discontinue treatment prior to confirmed PD should continue to complete disease assessments until up to 12 months from enrollment, death, loss to follow-up, withdrawal of consent or PD, whichever occurs first.

9.2.2.1 Bone Marrow Sample Evaluation Including FISH Assessment

A baseline bone marrow sample evaluation with fluorescence in-situ hybridization (FISH, aspirate slides and/or biopsy) will be performed prior to first dose and will be used to confirm the diagnosis and quantify the percent (%) of myeloma cell involvement. Biopsy or aspirate slides obtained as standard of care may be used as baseline if performed within 28 days of cycle 1 day 1.

Additional bone marrow biopsy or aspirate should be obtained as clinically indicated to confirm a response of CR or stringent CR.

9.2.2.2 Bone Lesion Assessment (Skeletal Survey, Computed Tomography, or Positron Emission Tomography/Computed Tomography)

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 (CT) or fluorodeoxyglucose-positron emission tomography/computed tomography (PET/CT) may be used in place of skeletal survey. Bone lesion assessment will be conducted at screening and for confirmation of PD, if PD is based on bone lesions (see IMWG criteria in Section 12.8). Bone lesion assessments obtained as part of standard of care may be used as baseline if performed within 28 days of cycle 1 day 1. The same method of assessment used at baseline will be used throughout the study. These imaging studies will be read locally.

9.2.2.3 Extramedullary Plasmacytoma

Extramedullary plasmacytoma evaluation will be conducted at screening only if a lesion is clinically suspected. The evaluation may be performed within 28 days of cycle 1 day 1 if performed as a part of standard of care. If an extramedullary plasmacytoma is detected, evaluation will be repeated to confirm a response of MR or better or to confirm PD (see IMWG criteria in Section 12.8). Assessment of sites of extramedullary disease measurable by physical examination may be performed once per cycle. If assessment

can only be performed radiologically, then evaluation of extramedullary plasmacytomas should be done to confirm a response or as clinically indicated. 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 (Section 12.8). Bidimensional lesion measurements should be performed (see Section 9.2.2.3.1).

9.2.2.3.1 Sum of Perpendicular Dimensions

Response and progression of soft tissue plasmacytomas or progression of bone lesions should be determined by the change in the sum of perpendicular dimensions (SPD) measured radiographically or by physical examination, as clinically indicated.

The SPD is defined as the sum of the longest dimension added to the second longest dimension that is perpendicular to the longest dimension. Sum of perpendicular dimensions of bone lesions will be measured only for evidence of progression. The SPD for a bone lesion is defined the same as it is for a plasmacytoma. An increase of 50% or more from the nadir in the size of any bone lesion provides evidence for PD, see Section 12.8 for more details.

9.2.2.4 Progressive Disease Assessment

Progressive disease (including PD due to development of hypercalcemia attributed solely to recurrence/progression of multiple myeloma) will be based on local laboratory evaluation. Confirmation of PD (using 2 consecutive assessments) will be required only when it is determined by laboratory evaluations and not if identified via imaging as per IMWG criteria. The assessments outlined in Section 12.8 are required for determination of PD. Subjects should 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 should not 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 study drug(s) are reported using the Event CRF.

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 study drug(s) are reported using the Event CRF.

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

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. Per local requirements in some countries, investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge 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.

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 CRF.

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, 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 Investigator's Brochure and will notify the IRB, if appropriate according to local requirements.

9.2.3.1.5 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and, if indicated, 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 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 at screening should be the same that is used throughout the study and documented on the vital signs CRF. Take at least 2 blood pressure measurements spaced 1 to 2 minutes apart and additional measurements if the first 2 are quite different (Section 12.15). Record the average blood pressure on the vital signs CRF.

The temperature location selected for a subject at screening should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

9.2.3.3 Electrocardiograms (ECGs)

Electrocardiograms will be required for all subjects at screening.

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 PI or designated site physician) will review all ECGs. The presence of a low voltage ECG coded on the ECG output, will be entered on the appropriate eCRF. 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.

9.2.3.4 Other Safety

9.2.4 Echocardiogram

All subjects will have a baseline transthoracic echocardiogram during screening, including assessments of systolic and diastolic left ventricular function and right ventricular function, valvular insufficiency, right ventricular systolic pressure, intraventricular wall thickness, left and right ventricular wall thickness and left ventricular mass index, mitral annular early diastolic velocity, and left atrium value index.

9.2.5 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 CRF. 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 Schedule of Activities (Table 2-1).

9.2.5.1 Pregnancy Testing

A serum or urine pregnancy test must be completed at screening. A highly sensitive (urine or serum) pregnancy test should be completed within 24 hours of initiation of investigational/noninvestigational product for females of childbearing potential (FCBP).

Note: Females who have undergone a bilateral tubal ligation/occlusion should have 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 Worksheet, see Figure 12-2). Refer to Section 12.5 for contraceptive requirements. Additional pregnancy testing must also be performed during treatment, as per the Schedule of Activities (Table 2-1) and at the safety follow-up visit.

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

9.2.6 Clinical Outcome Assessments

9.2.6.1 European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30)

The European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30) is a questionnaire developed to assess the quality of life of cancer patients (Bjordal et al, 2000).

EORTC QLQ-C30 includes 30 items grouped into:

- five quality of life categories: physical, social, emotional, cognitive and role performance;
- three scales of symptoms: fatigue, pain, and nausea and vomiting;
- a global scale of quality-of-life and individual items related to the symptoms of the disease and its treatment; dyspnea, insomnia, loss of appetite, constipation, diarrhea and
- an item on economic impact

The responses to the scale items refer to "last week," with the exception of the subject's physical performance scale, where the timeframe involved is the present.

9.2.6.2 European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Multiple Myeloma Module (EORTC QLQ-MY20)

In addition to the QLQ-C30, a number of disease-specific modules have been produced by the EORTC. This modular approach was adopted by EORTC in recognition of the limitations of generic patient-reported outcome instruments to provide an appropriate coverage of disease-specific concerns. Modules specific to tumor site, treatment modality, and quality of life have been developed. These were designed to be administered alongside the core questionnaire (QLQ-C30); like the core questionnaire, the modules were designed for use in cancer clinical trials. The MM module (the QLQ-MY20) was developed by EORTC in 1999 (Bjordal et al, 2000). A summary of the QLQ-C30 and QLQ-MY20 subscales are provided in Section 12.16.

[redacted]

[redacted]

10. Statistical Considerations

10.1 Sample Size Determination

The study is descriptive in nature. Approximately 75 subjects will be enrolled in the study with approximately 25 subjects in each treatment arm.

The sample size is assessed in terms of the expected levels of precision for estimating the proportion of subjects completing 12 cycles of treatment, relative dose intensity (%), and incidence of adverse events.

