Title Page

Protocol Title:		An Open-label, Phase 2 Study Treating Subjects with First or Second Relapse of Multiple Myeloma with Carfilzomib, Pomalidomide, and Dexamethasone (KPd)
Short Protocol Title:		A Study Evaluating Treatment of Multiple Myeloma with Carfilzomib in Combination with Pomalidomide and Dexamethasone
Protocol Number:		20180117
Investigational Product:		Carfilzomib
Trade Name:		Kyprolis
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Version/Date:		**Data Element Standards Version** 6.1

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

Confidentiality Notice

Investigator's Agreement:

I have read the attached protocol entitled An Open-label, Phase 2 Study Treating Subjects with First or Second Relapse of Multiple Myeloma with Carfilzomib, Pomalidomide, and Dexamethasone (KPd), dated **16 May 2022**, 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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1. Protocol Synopsis

Protocol Title: An Open-label, Phase 2 Study Treating Subjects with First or Second Relapse of Multiple Myeloma with Carfilzomib, Pomalidomide, and Dexamethasone (KPd)

Short Protocol Title: A Study Evaluating Treatment of Multiple Myeloma with Carfilzomib in Combination with Pomalidomide and Dexamethasone

Study Phase: 2

Indication: Relapsed multiple myeloma

Rationale:

This trial is designed to estimate the efficacy of a carfilzomib-based triplet in first or second relapse of multiple myeloma for subjects refractory to lenalidomide.

Objective(s)/Endpoint(s)

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

Objectives	Endpoints
• Estimate the frequency of sustained MRD[-]CR at landmark 24 months	• sustained MRD[-]CR at a sensitivity of 10^{-5} using NGS-based method in the bone marrow at 24 months ± 4 weeks from start of treatment and calculated only within the subjects who reached MRD[-]CR in the time window for **key secondary endpoint** assessment
• Estimate duration of response, time to response, progression-free survival (PFS), and overall survival (OS)	• duration of response, defined as time from first date of PR or better to date of disease progression or death due to any cause • time to response, defined as time from start of treatment to first date of PR or better • PFS defined as time from start of treatment until progression or death from any cause • OS, defined as time from start of treatment until death from any cause
• Estimate rate of CR or better	• best overall confirmed response of CR or better

Hypotheses

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

Overall Design

The study is an open-label, phase 2 trial. Subjects may receive treatment until progression. Myeloma disease status will be monitored locally for response and progression per International Myeloma Working Group (IMWG) criteria (Kumar et al, 2016) every 28 ± 7 days from cycle 1 day 1 until confirmed progressive disease (PD), death, lost to follow-up, or withdrawal of full consent (whichever occurs first), regardless of cycle duration, dose delays or treatment discontinuation. Subjects with a suspected CR or better will have a bone marrow for minimal residual disease (MRD) assessment at 12 and 24 months (± 4 weeks) from start of treatment (unless a MRD assessment was performed within 4 months before planned assessment). Subjects who end study drug(s) without confirmed PD are required to complete disease response assessments and report new antimyeloma treatment every 28 ± 7 days until first subsequent antimyeloma treatment, death, lost to follow-up, withdrawal of full consent, confirmed PD, or end of study, whichever occurs first. Subjects who discontinue treatment and either start new antimyeloma treatment or have PD, will enter long-term follow-up every 12 weeks until death or end of study.

Number of Subjects

According to Protocol Amendment 3, approximately 85 subjects will be enrolled in the study, with approximately one-third of subjects in first relapse and two-thirds in second relapse. **In late 2021, enrollment was discontinued after 54 subjects were enrolled**.

Summary of Subject Eligibility Criteria

This study will enroll adults ≥ 18 years of age with first or second relapse multiple myeloma. Eligible subjects will have relapsed multiple myeloma after receiving 1 or 2 prior lines of therapy. Subjects must be refractory to lenalidomide. Subjects may not have received prior pomalidomide. Prior exposure to a proteasome inhibitor is allowed. Subjects previously exposed to carfilzomib must have responded with at least a partial response to carfilzomib, must not have discontinued carfilzomib due to toxicity, may not have relapsed while receiving or within 60 days of the last dose of carfilzomib, and must have at least a 6 month carfilzomib treatment-free interval since their last dose of carfilzomib. Prior exposure to daratumumab or other anti-CD38 antibody therapy are also allowed. Subjects must have measurable disease per IMWG consensus criteria, Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2, and at least partial response (PR) to 1 line of therapy.

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

Treatments

All carfilzomib doses should be administered on the scheduled day ± 2 days with each cycle consisting of 28 days of carfilzomib, pomalidomide, and dexamethasone (KPd).

- carfilzomib 20/56 mg/m^2, administered intravenously over 30 (± 5) minutes at a dose of 20 mg/m^2 on cycle 1 day 1 then 56 mg/m^2 thereafter
  - cycles 1-12: days 1, 8, 15
  - cycles 13+: days 1, 15
- pomalidomide 4 mg, administered orally
  - all cycles; days 1-21 (daily)
- dexamethasone, administered orally or IV between 30 minutes to 4 hours prior to carfilzomib administration
  - 40 mg (20 mg for subjects ≥ 75 years of age), cycles 1-12: days 1, 8, 15, 22 (day 22 dose may be self-administered at home)
  - 20 mg (10 mg for subjects ≥ 75 years of age), cycles 13+: days 1, 15