With a sample size of 25 subjects for each treatment arm, assuming 50%, 75%, or 90% of subjects will complete 12 cycles of treatment, the expected half-widths of the 95% CI for estimating the proportion of subjects completing 12 cycles of treatment are calculated as below.

Sample Size	95% Confidence Interval Half-width (%)		
	50%	75%	90%
25	20.5	18.1	13.5

In the A.R.R.O.W. trial, the mean (standard deviation) of relative dose intensity of carfilzomib is 92.2 (11.2) in Once-weekly subjects. In this study with a sample size of 25 subjects in each treatment arm, assuming standard deviation ranges from 5% to 15%, the expected half-widths of the 95% CI for estimating the mean relative dose intensity are calculated as below.

Sample Size	95% Confidence Interval Half-width (%)		
	SD = 5	SD = 10	SD = 15
25	2.0	3.9	5.9

For subject incidence of adverse events of 1%, 5%, 10%, 50%, 80%, the expected half-widths of the 95% confidence interval (CI) for estimating the subject incidences of adverse events are calculated as below.

Sample Size	95% Confidence Interval Half-width (%)				
	1%	5%	10%	50%	80%
25	7.8	10.8	13.5	20.5	16.9

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

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

Safety Analysis Set: The safety population will include all enrolled subjects who received at least 1 dose of any study treatment (ie, carfilzomib, dexamethasone, lenalidomide, or pomalidomide).

The full analysis set will be the same as the safety analysis set for this study.

10.2.2 Covariates

The following covariates will be used to examine primary and secondary endpoints in subgroups as appropriate:

Baseline demographics and characteristics:

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

Baseline organ function and comorbid conditions:

- ECOG performance status (0 or 1)
- estimated GFR (< 50 vs ≥ 50 mL/min/1.73 m^2)
- hypertension history (include use of anti-hypertensive medications) (yes, no)
- history of ischemic heart disease (myocardial infarction or coronary artery disease), congestive heart failure (NYHA class ≤ 2), stroke, or history of peripheral vascular disease (yes, no)
- family history of coronary artery disease in first degree relatives with onset < 65 years of age for female relative or < 55 years of age for male relative (yes, no)
- smoking history (yes, no)
- history of hyperlipidemia (yes, no)
- history of diabetes (yes, no)
- history or chronic mild hepatic impairment (yes, no; see Section **7.4.1.1.1**)

Baseline disease characteristics:

- revised international staging system stage (stage 1 vs stage 2 vs stage 3 vs unknown)
- determination of measurable disease at baseline (based on serum or urine M−protein, based on SFLC only)
- β2-microglobulin level (< 2.5, ≥ 2.5 and < 5.5, ≥ 5.5 mg/L)
- presence of soft tissue plasmacytoma (yes, no)
- progressive disease on lenalidomide during or within 60 days of discontinuation of treatment (yes, no)

10.2.3 Subgroups

The subgroups defined by covariates stated above will be used to examine primary and secondary endpoints as appropriate, including examination of safety in subgroups as appropriate. The subgroup analysis will not be carried out if the number of subjects in a subgroup for any treatment arm is smaller than 20% of the total number of subjects in the treatment arm.

10.2.4 Handling of Missing and Incomplete Data

Subjects may have missing data points for a variety of reasons. The procedures outlined below describing what will be done when data are missing may be refined during the blind review of the data.

Incomplete adverse event start dates, concomitant medications start or stop dates, and death date will be imputed and the detailed rules will be specified in statistical analysis plan (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 Data Review Team

A Data Review Team (DRT) will review safety data for the KPd treatment arm on an ongoing basis. A DRT is a group, internal to Amgen but external to the relevant carfilzomib product team, that reviews accumulating data from the ongoing clinical trial to ensure no avoidable increased risk for harm to subjects. The DRT includes a clinician, a

safety physician, and a biostatistician. Membership procedures and meeting timing will be described in detail in the study DRT charter.

10.3.1.2 Final Analysis

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

10.3.2 Methods of Analyses

10.3.2.1 General Considerations

In principle, summary statistics including non-missing sample size (n) mean, standard deviation, median, minimum and maximum quartiles, will be provided for continuous variables. Frequency and percentage will be summarized for binary and categorical variables. Proportions and the corresponding 95% confidence intervals will be based on normal approximations unless otherwise specified. The Clopper-Pearson method of exact binomial confidence intervals will be used to calculate the confidence intervals as appropriate.

Details of all the analyses will be provided in the statistical analysis plan, which will be developed and finalized before database lock. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 5.3.1.

10.3.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Not applicable
Secondary	Unless otherwise specified, the following analyses will be based on the safety analysis set. The analyses will be carried out for subjects on the Kd, KRd, and KPd regimens, respectively. All EORTC QLQ-C30 and EORTC QLQ-MY20 subscale scores up to cycle 12 or disease progression will be summarized descriptively by cycle. The rate of PFS at 1 year will be estimated using the Kaplan-Meier method and with CI estimated using the method by Kalbfleisch and Prentice, 1980 with log-log transformation. The response rate and 1-year PFS rate will be summarized descriptively by line of prior therapy 1 vs ≥ 2.
Exploratory	[redacted]

10.3.2.3 Safety Analyses

10.3.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	Unless otherwise specified, following analyses will be based on the safety analysis set. The analyses will be carried out for subjects on the Kd, KRd, and KPd regimens, respectively. The proportion of subjects completing 12 cycles of Kd, KRd, and KPd treatment will be calculated based on the safety analysis set. The proportion of actual cumulative dose received to the full intended cumulative dose in cycles 1-12 will be summarized descriptively. The full intended cumulative dose is defined as all therapy specified per Sections 7.1.1.2 and 7.1.2 without consideration for dose modification or skipped doses. Relative dose intensity in cycles 1-12 will be summarized descriptively. Dose modifications including dose reduction, dose withheld, and dose delay in cycles 1-12 will be summarized along with reasons including adverse events and non-adverse events. Treatment-emergent adverse events and serious adverse events in cycles 1-12 will be summarized descriptively following the methods specified in Section 10.3.2.3.
Secondary	Not applicable
Exploratory	Not applicable

10.3.2.3.2 Adverse Events

Subject 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 significant treatment emergent adverse events will also be provided.

10.3.2.3.3 Laboratory Test Results

The analyses of safety laboratory endpoints will include summary statistics over time. Post dose shifts in grades of safety laboratory values relative to baseline will be tabulated.

10.3.2.3.4 Vital Signs

The analyses of vital signs will include summary statistics over time.

10.3.2.3.5 Physical Measurements

The analyses of physical measurements will include summary statistics over time.

10.3.2.3.6 Electrocardiogram

The ECG measurements from this clinical study will be performed as per standard of care for routine monitoring, rather than for purposes of assessment of potential QTc

effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials.