Procedures

Written informed consent must be obtained from all subjects or legally acceptable representatives before any study-specific screening procedures are performed. The following procedures will occur per the Schedule of Activities: demographics, medical/surgical history, substance use, complete physical examination, physical measurements, 12-lead electrocardiogram (ECG) with corrected QT interval (QTc), vital signs, ECOG PS, complete echocardiogram (ECHO), pulmonary function tests (PFTs), review of adverse events and serious adverse events, recording of concomitant medications and antimyeloma therapies. Imaging studies will be performed for bone lesion assessments (all subjects) and extramedullary plasmacytoma evaluation (if clinically indicated). Laboratory testing will be performed to confirm disease status and/or stage, including collection of bone marrow aspirate for MRD response testing, fluorescence in situ hybridization (FISH) analysis for cytogenic risk, and for confirmation

of complete response (CR) or stringent complete response (sCR). Additional laboratory testing will include coagulation, hematology, chemistry, hepatic and renal function, quantitative immunoglobulins, fasting lipid profile and glucose, hemoglobin A1c (HbA1c), NT-proBNP (b-type natriuretic peptide) or if unavailable then BNP, and pregnancy testing for females of childbearing potential. Samples will also be taken to perform pharmacokinetics (PK) and pharmacodynamics (PDn) assessments by those subjects providing additional consent (up to 20 subjects) and pharmacogenetic testing in consenting subjects.

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

Originally it was designed that using the Safety Analysis Set (approximately 85 subjects), the true **ORR** will be between [0.**715**, 0.**868**] 90% of the times when the observed **ORR** is 0.**8**. When the true **ORR** is 0.**8**, the chance that 90% CI of the observed **ORR** will be higher than 0.**6** is 9**9.3**%. With 85 subjects, the true **MRD[-]CR rate** will be between [0.**067**, 0.**194**] 90% of the times when the observed **MRD[-]CR rate** is 0.**12**. When the true **MRD[-]CR rate** is 0.**12**, the chance that 90% CI of the observed **MRD[-]CR** will be higher than **and exclude the unpromising MRD[-]CR rate of** 0.**03** is 9**5.1**%.

In late 2021, enrollment was discontinued after 54 subjects were enrolled. **Based on the actual total number of subjects who received at least one dose of carfilzomib (52 subjects),** the true ORR will be between **[0.687, 0.886]** 90% of the times when the observed ORR is 0.8. When the true ORR is 0.8, the chance that 90% CI of the observed ORR will be higher than 0.6 is **91.8%. With 52 subjects, the true MRD[-]CR rate will be between [0.055, 0.221]. When the true MRD[-]CR rate is 0.12, the chance that 90% CI of the observed MRD[-]CR will be higher than and exclude the unpromising MRD[-]CR rate of 0.03 is 76.3%.**

Continuous variables will be summarized by the non-missing sample size (n), mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by the n and percentage in each category. Time to event endpoints will be summarized with Kaplan-Meier (KM) curves, KM proportions at select time points, KM quartiles (when estimable), the number of subjects with events, the number of subjects censored, and censoring reasons. Duration of follow-up for time to event endpoints will be estimated using the reverse Kaplan Meier method. Point estimates for efficacy endpoints will be accompanied by 2-sided 90% and 95% CIs including estimates of KM quartiles, KM proportions, and binomial proportions.

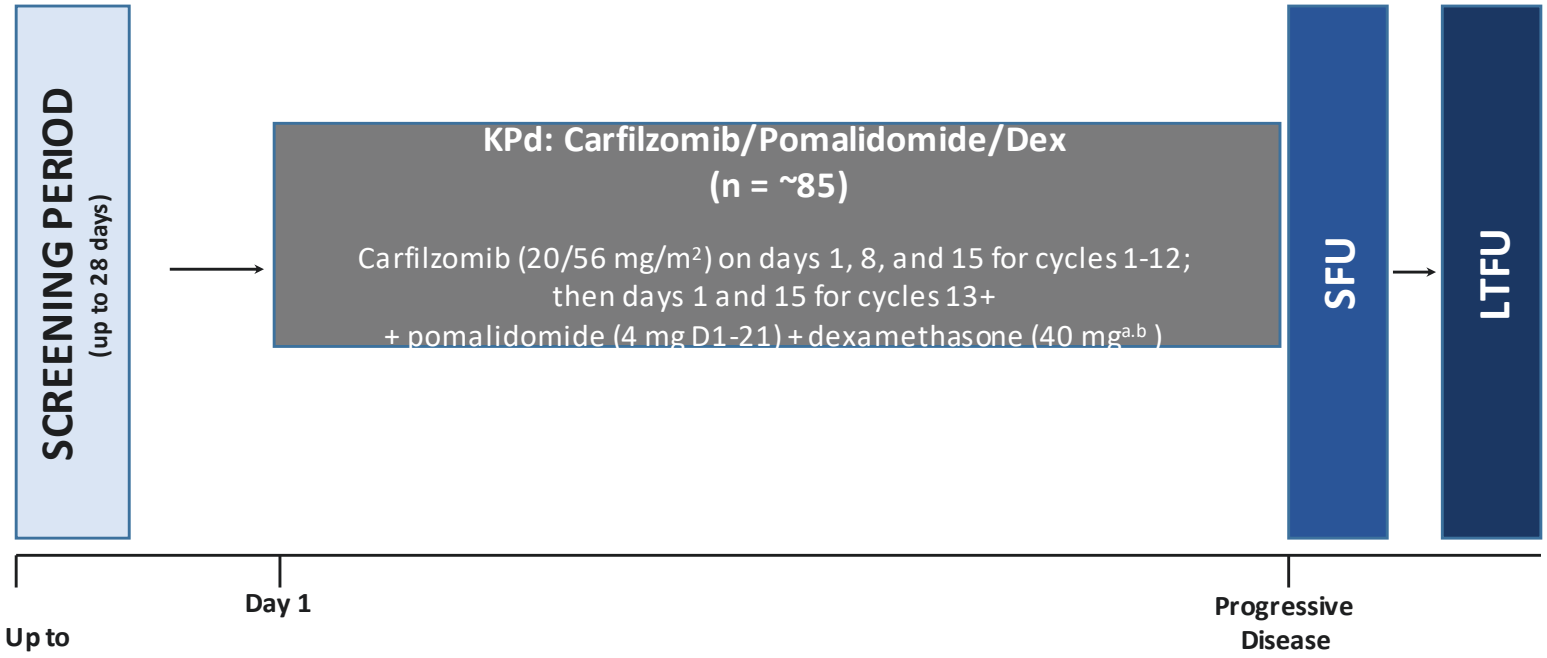
For a full description of statistical analysis methods, please refer to Section 10.4.2.

Sponsor Name: Amgen Inc.

2. Study Schema and Schedule of Activities

2.1 Study Schema

Figure 2-1. Study Schema



D = day; Dex = dexamethasone; KPd = carfilzomib in combination with pomalidomide and dexamethasone; LTFU = long-term follow-up; SFU = safety follow-up.

[a] For subjects ≥75 years of age, the dexamethasone dose is 20mg during cycles 1-12: days 1, 8, 15, 22

[b] During cycles 13+, dexamethasone dose is 20mg. For subjects ≥75 years of age, dexamethasone dose is 10mg

2.2 Schedule of Activities

Table 2-1. Schedule of Activities

Assessment	SCR[a]	Treatment Cycle Days 1	8	15	22	SFU[b]	LTFU	Notes
GENERAL AND SAFETY ASSESSMENTS (each cycle consists of 28 days)								
Informed consent	X							
Eligibility criteria	X							
Demographics	X							
Medical/surgical history	X							Includes cardiopulmonary history, multiple myeloma history, and family history of cardiovascular disease
Tobacco use	X							
Adverse events	Continually							
Serious adverse events	Continually							
Concomitant medications	Continually							Antimyeloma therapies recorded after discontinuation of study treatment
Reproductive status and Contraceptive methods	X	X						
Complete physical examination	X					X		
Physical measurements (weight, BSA)	X	X						BSA should be calculated per Mosteller formula and utilized to calculate required carfilzomib doses.
Physical measurement (height)	X							
ECOG performance status	X					X		
12-lead ECG with QTc interval	X							
ECG: cycle 1			X					To be performed at the end of carfilzomib infusion, and as clinically indicated
ECG: cycle 2		X						
Vital signs: cycles 1, 2 & SFU	X	X	X	X	X	X		Checked prior to administration of carfilzomib in all cycles.
Vital signs: cycles 3-12		X	X	X				
Vital signs: cycles 13+		X		X				

Footnotes defined on last page of the table

Table 2-1. Schedule of Activities

Assessment	SCR[a]	Treatment Cycle Days 1	8	15	22	SFU[b]	LTFU	Notes
GENERAL AND SAFETY ASSESSMENTS (continued)								
Complete ECHO	X	(X)				X		(X): Repeated approximately every 6 months (± 2 weeks) from C1D1 until SFU visit, or more often if clinically indicated. An ECHO must be performed within 72 hours of the onset of a suspected cardiac failure event.
PFTs	X	(X)				X		Includes spirometry with FEV1, %FEV1, FEV1/forced vital capacity, and FVC plus DLCO. (X): Assessed approximately every 6 months (± 2 weeks) from C1D1, until SFU visit, or more often if clinically indicated.
Survival							(X)	(X): Only required for subjects who progress or discontinue response assessments prior to end of study. Every 12 weeks (± 2 weeks) after safety follow-up visit until end of study.
LABORATORY ASSESSMENTS								
Hematology: cycles 1-2 & SFU	X	X	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.
Hematology: cycles 3+		X						
Chemistry	X	X				X		
Urinalysis, microscopic	X							
Hepatitis B Virus (HBV)	X	X						Local serology testing for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and hepatitis B core antibody (anti-HBc). Testing is required: For subjects with a prior history of HBV infection at screening, HBV DNA testing will be performed every 12 weeks (± 2 weeks) through safety follow-up. For all other subjects at screening unless obtained within 6 months of screening and there was no change in the subject's risk factors within these 6 months. For subjects positive at screening, who become positive for serology during treatment, or who are at risk of becoming positive, HBV DNA testing will be performed every 12 weeks (± 2 weeks) (and as clinically indicated) through safety follow-up. A specialist should be consulted for all subjects who test positive for HBV serology. Subjects who have received Hepatitis B vaccination with only anti-HBs positivity and no clinical signs of hepatitis do not require HBV DNA monitoring. See Section 9.2.4.10.3.

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Table 2-1. Schedule of Activities

Assessment	SCR[a]	Treatment Cycle Days 1	8	15	22	SFU[b]	LTFU	Notes
LABORATORY ASSESSMENTS								
Beta-2 microglobin	X							
Coagulation tests	X							
Fasting lipid profile and Fasting glucose	X							Subject must fast for a minimum of 9 hours prior to testing
HbA1c	X							
NT-proBNP	X							Or if unavailable, BNP
Pregnancy test (FCBP) Screening and cycle 1	X	X	X	X	X			Screening: Due to embryo-fetal toxicity, females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable contraception, beginning 4 weeks prior to initiating treatment with pomalidomide. Perform pregnancy testing 14 days prior to first dose of study drug and within the 24 hours prior to first dose (C1D1). Negative pregnancy test must be confirmed prior to dosing. More frequent pregnancy tests may be conducted if required per local regulations.
Pregnancy test (FCBP) Cycle 2+		X		(X)		X		Pregnancy test every 4 weeks in females with regular menses, OR (X): every 2 weeks in females with irregular menstrual cycles