10.3.2.3.7 Exposure to Investigational Product

The number of days on investigational product, the daily dose, the total dose of investigational product, and the proportion of subjects receiving each dose level will be summarized using descriptive statistics.

10.3.2.3.8 Exposure to Other Protocol-required Therapy

Descriptive statistics will be produced to describe the exposure to other protocol-required therapies, if relevant.

10.3.2.3.9 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized by preferred term as coded by the World Health Organization Drug (WHODRUG) dictionary.

10.3.2.4 Other Analyses

The descriptive summary of cardiopulmonary events by baseline covariates to be specified in the SAP may be performed.

The descriptive summary of cardiovascular reasons for screen failure will be captured for exclusion criteria 230-234 (Section 6.2) from the IXRS system. The specific analyses will be specified in the SAP.

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

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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
[redacted]	
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BMI	body mass index
BNP	brain natriuretic peptide
BSA	body surface area
CFR	US Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COA	Clinical Outcome Assessment
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CT	computed tomography
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	electronic data capture
eCRF	electronic case report form
End of Treatment	defined as the last day the subject receives protocol-specified treatment for an individual subject
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
EORTC QLQ-MY20	European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Multiple Myeloma Module
FCBP	females of childbearing potential
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HR	hazard ratio
HRQoL	health-related quality-of-life
ICF	informed consent form
ICH	International Council for Harmonisation
Ig	immunoglobulin
IMiD	immunomodulatory drug

Abbreviation or Term	Definition/Explanation
IMWG	International Myeloma Working Group
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
IV	intravenous
K	Kyprolis
Kd	carfilzomib with dexamethasone regimen
Kd56	Kd 56 mg/m^2 twice weekly
Kd70	Kd 70 mg/m^2 once weekly
KPd	carfilzomib with pomalidomide and dexamethasone regimen
KPd27	KPd 27 mg/m^2 twice weekly
KPd56	KPd 56 mg/m^2 once weekly
KRd	carfilzomib with lenalidomide and dexamethasone regimen
KRd27	KRd 27 mg/m^2 twice weekly
KRd56	KRd 56 mg/m^2 once weekly
MM	multiple myeloma
MR	minimal response
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET/CT	positron emission tomography/computed tomography
PFS	progression-free survival
PI	proteasome inhibitor
PR	partial response
PRES	posterior reversible encephalopathy syndrome
RBC	red blood cell
RRMM	relapsed or refractory multiple myeloma
SAP	Statistical Analysis Plan
sCR	stringent complete response
SFLC	serum free light chain
SIFE	serum immunofixation

Abbreviation or Term	Definition/Explanation
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 trial 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	sum of perpendicular dimensions
SPEP	serum protein electrophoresis
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
TLS	tumor lysis syndrome
TMA	thrombotic microangiopathy
UIFE	urine immunofixation
UPEP	urine protein electrophoresis
ULN	upper limit of normal
US	United States
Vd	bortezomib with dexamethasone regimen
VGPR	very good partial response

12.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 12-1 will be performed by a local laboratory.

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

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

Screening only	Chemistry	Hematology	Other Labs
β-2 microglobulin	Albumin	Hemoglobin	Serum or Urine Pregnancy
Bone marrow aspirate with FISH	ALP	Hematocrit	
Creatinine	ALT (SGPT)	Platelets	
Glucose (fasting)	AST (SGOT)	RBC	
HbA1c	Bicarbonate	WBC	
LDH	BUN or Urea	Differential	
Lipid panel (fasting):	Calcium	• Bands/stabs	
•Total cholesterol	Chloride	• Eosinophils	
•HDL	Creatinine	• Basophils	
•LDL	Glucose	• Lymphocytes	
•triglycerides	Magnesium	• Monocytes	
NT-proBNP (or BNP)[a]	Phosphorus	• Neutrophils	
SFLC	Potassium		
SIFE	Sodium		
SPEP	Total bilirubin		
UIFE	Direct bilirubin		
UPEP	Total protein		
Uric acid			
Urine albumin			
Urine creatinine			

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BNP = brain natriuretic peptide; BUN = blood urea nitrogen; FISH = fluorescence in-situ hybridization; HbA1c = hemoglobin A1c; HDL = high-density lipoproteins; LDH = lactate dehydrogenase; LDL = low-density lipoproteins; NT-proBNP = N-terminal of the prohormone brain natriuretic peptide; RBC = red blood cells; SFLC = serum free light chain; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamate-pyruvate transaminase; SIFE = serum immunofixation electrophoresis; SPEP = serum protein electrophoresis; UIFE = urine immunofixation electrophoresis; UPEP = urine protein electrophoresis; WBC = white blood cells.
[a] Either NT-proBNP or BNP may be used per investigator's discretion.

12.3 Appendix 3. Study Governance Considerations

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 International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board (IRB) by the investigator and reviewed and approved by the IRB. 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 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 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 annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
- Obtaining annual IRB approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be sent to Amgen
- Notifying the IRB 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 U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB, 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 (Amgen Inc.) and the local IRB.

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 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 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 or study site.

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 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.

If a potential subject is illiterate or visually impaired, 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.

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 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 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 Quality, 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.

Amgen (or designee) will perform Self-Evident Corrections to obvious data errors in the clinical trial database. Self-Evident Corrections will be documented in the CRF Standard Instructions and the CRF Specific Instructions, both of these will be available through the electronic data capture (EDC) system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same date with different visit) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).

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/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 clinical outcome assessment).

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.

Elements to include:

- 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 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 site 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 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.
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, 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, metastatic pancreatic cancer). 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 in-patient 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
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). • The investigator must assign the following adverse event attributes: o Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms); o Dates of onset and resolution (if resolved); o Severity (or toxicity grade defined below); o Assessment of relatedness to carfilzomib; and o Action taken. • 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 sponsor in lieu of completion of the Event CRF page. • 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 attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the 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 4.03 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 procedure 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.
- 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.
- 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 Safety Report Form.
- If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an electronic Serious Adverse 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 a paper Serious Adverse Event Report Form (see Figure 12-1).

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

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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 # 20170596
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? PEMBRO No✓ PEMBRO Yes✓ PEMBRO No✓ PEMBRO Yes✓ PEMBRO No✓ PEMBRO Yes✓ PEMBRO No✓ PEMBRO Yes✓	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐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:		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 #
	☐blinded ☐open label							Lot #_____ ☐ Unknown Serial #_____ ☐ Unavailable / Unknown
	☐blinded ☐open label							Lot #_____ ☐ Unknown Serial #_____ ☐ Unavailable / Unknown

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AMGEN Study # 20170596 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											

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 # 20170596 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 - *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.*	Title	Date

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

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

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.

Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use highly effective methods of contraception and/or for an increased length of time. In addition, male subjects may also be required to use contraception for an increased length of time. The investigator must discuss these contraceptive changes with the subject.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- 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 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.

Contraception Methods for Female Subjects

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 trial and the preferred and usual lifestyle of the subject)

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 trial and the preferred and usual lifestyle of the subject)
- Use a condom during treatment and for an additional 90 days after the last dose of protocol-required therapies

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 must not donate sperm during treatment and for an additional 90 days after the last dose of carfilzomib.

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.

Unacceptable Methods of Birth Control for Male and Female Subjects

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

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

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 Worksheet (see Figure 12-2). The worksheet 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 Worksheet 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 the study drug. 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 report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate 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 experiences 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 post-study 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 or Were Pregnant at the Time of Enrollment

- 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 Worksheet. The worksheet (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 Worksheet 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.

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 Worksheet (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.
- 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 Worksheet

Amgen Proprietary - Confidential

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: 20170596

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: 20170596

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

Not applicable.

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 7.4.1.1.3.

12.8 Appendix 8. International Uniform Response Criteria for Multiple Myeloma

Summary of International Myeloma Working Group Uniform Response Criteria (IMWG-URC).

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 and • Normal SFLC ratio and • Absence of clonal plasma cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤ 4:1 or ≥ 1:2 for κ and λ patients, respectively, after counting ≥ 100 plasma cells)
CR	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow • In patients with measurable disease only by SFLC, normal SFLC ratio (0.26 to 1.65)
VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-component with urine M-component < 100 mg per 24 hours (requires a 24-hour urine collection) • In patients with measurable disease only by SFLC, a decrease ≥ 90% in the difference between involved and uninvolved FLC levels
PR	• ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours (if both are measurable at baseline) • In patients 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. • If the serum and urine M-protein are not measurable, and SFLC assay is also not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥ 30%. • In addition to the above criteria, if present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.
MR	• ≥ 25% but ≤ 49% reduction of serum M-protein and reduction in 24-hour urinary M-protein by 50% to 89%. In addition to the above listed criteria, if present a baseline a ≥ 50% reduction in the size (SPD) of soft tissue plasmacytoma is required

Page 1 of 2

Footnotes defined on next page

Response Subcategory	Multiple Myeloma Response Criteria
Stable Disease	• Not meeting criteria for CR, VGPR, PR, or PD
PD	• Increase of 25% from lowest response value in any of the following: – Serum M-component (absolute increase must be ≥ 0.5 g/dL) – Serum M-protein increase ≥ 1 g/dL, if the lowest M component was ≥ 5 g/dL – Urine M-component (absolute increase must be ≥ 200 mg per 24 hours) – In patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) – In patients without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥ 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in size of existing bone lesions or soft tissue plasmacytomas, ≥ 50% increase from nadir in SPD of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion that is > 1 cm in short axis. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD. • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.75 mmol/L) attributed solely to the plasma cell proliferative disorder.

Page 2 of 2

CR = complete response; CT = computed tomography; MR = minimal response; MRI = magnetic resonance imaging; PD = progressive disease; PET/CT = positron emission tomography/computed tomography; PR = partial response; sCR = stringent complete response; SFLC = serum free light chain; SPD = sum of the products of the maximal perpendicular diameters of measured lesions; VGPR = very good partial response.

All response categories (complete response [CR], stringent complete response [sCR], very good partial response [VGPR], partial response [PR]) require 2 consecutive assessments made at any time 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.

For sCR: presence/absence of clonal cells in bone marrow is based upon the normalization of kappa lambda ratio. “Measurable” disease is defined by at least one of serum protein electrophoresis (SPEP) ≥ 1.0 g/dL, urine protein electrophoresis (UPEP) ≥ 200 mg per 24 hours, or in subjects without detectable serum or urine

M-protein, serum free light chain (SFLC) ≥ 100 mg/L (involved light chain) and an abnormal kappa lambda ratio.

Determination of progressive disease (PD) while on study requires 2 consecutive assessments made at any time before classification of PD and/or the institution of new therapy. Serum M-component increases of ≥ 1 g/dL from nadir are sufficient to define progression if nadir M-component is ≥ 5 g/dL.

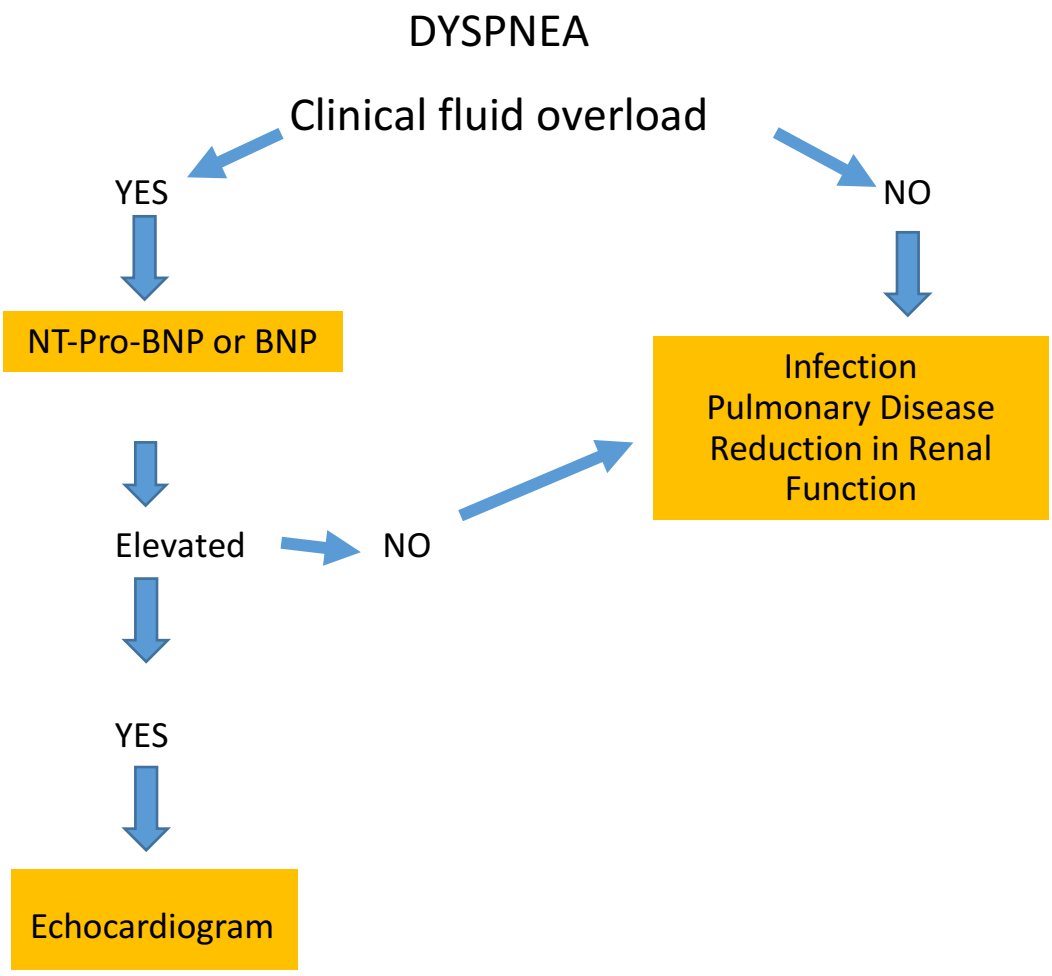
Plasmacytomas: A definite increase in the size is defined as a ≥ 50% increase from nadir as measured serially by the sum of the products of the maximal perpendicular diameter (SPD) of the measurable lesion or a ≥ 50% increase in the longest diameter of a previous lesion with ≥ 1 cm short axis. A plasmacytoma 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. Plasmacytomas of lesser size will be considered non-measurable. The requirement for bi-directional measurements applies only to plasmacytomas. The plasmacytoma specifications for PD are based on the sponsor's interpretation of the IMWG-URC and practical considerations for study execution.