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Table 2-1. Schedule of Activities

Assessment		SCR[a]	Every 28 (± 7) days	SFU[b]	LTFU	Notes
DISEASE-SPECIFIC ASSESSMENTS[c]						
SPEP/UPEP/SFLC/SIFE/UIFE		X	X			Screening disease-specific assessments must be done within 28 days prior to enrollment and repeated if not performed within 14 days of C1D1.
Quantitative immunoglobulins		X	(X)			(X): After screening, quantitative IgA, IgD or IgE at every disease assessment in subjects with IgA, IgD or IgE myeloma, respectively. For all subjects, quantitative immunoglobulins (IgG, IgM, IgA) will be repeated every 12 months ± 2 weeks from C1D1 in subjects with PR or better, or if applicable, may be done at time of MRD assessment. May be obtained more frequently as clinically indicated
Bone lesion assessment		X	(X)			Screening evaluation may be done within 28 days prior to enrollment, if performed as a part of standard of care. (X): Repeat if worsening clinical symptoms suggest PD or as clinically indicated.
Extramedullary Plasmacytoma evaluation		(X)	(X)			(X): Will be done at screening only if clinically suspected. Screening evaluation may be done within 28 days prior to enrollment, if performed as a part of standard of care. For subjects with a history of plasmacytoma, clinical assessment will be performed locally every 28 (± 7) days from C1D1. Radiological exam will be performed only to confirm a response of PR or better, or to confirm PD, or as clinically indicated (see Section 9.2.2.5 for more details).
Bone marrow aspirate	FISH analysis for cytogenic risk	X				To be collected no later than C1D1 predose (ie, screening). An informative result that was obtained as part of SOC within 45 days prior to enrollment may be used.
	To confirm CR or sCR		(X)			(X): As clinically indicated. Bone marrow biopsy is required to confirm sCR.
	For MRD[-]CR assessment	X	(X)			At screening AND (X): at suspected CR or better (12 months ± 4 weeks from start of treatment, unless performed within 4 months prior to scheduled landmark assessment) AND (X) Subjects with a MRD[-]CR response at the first time point should have the subsequent MRD assessment 12 months ± 4 weeks after the earlier assessment, if subjects have not relapsed nor started new antimyeloma therapy prior to this subsequent MRD assessment.

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Footnotes defined on last page of the table

Table 2-1. Schedule of Activities

Assessment	SCR[a]	Treatment Cycle Days 1	8	15	22	SFU[b]	LTFU	Notes
OPTIONAL ASSESSMENTS (additional consent must be obtained)								
Carfilzomib PK: cycle 2		X						Up to 20 subjects • Pre-dose (within 5 min before the start of infusion) • 15 minutes after the start of infusion (± 5 min) • Immediately prior to (within 2 min before) the end of infusion • 15 min after the end of infusion (± 5 min) • 60 min (1 hr) after the end of infusion (± 5 min) • 120 min (2 hr) after the end of infusion (± 5 min)
Carfilzomib PDn: cycle 1		X	X					Up to 20 subjects • C1D1: 15 minutes predose • C1D8, C2D1, C3D1: 15 minutes predose and 1 hour (± 15 min) after end of infusion
Carfilzomib PDn: cycles 2 and 3		X						
KPd: Pharmacogenetics (PG) sample:	X	(X)				X		(X): If a bone marrow is performed to confirm relapse, a 1-mL of bone marrow aspirate sample for PG analyses may be collected
Biomarker Samples	X	(X)						2 - 5 mL of peripheral blood will be collected at screening AND (X): at the time of bone marrow evaluation for determination of MRD (at suspected CR or better and/or at 12 and 24 months [± 4 weeks] from start of treatment)

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Table 2-1. Schedule of Activities

Assessment	SCR[a]	Treatment Cycle Days 1	8	15	22	SFU[b]	LTFU	Notes
STUDY DRUG ADMINISTRATION (± 2 days) with a minimum of 5 days between doses of carfilzomib; each cycle consists of 28 days								
Carfilzomib: cycles 1-12		X	X	X				C1D1 = 20 mg/m^2 (IV); C1D8 onwards = 56 mg/m^2 (IV)
Carfilzomib: cycles 13+		X		X				
Pomalidomide		X						4 mg daily, days 1-21
Dexamethasone: cycles 1-12		X	X	X	X			40 mg (oral or IV). For subjects ≥ 75 years of age, dose = 20 mg (oral or IV); (X): cycles 1 to 12 only; day 22 dose may be self-administered at home
Dexamethasone: cycles 13+		X		X				20 mg (oral or IV). For subjects ≥ 75 years of age, dose = 10 mg (oral or IV)
IV prehydration		(X)	(X)	(X)				As clinically indicated; (X): Investigators must consider IV prehydration in cycle 1 in subjects at high-risk for tumor lysis or renal toxicity. After cycle 1 only administer prehydration if the subject's risk factors require it. Refer to Section 7.1.1.1.3.