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

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

12.9 Appendix 9. Guidance for Dyspnea Adverse Events

If a subject reports dyspnea, it is recommended that subject be evaluated clinically for fluid overload. If clinical fluid overload is present (eg, > 5% weight gain, peripheral edema, jugular venous distension) obtain an N terminal of the prohormone brain natriuretic peptide (NT-Pro-BNP) or brain natriuretic peptide (BNP) (use same test as was used at baseline evaluation) and serum creatinine. If the NT-Pro-BNP (or BNP) is elevated or higher than baseline, obtain an echocardiogram within 72 hours of onset of dyspnea or as soon as possible. In the absence of clinical evidence of fluid overload or if otherwise clinically indicated, it is recommended to evaluate for the present of infection, pulmonary disease (including pulmonary embolus), or significant reduction in renal function.



12.10 Appendix 10. Eastern Cooperative Oncology Performance Status

GRADE	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, 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

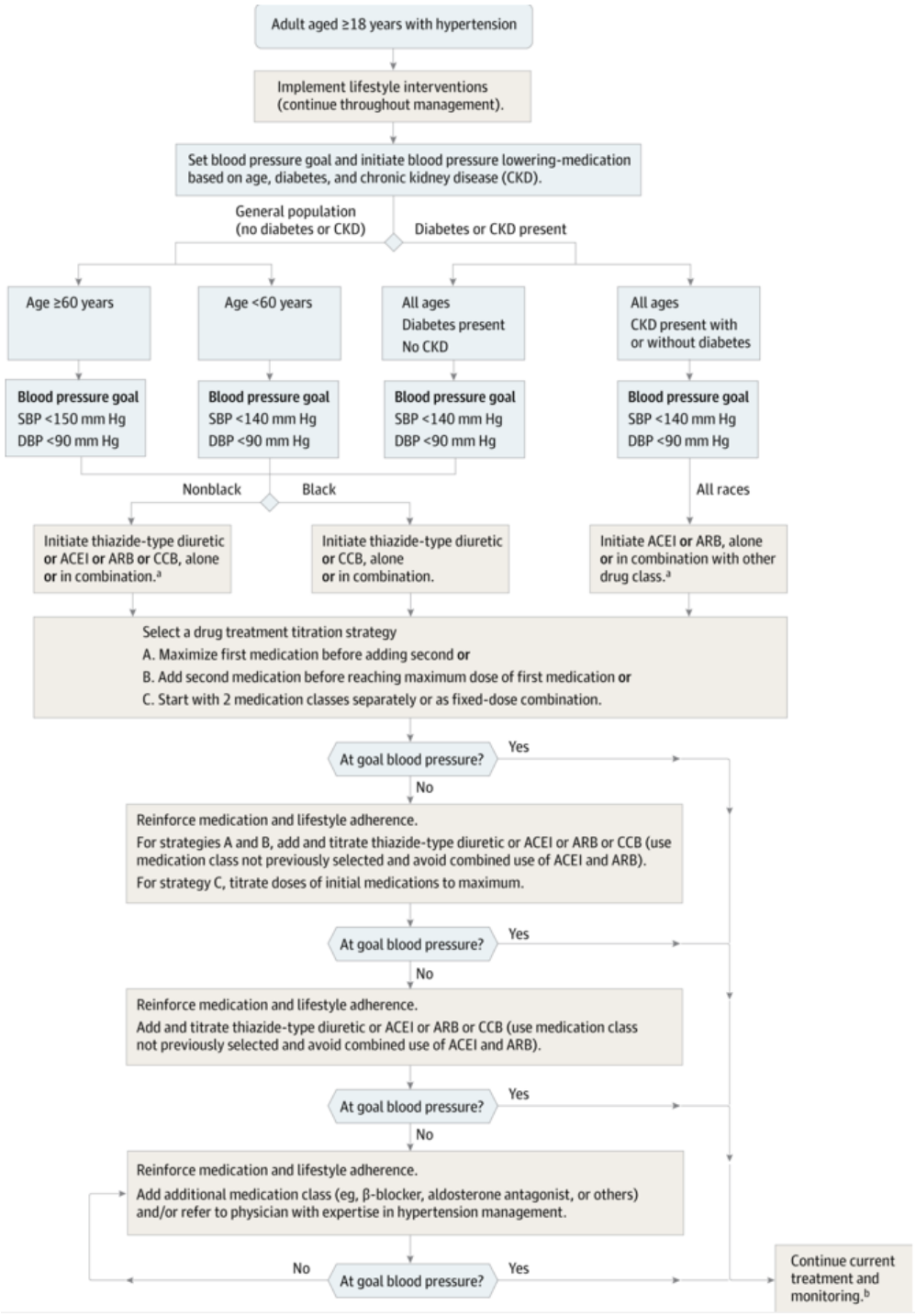
Source: Oken et al, 1982.
Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair

12.11 Appendix 11. Guidelines for Documenting Prior Treatment

Patients must have documented relapse after at least 1, but no more than 3 prior treatment regimens or lines of therapy for multiple myeloma. When documenting prior treatments for multiple myeloma, the following guidelines should be used (Rajkumar et al, 2015):

- 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 patient 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 off 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 patient was not removed from carfilzomib therapy due to toxicity must also be available. For patients with prior therapy with carfilzomib, the start of the 6-month treatment-free interval is when carfilzomib is discontinued even if other portions of the regimen are continued.