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AE = adverse event; BNP = B-type natriuretic peptide; BSA = body surface area; CR = complete response; CXDX = cycle X day X; DNA = deoxyribonucleic acid; DLCO = diffusing capacity of the lungs for carbon monoxide; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; FCBP = female of childbearing potential; FEV = forced expiratory volume; FISH = fluorescence in situ hybridization; FVC = forced vital capacity; HBA1c = hemoglobin A1c; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IFE = immunofixation; IgA = immunoglobulin A; IgD = immunoglobulin D; IgE = immunoglobulin E; IgG = immunoglobulin G; IgM = immunoglobulin M; IV = intravenous; KPd = carfilzomib in combination with pomalidomide and dexamethasone; LTFU = long-term follow-up; MRD[-]CR = minimal residual disease negative complete response; NT-proBNP = N-terminal pro b-type natriuretic peptide; PCR = polymerase chain reaction; PD = progressive disease; PDn = pharmacodynamics; PFT = pulmonary function test; PK = pharmacokinetics; PR = partial response; QTc = corrected QT interval; RT-PCR = real-time polymerase chain reaction; SAE = serious adverse event; sCR = stringent complete response; SCR = screening; SFU = safety follow-up; SFLC = serum-free light chain; SIFE = serum immunofixation; SOC = standard of care; SPEP = serum protein electrophoresis; UIFE = urine immunofixation; UPEP = urine protein electrophoresis; VGPR = very good partial response

[a] Screening period up to 28 days.

[b] The safety follow-up visit occurs 30 (+3) days after the last dose of study drug.

[c] Refer to Section 9.2.2 for details regarding frequency of disease assessments.

3. Introduction

3.1 Study Rationale

The introduction of proteasome inhibitors (PI), immune modulatory drugs (IMiDs), and monoclonal antibodies for the treatment of multiple myeloma has resulted in significant improvements in survival over the last decade. Combinations of PIs and IMiDs frequently serve as the backbone agents for different phases (eg, induction, consolidation, maintenance) of therapy (Pawlyn et al, 2015). Given that context, lenalidomide- and bortezomib-based regimens have been approved for the treatment of patients with relapsed multiple myeloma and play a central role in this population. In particular, lenalidomide is standard of care in the newly diagnosed setting, maintenance setting after autologous stem cell transplantation (ASCT), and relapsed/refractory setting (Holstein et al, 2018). Lenalidomide movement into front line therapy for multiple myeloma (FDA approval 2015) is changing the patterns of care in relapse. Extended maintenance therapy has demonstrated prolongation of survival and is now a standard of care following stem cell transplant and for patients who are not transplant eligible (Gay et al, 2018; Jagannath et al, 2018; Willenbacher et al, 2018). Despite these achievements, for most patients, the disease remains incurable, and relapse while receiving or after prolonged exposure to lenalidomide reduces its efficacy following relapse (Harrouseau and Attal, 2017). The clinical course of multiple myeloma is characterized by a recurring pattern of remission and relapse (Laubach et al, 2016; Durie et al, 2006; Jakubowiak et al, 2017**)**. With successive lines of treatment, patients have lower response rates and a shorter DOR (Kumar et al, 2012; Kumar et al, 2017), remissions become increasingly transient, and the disease eventually becomes refractory (Laubach et al, 2016). There is a need for effective regimens that can treat recurrent multiple myeloma that has become refractory to lenalidomide therapy.

This study is designed to estimate the efficacy of the carfilzomib-based triplet KPd in first or second relapse of multiple myeloma for subjects refractory to lenalidomide.

3.2 Background

3.2.1 Disease

Multiple myeloma, a clonal neoplastic proliferation of plasma cells, is the second most common hematologic malignancy with a global incidence of approximately 140 000 in 2016 (Cowan et al, 2018). Multiple myeloma may represent less than 1% of all cancer diagnoses (Bray et al, 2013), but contributes to significant disease burden with over 2 million disability adjusted life years (Cowan et al 2018). Although recent therapeutic

advances have prolonged survivorship and decreased mortality rates (Kazandjian, 2016), multiple myeloma still remains a fatal disease with nearly 100 000 annual deaths worldwide (~1% of cancer deaths; Cowan et al, 2018; Ferlay et al, 2015). The 5-year prevalence of MM worldwide was estimated in 2012 at 229 000 persons. The difficulty in treating this disease is also appreciated through the 5-year overall survival rates, which varies by region and even country. The rates are about 50% in the United States as well as England and Wales, 35% in Sweden, and 8% in Nigeria (Cowan et al, 2018; London School of Hygiene and Tropical Medicine, 2014; Blimark et al, 2018). Multiple myeloma is uniquely characterized by a recurring pattern of remission and relapse (Laubach et al, 2016; Durie et al, 2012; Jakubowiak et al, 2012) with all patients eventually relapsing. Multiple myeloma is a disease of older adults, with a median age at diagnosis of 69 years (Howlader et al, 2013). For this incurable systemic disease, chemotherapy with or without autologous stem cell transplantation is indicated for management of active myeloma (Rajkumar, 2014).

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 except the brain. It is metabolized largely extra-hepatically and rapidly cleared from the circulation by biliary and renal excretion ($t_{1/2}$ = 15 to 30 minutes); < 1% is excreted intact (Kortuem and Stewart, 2013).

Carfilzomib entered clinical studies in September 2005. On 20 July 2012, Kyprolis® (carfilzomib for injection) was granted accelerated approval by the US Food and Drug Administration (FDA) for the treatment of patients with multiple myeloma who have received at least 2 prior therapies, including bortezomib and an IMiDs, 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 was based on 2 phase 3 studies: PX-171-009 ASPIRE and 2011-003 ENDEAVOR. Following these approvals, Kyprolis in combination with either lenalidomide and

dexamethasone or dexamethasone alone is indicated for the treatment of relapsed or relapsed and refractory multiple myeloma. The exact indication wording varies by region.

As of 19 January 2019, an estimated 4462 subjects have been treated with carfilzomib in clinical studies since the beginning of the development program and approximately 108 932 patients have received carfilzomib in the postmarketing setting.