12.12 Appendix 12. 2014 Antihypertensive Management by Joint National Committee 8 (JNC8)



2014 Hypertension Guideline Management Algorithm (James et al, 2014)
ACEI = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; DBP = diastolic blood pressure; SBP = systolic blood pressure.
[a] ACEIs and ARBs should not be used in combination.
[b] If blood pressure fails to be maintained at goal, reenter the algorithm where appropriate based on the current individual therapeutic plan.

12.13 Appendix 13. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation

Table 12-2. CKD-EPI Equation for Estimating Glomerular Filtration Rate (GFR) Expressed for Specified Race, Sex, and Serum Creatinine in mg/dL

Race	Sex	Serum Creatinine, S_{cr} (mg/dL)	Equation (age in years for ≥ 18)
Black	Female	≤ 0.7	$GFR = 166 \times (S_{cr}/0.7)^{-0.329} \times (0.993)^{Age}$
Black	Female	> 0.7	$GFR = 166 \times (S_{cr}/0.7)^{-1.209} \times (0.993)^{Age}$
Black	Male	≤ 0.9	$GFR = 163 \times (S_{cr}/0.9)^{-0.411} \times (0.993)^{Age}$
Black	Male	> 0.9	$GFR = 163 \times (S_{cr}/0.9)^{-1.209} \times (0.993)^{Age}$
White or other	Female	≤ 0.7	$GFR = 144 \times (S_{cr}/0.7)^{-0.329} \times (0.993)^{Age}$
White or other	Female	> 0.7	$GFR = 144 \times (S_{cr}/0.7)^{-1.209} \times (0.993)^{Age}$
White or other	Male	≤ 0.9	$GFR = 141 \times (S_{cr}/0.9)^{-0.411} \times (0.993)^{Age}$
White or other	Male	> 0.9	$GFR = 141 \times (S_{cr}/0.9)^{-1.209} \times (0.993)^{Age}$

Source: Levey et al, 2009.

CKD-EPI equation expressed as a single equation (Levey et al, 2009):

$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] x 1.159 [if black]

where:

- Scr is serum creatinine in mg/dL
- κ is 0.7 for females and 0.9 for males
- α is -0.329 for females and -0.411 for males
- min indicates the minimum of S_{cr}/κ or 1, and
- max indicates the maximum of S_{cr}/κ or 1.

12.14 Appendix 14. Venous Thromboembolic Disease (VTE) Risk Assessment and Prophylaxis for Multiple Myeloma

Table 1. VTE Risk Assessment and Prophylaxis for Multiple Myeloma Patients

Risk Factors	Recommendation
BMI ≥30 kg/m^2 History of VTE CVA device or pacemaker Comorbidities: heart disease, kidney disease, diabetes mellitus, infection, immobilization Surgery Erythropoietin use Clotting disorder	≤1 risk factor: aspirin 81-325 mg daily ≥2 risk factors: LMWH (enoxaparin 40 mg once daily) or full-dose warfarin (target INR 2-3)
Thalidomide or lenalidomide in combination with HD dexamethasone (≥480 mg/month), doxorubicin, multiagent chemotherapy	LMWH (enoxaparin 40 mg once daily) or full-dose warfarin (target INR 2-3)

BMI: body-mass index; CVA: central venous access; HD: high-dose; INR: international normalized ratio; LMWH: low-molecular-weight heparin; VTE: venous thromboembolism. Source: Reference 1.

Source: Streiff et al, 2011.

12.15 Appendix 15. 2013 European Society of Hypertension/European Society of Cardiology Office Blood Pressure Measurement

Table 5 Office blood pressure measurement

When measuring BP in the office, care should be taken:
• To allow the patients to sit for 3–5 minutes before beginning BP measurements.
• To take at least two BP measurements, in the sitting position, spaced 1–2 min apart, and additional measurements if the first two are quite different. Consider the average BP if deemed appropriate.
• To take repeated measurements of BP to improve accuracy in patients with arrhythmias, such as atrial fibrillation.
• To use a standard bladder (12–13 cm wide and 35 cm long), but have a larger and a smaller bladder available for large (arm circumference >32 cm) and thin arms, respectively.
• To have the cuff at the heart level, whatever the position of the patient.
• When adopting the auscultatory method, use phase I and V (disappearance) Korotkoff sounds to identify systolic and diastolic BP, respectively.
• To measure BP in both arms at first visit to detect possible differences. In this instance, take the arm with the higher value as the reference.
• To measure at the first visit, BP 1 and 3 min after assumption of the standing position in elderly subjects, diabetic patients, and in other conditions in which orthostatic hypotension may be frequent or suspected.
• To measure, in case of conventional BP measurement, heart rate by pulse palpation (at least 30 s) after the second measurement in the sitting position.

BP = blood pressure.

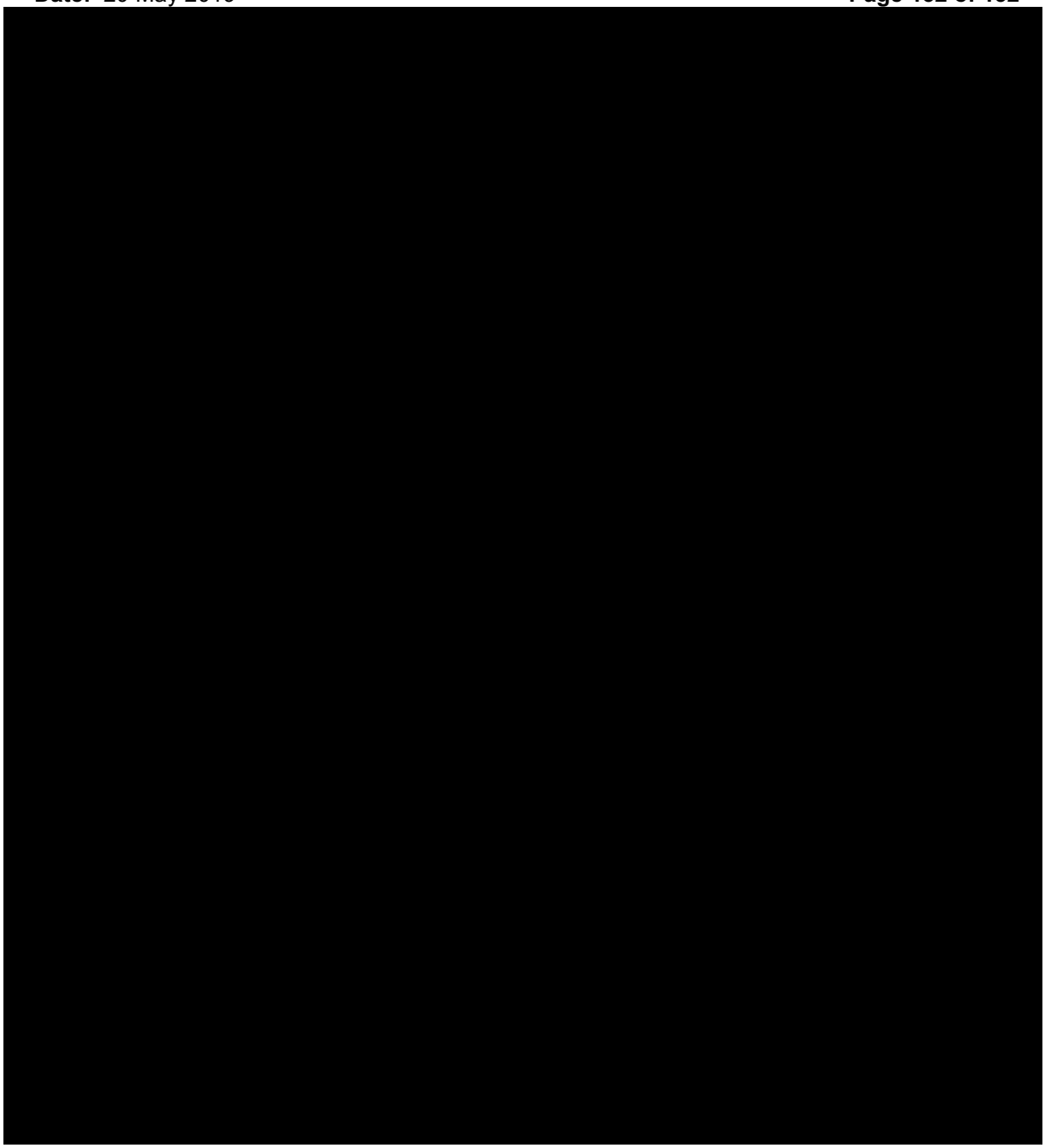
12.16 Appendix 16. Overview of QLQ-C30 and QLQ-MY20 Scales