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

3.2.3 Non-Amgen Investigational Product Background

3.2.3.1 Pomalidomide

Pomalidomide, a thalidomide analogue that displays similar antiangiogenic activity, but greater anti-proliferative and immunomodulatory activity (Quach et al, 2010; Galustian et al, 2009; Hayashi et al, 2005). Pomalidomide and low-dose dexamethasone (Pd) was compared to high-dose dexamethasone (D) in a randomized phase 3 trial in patients with relapsed and refractory multiple myeloma who had received two or more prior therapies including bortezomib and lenalidomide based therapies (NCT01311687). Both treatment arms had received a median of 5 prior treatments. After a median follow-up of 10 months the overall response rate (ORR), was 31% for patients treated with Pd vs 10% for patients treated with D. The mPFS (4.0 versus 1.9 months, hazard ratio [HR] = 0.48) was significantly longer in the Pd arm regardless of the previous treatment, including patients refractory to lenalidomide (3.9 versus 1.9 months), or refractory to both lenalidomide and bortezomib (3.7 versus 2 months). Similarly, overall survival (OS) was significantly improved in the Pd arm for each of these subgroups, from 8.1 to 12.7 months overall (San-Miguel et al, 2013). The ability of pomalidomide to overcome resistance to lenalidomide may, in part, be due to the antimyeloma activity of pomalidomide having less dependence on the level of cereblon expression, compared to the dependence of lenalidomide on cereblon expression (Rychak et al, 2016). Efficacy and safety of the Pd regimen was confirmed in the STRATUS trial, a large phase 3b study that evaluated the safety and efficacy of Pd in patients who had failed treatment with bortezomib and lenalidomide-based therapies. This study reported a median PFS of 4.6 months and a median OS of 12.9 months (Dimopoulos et al, 2016).

Pomalidomide has been approved by the United States FDA and EMA in 2013 (Imnovid® SmPC; Pomalyst® USPI) for its use alone or in combination with dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma who have received at least 2 prior therapies including lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

Refer to the regional manufacturer package insert for additional information.

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

Left untreated, multiple myeloma is a fatal disease. Treatment of relapsed or refractory multiple myeloma treatment has evolved rapidly in recent years. Progress has included the use of high dose chemotherapy with autologous stem cell transplantation along with the introduction of several breakthrough drugs, including IMiDs, PIs, and monoclonal antibodies, which have led to significant improvements in response rate as well as survival (Mateos and San Miguel, 2017). However, while treatment typically induces remission, most patients experience relapse. Multiple myeloma is characterized by a recurring pattern of remission and relapse with each subsequent line of treatment resulting in both diminished duration and depth of response (Cook et al, 2018), culminating in treatment resistance (Papadas and Asimakopoulos, 2017).

Given various mechanisms of drug resistance such as overexpression of efflux pumps, genetic and epigenetic aberrations, and changes in the bone marrow microenvironment (Nass and Efferth, 2018), there is a need for innovative sequencing approaches, new combinations of currently available agents, and perhaps agents with different mechanisms of action. Approximately one quarter of patients show primary resistance to bortezomib, which has an ORR of 74% in phase 3 studies (San Miguel et al, 2008). In addition, treatment-induced peripheral neuropathy is frequently reported with antimyeloma agents, in particular IMiDs and bortezomib, leading to significant morbidity and dose reductions or treatment discontinuations, which may limit the potential of these agents (Velcade [bortezomib] USPI, 2014; Martin, 2013). Relapse while receiving or after prolonged exposure to lenalidomide reduces its efficacy following relapse (Harrouseau and Attal, 2017) and patients with dual lenalidomide-bortezomib refractory relapse do extremely poorly (Kumar et al, 2012; Kumar et al, 2017). Such limitations

and anticipated resistance highlight the continued need for highly efficacious treatment options in relapsed or refractory multiple myeloma (RRMM) that prolong progression-free survival (PFS), OS, durable responses and control symptoms of disease, and/or have improved or nonoverlapping side effect profiles compared with currently available agents. Specifically, there is a current clinical unmet need in the relapsed setting for patients who are lenalidomide-refractory. The triplet KPd may fulfil this unmet need.

3.3.2 Key Benefits

Carfilzomib combinations, including carfilzomib in combination with lenalidomide and dexamethasone (KRd), are an important and commonly used option for many patients with relapsed or relapsed and refractory multiple myeloma. The key benefits of carfilzomib therapy include: increases in OS, PFS, and ORR; as well as improvements in quality-of-life.

ASPIRE evaluated KRd 20/27 mg/m^2 twice-weekly vs lenalidomide with dexamethasone (Rd) for treatment of relapsed multiple myeloma: the addition of carfilzomib to lenalidomide and dexamethasone reduced the risk of death or progression by 31% when compared with lenalidomide and dexamethasone alone. The median PFS with KRd was 26.3 months compared with carfilzomib and dexamethasone (Kd) at 17.6 months (HR = 0.69, 95% CI: 0.57, 0.83; $p < 0.0001$). Further, KRd 27 mg/m^2, twice-weekly was associated with a higher ORR of 87.1% vs 66.7% in the control arm (odds ratio [OR] = 3.47; $p < 0.0001$) (Stewart et al, 2015) and improved OS by 8 months (median OS 48.3 vs 40.4 months; HR = 0.79; $p = 0.0045$) (Siegel et al, 2018). The European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30) instrument with a global health status/quality of life (GHS/QOL) subdomain was used to assess health-related quality-of-life (HRQOL) as a secondary endpoint in ASPIRE. Subjects had higher QLQ-C30 GHS/QOL scores in the KRd group versus the Rd group over 18 cycles of treatment (overall treatment difference: 4.23, 95% CI: 2.09, 6.37 [Stewart et al, 2016]), with a nominal 1-sided $p = 0.0001$. Thus, in ASPIRE KRd improved overall health and quality-of-life compared with Rd.