	QLQ-C30	QLQ-MY20
Total number of items	30	20
Subscales	▪ 5 functional scales – Physical functioning – Role functioning – Emotional functioning – Cognitive functioning – Social functioning ▪ 3 symptom scales – Fatigue – Pain – Nausea and vomiting ▪ A global health status (GHS)/Quality of life (QOL) scale ▪ Single items – Additional symptoms (dyspnoea, appetite loss, insomnia, constipation, and diarrhoea) – Financial difficulties	▪ Disease symptoms ▪ Side effects of treatment ▪ Body image ▪ Future perspectives
Response scales	4- or 7-point scales	4-point scale
Score range	0-100 (high score = high response) ▪ Functional scales: High score = better functioning, ▪ GHS/QOL: High score = better GHS/QOL, ▪ Symptom scales and single symptom items: High score = worse symptoms	0-100 (high score = high response) ▪ Disease symptoms and side effects of treatments scales: High score = worse symptoms ▪ Body image and future perspectives scales: High score = better functioning
Recall period	Past week	Past week

QOL = quality of life.

Source: Bjordal et al, 2000.

[redacted]



Amendment 4

Protocol Title: An Open Label Phase 2 Study of Carfilzomib Combinations (Carfilzomib Plus Dexamethasone, Carfilzomib Plus Lenalidomide and Dexamethasone, and Carfilzomib Plus Pomalidomide and Dexamethasone), To Assess Tolerability and Adherence in Subjects With Relapsed or Refractory Multiple Myeloma at US Community Oncology Centers

Amgen Protocol Number 20170596

Amendment 4 Date: 20 May 2019

Rationale:

- Protocol amendment 4 has been issued to address carfilzomib dosing errors within the Schedule of Activity during Cycle 1 for the Kd and KRd regimens. An error in the dose of carfilzomib during cycle 3 through 12 for subjects with mild hepatic insufficiency has also been corrected.

Description of Changes:

Section: Global

Change: Header has been updated to reflect the date of Amendment 4.

Section: Title Page; Protocol Date

Add: **Protocol Amendment 4 20 May 2019**

Section: Investigator's Agreement

Replace:

I have read the attached protocol entitled An Open-label Phase 2 Study of Carfilzomib Plus Dexamethasone To Assess Tolerability and Adherence in Subjects With Relapsed or Refractory Multiple Myeloma at US Community Oncology Centers, dated 25 February 2019, and agree to abide by all provisions set forth therein.

With:

I have read the attached protocol entitled An Open-label Phase 2 Study of Carfilzomib Combinations (Carfilzomib Plus Dexamethasone, Carfilzomib Plus Lenalidomide and Dexamethasone, and Carfilzomib Plus Pomalidomide and Dexamethasone), To Assess Tolerability and Adherence in Subjects With Relapsed or Refractory Multiple Myeloma at US Community Oncology Centers, dated
~~29 March 2019~~**20 May 2019**, and agree to abide by all provisions set forth therein..

Section: Table 2-1 Schedule of Activities

Replace:

PROCEDURE	Screening[a] [b] (up to 21 days before Day 1)	Treatment Period													
		Cycle 1-2								Cycle 3-12					
		Day 1	2	8	9	15	16	22	23	1	8	15	21		
STUDY TREATMENT															
Kd ARM															
Carfilzomib administration[h]		X	X	X	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 Cycle 2: 56 mg/m^2 Cycles 3-12: 70 mg/m^2 For subjects with baseline hepatic function abnormalities (bilirubin or AST > ULN), see Section 7.1.1.2.1 for modification of the initial dose. For cycle 3, for subjects who were previously dose reduced, see Section 7.1.1.2 for starting dose.

With:

PROCEDURE	Screening[a] [b] (up to 21 days before Day 1)	Treatment Period												Safety FU[c] (30 [+3] days post last dose)	Notes
		Cycle 1-2								Cycle 3-12					
		Day 1	2	8	9	15	16	22	23	1	8	15	21		
STUDY TREATMENT															
Kd ARM															
Carfilzomib administration[h]		X	X	X	X	X	X	With		X	X	X			Cycle 1: 20 mg/m^2 on days 1 and 2; ~~27~~**56** mg/m^2 on days 8, 9, 15, and 16 Cycle 2: 56 mg/m^2 Cycles 3-12: 70 mg/m^2 For subjects with baseline hepatic function abnormalities (bilirubin or AST > ULN), see Section 7.1.1.2.1 for modification of the initial dose. For cycle 3, for subjects who were previously dose reduced, see Section 7.1.1.2 for starting dose.

Replace:

KRd ARM														
Carfilzomib administration[h]		X	X	X	X	X	X			X	X	X		Cycle 1: 20 mg/m^2 on days 1 and 2; 56 mg/m^2 on days 8, 9, 15, and 16 Cycle 2: 27 mg/m^2 Cycles 3-12: 56 mg/m^2 For subjects with baseline hepatic function abnormalities (bilirubin or AST > ULN), see Section 7.1.1.2.1 for modification of the initial dose. For cycle 3, for subjects who were previously dose reduced, see Section 7.1.1.2 for starting dose.