The ongoing phase 1b Study CFZ013 (NCT02335983) evaluates once-weekly carfilzomib plus Rd 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) have 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).

Treatment for multiple myeloma continues to evolve and as previously discussed, continuous therapy with lenalidomide either as primary therapy or post-transplant maintenance has become a standard of care. In this setting the development of carfilzomib-based triplet therapies that use other alternatives to lenalidomide may provide significant clinical benefit. Pomalidomide is capable of overcoming resistance to lenalidomide (reviewed in Section 3.2.3.1). The combination of carfilzomib with Pd in subjects ranging from first relapse to advanced myeloma (5 to 6 prior therapies) and in the setting of dual refractory relapse (lenalidomide-bortezomib) has demonstrated significant improvement in PFS (reviewed in Section 5.4.1) compared to historical outcomes (Kumar et al, 2012).

3.3.3 Key Risks

Multiple important identified and potential risks for carfilzomib have been identified based on pooled safety data from completed studies where carfilzomib was used in combination (with lenalidomide-dexamethasone, cyclophosphamide dexamethasone, melphalan prednisone, or carboplatin etoposide), with dexamethasone alone, or in monotherapy studies (n = 3417). Dose modification instructions for the management of toxicities is provided in Section 7.4.

Although the key identified risks (ie, cardiac failure, acute renal failure, and hypertension) are underlying comorbidities in patients with multiple myeloma (Kistler et al, 2014; Christiansen et al, 2011; Knauf et al, 2009), these risks were identified as key risks with carfilzomib based on a greater incidence and severity of adverse events in the carfilzomib treatment groups versus the comparators in the randomized clinical studies.

Data describing the key identified risks from phase 3 pivotal trials of KRd (ie, the ASPIRE study), or dexamethasone alone (ie, the ENDEAVOR and A.R.R.O.W. studies) are summarized below.

Additional information regarding important identified risks as well as adverse drug reactions for carfilzomib are detailed in the Carfilzomib Investigator's Brochure.

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 Risk Evaluation and Mitigation Strategy

[REMS] program in the United States). Additional information regarding risks for pomalidomide are described in Pomalyst® USPI and Imnovid SmPC or local prescribing information.

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

3.3.3.1 Risks

3.3.3.1.1 Cardiac Toxicity

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

Cardiac failure (all grades) occurred in ASPIRE (KRd: 7.1%, lenalidomide with dexamethasone [Rd]: 4.1%), ENDEAVOR (Kd: 10.8%, Vd: 3.3%), and A.R.R.O.W. (Kd 20/70 mg/m^2 once-weekly: 3.8%, Kd 20/27 mg/m^2 twice-weekly: 5.1%). Serious adverse events of cardiac failure were reported in ASPIRE (KRd: 4.1%, Rd: 2.1%), ENDEAVOR (Kd: 3.9%, bortezomib with dexamethasone [Vd]: 1.3%) and A.R.R.O.W. (Kd 20/70 mg/m^2 once-weekly: 3.4%, Kd 20/27 mg/m^2 twice-weekly: 3.4%). Grade $\geq$ 3 cardiac failure adverse events occurred in ASPIRE (KRd: 4.3%, Rd: 2.1%), ENDEAVOR (Kd: 5.8%, Vd: 2.0%), and A.R.R.O.W. (Kd 20/70 mg/m^2 once-weekly: 2.9%, Kd 20/27 mg/m^2 twice-weekly: 4.3%). Cardiac failure adverse events (all grades) led to discontinuation of any investigational product in ASPIRE (KRd: 0.5%, Rd: 0.8%), ENDEAVOR (Kd: 3.7%, Vd: 0.9%), and A.R.R.O.W. (Kd 20/70 mg/m^2 once-weekly: 2.9%, Kd 20/27 mg/m^2 twice-weekly: 2.6%).

Adverse event outcomes were reported for all adverse events in ASPIRE and ENDEAVOR, and reported for serious adverse events only in A.R.R.O.W. In ASPIRE and ENDEAVOR, most of the cardiac failure adverse events (all grades) were resolved (ASPIRE KRd: 3.3%, Rd: 1.5%; ENDEAVOR Kd: 3.7%, Vd: 2.0%) or stabilized/not resolving (ASPIRE KRd: 2.6%; Rd: 1.5%; ENDEAVOR Kd: 6.7%, Rd: 0.9%). Fatal outcomes were reported in ASPIRE (KRd: 0.8%; Rd: 1.0%) and ENDEAVOR

(Kd: 0.2%, Vd: 0.4%). Additionally, resolved with sequelae outcome was reported in ASPIRE (KRd: 0.5%, Rd: 0%); however, this outcome was not collected in ENDEAVOR.

In A.R.R.O.W., almost all the cardiac failure serious adverse events were resolved (Kd 20/70 mg/m^2 once-weekly: 2.9%, Kd 20/27 mg/m^2 twice-weekly: 1.7%) or not resolved (Kd 20/70 mg/m^2 once-weekly: 0.4%, Kd 20/27 mg/m^2 twice-weekly: 1.3%). One fatal outcome was reported (Kd 20/70 mg/m^2 once-weekly: 0%, Kd 20/27 mg/m^2 twice-weekly: 0.4%).

The risk of cardiac failure is increased in elderly patients (≥ 75 years of age) and in Asian patients. Subjects with New York Heart Association Class III and IV heart failure, recent myocardial infarction, and conduction abnormalities uncontrolled by medications were not eligible for the clinical study and may be at greater risk for cardiac complications. While adequate hydration is required prior to dosing in cycle 1, all subjects should be monitored for evidence of volume overload, especially subjects at risk for cardiac failure. The total volume of fluids may be adjusted as clinically indicated in subjects with baseline cardiac failure or who are at risk for cardiac failure.