With:

KRd ARM														
Carfilzomib administration[h]		X	X	X	X	X	X			X	X	X		Cycle 1: 20 mg/m^2 on days 1 and 2; ~~56~~**27** mg/m^2 on days 8, 9, 15, and 16 Cycle 2: 27 mg/m^2 Cycles 3-12: 56 mg/m^2 For subjects with baseline hepatic function abnormalities (bilirubin or AST > ULN), see Section 7.1.1.2.1 for modification of the initial dose. For cycle 3, for subjects who were previously dose reduced, see Section 7.1.1.2 for starting dose.

Section: 7.1.1.2.1 Starting Dose in Hepatic Insufficiency

Replace:

For subjects with mild hepatic insufficiency during screening, the initial dose of carfilzomib on days 1 and 2 of cycle 1 should be reduced by 25% to 15 mg/m^2. For subjects in the Kd arm, starting on day 8 and for all subsequent doses of carfilzomib during cycles 1 and 2, the dose should be 42 mg/m^2 (Brown et al, 2017); the dose in cycle 3 through 12 should be 52 mg/m^2.

With:

For subjects with mild hepatic insufficiency during screening, the initial dose of carfilzomib on days 1 and 2 of cycle 1 should be reduced by 25% to 15 mg/m^2. For subjects in the Kd arm, starting on day 8 and for all subsequent doses of carfilzomib during cycles 1 and 2, the dose should be 42 mg/m^2 (Brown et al, 2017); the dose in cycle 3 through 12 should be ~~52~~**53** mg/m^2.

Amendment 3

Protocol Title: An Open Label Phase 2 Study of Carfilzomib Combinations (Carfilzomib Plus Dexamethasone, Carfilzomib Plus Lenalidomide and Dexamethasone, and Carfilzomib Plus Pomalidomide and Dexamethasone), To Assess Tolerability and Adherence in Subjects With Relapsed or Refractory Multiple Myeloma at US Community Oncology Centers

Amgen Protocol Number *20170596*

Amendment Date: 29 March 2019

Rationale:

- With the results from the A.R.R.O.W. study, the Kd 70mg/m^2 once weekly dosing schedule was approved in the US, providing the US practicing centers one more option to treat relapse or refractory multiple myeloma (RRMM) patients with more convenience. In the light of A.R.R.O.W. approval, and based on the feedback from investigators, the protocol amendment increased the cycles of Kd once weekly dosing schedule while keeping the total treatment cycles. The initial treatment with 2 cycles of twice weekly therapy is designed to provide the more familiar labelled treatment for subjects with RRMM.
- Triplet therapy are emerging as standard of care for RRMM patients. The ASPIRE study demonstrated the superiority of the combination of carfilzomib with lenalidomide and dexamethasone (KRd; 27 mg/m^2 twice-weekly) over lenalidomide with dexamethasone. However, despite the favorable benefit-risk profile of the KRd regimen, 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 ongoing Study CFZ013 evaluates once-weekly KRd in patients with RRMM and newly diagnosed multiple myeloma. Available efficacy results have shown similar efficacy to the effect previously reported for twice-weekly KRd (27 mg/m^2) in the ASPIRE study (Biran et al, 2018). Hence, to better reflect the clinical practice, and to investigate a more convenient KRd once weekly dosing schedule in the community setting, the protocol amendment is adding a KRd arm, starting with 2 cycles of the approved twice weekly dosing schedule followed by 10 cycles of the investigational once weekly dosing schedule.
- Pomalidomide and dexamethasone (Pd) has been approved for subjects with RRMM. Several phase 2 studies have demonstrated improved efficacy of adding carfilzomib to Pd (KPd) in patients with RRMM compared to historical data for Pd with safety consistent with carfilzomibs known profile. Based on the phase 2 studies, the protocol amendment is adding a KPd arm and will further investigate the once weekly KPd dosing regimen. Considering the safety data on KPd is limited compared to other Kyprolis containing regimens, a Data Review Team will be implemented to review the safety data.

Amendment 2

Protocol Title: An Open-label Phase 2 Study of Carfilzomib Plus Dexamethasone To Assess Tolerability and Adherence in Subjects With Relapsed or Refractory Multiple Myeloma at US Community Oncology Centers

Amgen Protocol Number (Carfilzomib) 20170596

Amendment Date: 05 October 2018

Rationale:

This protocol is being amended to:

- Add clarifying language to the dose intensity parts of the primary and secondary endpoints and statistical analyses
- Update the wording of several eligibility criteria including measureable disease to align with the CANDOR study, and cardiac and graft versus host disease exclusion criteria

Amendment 1

Protocol Title: An Open label Phase 2 Study of Carfilzomib Plus Dexamethasone To Assess Tolerability and Adherence in Subjects With Relapsed or Refractory Multiple Myeloma at US Community Oncology Centers

Amgen Protocol Number Carfilzomib 20170596

Amendment Date: 06 March 2018

Rationale:

This protocol is being amended for the following reasons:

- Update the study phase from phase 4 to phase 2 as determined by Amgen Clinical Study Team in alignment with definition of a phase 2 study.
- Provide additional rationale for once weekly dosing in response to request from US Central IRB.
- Update the protocol to remove biospecimen destruction language in order to maintain consistency in the protocol as no samples are collected.
- Update sample size justification to state that study is descriptive to address request from US Central IRB.
- Remove references to legally authorized representatives in order to maintain consistency in the protocol and address US Central IRB concerns.
- Update schedule of activities and analyte table by addition of a screening urinalysis to support exclusion criteria requiring albumin/creatinine ratio.
- Update schedule of activities by addition of myeloma response assessment and footnote to maintain consistency with the protocol.
- Update study assessments and procedures section with additional instruction for echocardiogram data to align with data required to confirm eligibility.
- Update instructions for the subject satisfaction and convenience questionnaire to clarify when the end of treatment items are completed.
- Make minor corrections and clarifications throughout the document, including administrative, typographical, and formatting errors.

Superseding Original Protocol

Protocol Title: An Open Label Phase 4 Study of Carfilzomib Plus Dexamethasone To Assess Tolerability and Adherence in Subjects With Relapsed or Refractory Multiple Myeloma at US Community Oncology Centers

Amgen Protocol Number Carfilzomib 20170596

Superseding Original Protocol Date: 26 January 2018

Rationale:

A formatting mistake was identified in the original protocol: in Table 2-1 (Schedule of Activities): the header row was missing from the second and third pages of the table. In the superseding version, this formatting mistake was fixed.