3.3.3.1.2 Hypertension

Hypertension has been reported as one of the common comorbidities in patients with multiple myeloma. Based on the MarketScan claims database, the prevalence of hypertension as a comorbidity among multiple myeloma patients is 46.9% (Song et al, 2016) and there was a 30% increase in the risk of hypertension in multiple myeloma versus non-multiple myeloma patients (Chari et al, 2016).

Hypertension adverse events (all grades) occurred in the combination therapy studies in ASPIRE (KRd: 17.1%, Rd: 8.7%), ENDEAVOR (Kd: 33.7%, Vd: 10.5%), and A.R.R.O.W. (Kd 20/70 mg/m2 once-weekly: 21.8%, Kd 20/27 mg/m2 twice-weekly: 21.3%). Serious adverse events of hypertension were reported in ASPIRE (KRd: 0%, Rd: 0.3%), ENDEAVOR (Kd: 0.9%, Vd: 0.2%), and A.R.R.O.W. (Kd 20/70 mg/m^2 once-weekly: 0%, Kd 20/27 mg/m^2 twice-weekly: 0.4%). Grade ≥ 3 hypertension adverse events occurred in ASPIRE (KRd: 6.4%, Rd: 2.3%), ENDEAVOR (Kd: 15.6%, Vd: 3.3%), and A.R.R.O.W. (Kd 20/70 mg/m^2 once-weekly: 5.9%, Kd 20/27 mg/m^2 twice-weekly: 5.5%). Hypertension adverse events (all grades) led to discontinuation of any investigational product in ASPIRE (KRd: 0.3%, Rd: 0.3%), ENDEAVOR (Kd: 0.2%, Vd: 0%), and A.R.R.O.W. (Kd 20/70 mg/m^2 once-weekly: 1.3%, Kd 20/27 mg/m^2 twice-weekly: 0%).

The incidence of hypertension (all grades) was higher in subjects with a history of hypertension in ASPIRE (with history of hypertension: KRd: 20.5%, Rd: 10.7%; without history of hypertension: KRd: 13.7%, Rd: 7.1%). A similar increase in incidence of hypertension (all grades) in subjects with a history of hypertension was not observed in carfilzomib-treated subjects in ENDEAVOR (subjects with history of hypertension: Kd: 31.1%, Vd: 10.8%; subjects without history of hypertension: Kd: 36.4%, Vd: 10.3%). In A.R.R.O.W., the difference in incidence of hypertension (all grades) among subjects with or without a history of hypertension was similar between treatment groups (with history of hypertension: Kd 20/70 mg/m^2 once-weekly: 22.2%, Kd 20/27 mg/m^2 twice-weekly: 20.6%; subjects without history of hypertension: Kd 20/70 mg/m^2 once-weekly: 21.6%, Kd 20/27 mg/m^2 twice-weekly: 21.9%.

Adverse event outcomes were reported for all adverse events in ASPIRE and ENDEAVOR, and reported for serious adverse events only in A.R.R.O.W. No fatal outcomes for hypertension adverse events (all grades) were reported in ASPIRE and ENDEAVOR. In ASPIRE, almost all the hypertension adverse events (all grades) were stabilized/not resolving (KRd: 8.7%; Rd: 4.4%) or resolved (KRd: 8.4%, Rd: 4.1%); resolved with sequelae was also reported (KRd: 0%, Rd: 0.3%). The outcomes reported in ENDEAVOR were stabilized/not resolving (Kd: 19.4%, Vd: 4.2%) and resolved (Kd: 14.0%, Vd: 6.1%).

In A.R.R.O.W., there was 1 serious event of hypertension which resolved (Kd 20/70 mg/m^2 once-weekly: 0%, Kd 20/27 mg/m^2 twice-weekly: 0.4%). Hypertensive crisis occurred in $\leq$ 0.5% of subjects in the combination therapy studies (ASPIRE: KRd: 0.5%, Rd: 0.3%; ENDEAVOR: Kd: 0.2%, Vd: 0%; A.R.R.O.W.: Kd 20/70 mg/m2 once-weekly: 0%, Kd 20/27 mg/m^2 twice-weekly: 0.4%), all of which were grade $\geq$ 3.

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

3.3.3.1.3 Acute Renal Failure

Renal failure is a relatively common problem in patients with multiple myeloma (Dimopoulos et al, 2016; Bladé and Rosiñol, 2005). Acute renal failure occurs most often in patients with multiple myeloma who have high rates of production and excretion

of Ig-free light chains, which may be toxic to the basement membranes of the glomeruli and/or the renal tubules and form obstructing tubular casts, particularly if the patient is dehydrated (Dimopoulos et al, 2016; Sanders and Booker, 1992).

Acute renal failure (all grades) occurred in ASPIRE (KRd: 9.2%, Rd: 7.7%), ENDEAVOR (Kd: 10.4%, Vd: 6.1%), and A.R.R.O.W. (Kd 20/70 mg/m^2 once-weekly: 7.1%, Kd 20/27 mg/m^2 twice-weekly: 6.8%). Serious adverse events of acute renal failure were reported in ASPIRE (KRd: 2.6%, Rd: 1.8%), ENDEAVOR (Kd: 3.9%, Vd: 2.0%), and A.R.R.O.W. (Kd 20/70 mg/m^2 once-weekly: 4.6%, Kd 20/27 mg/m^2 twice-weekly: 5.1%). Grade ≥ 3 acute renal failure adverse events occurred in ASPIRE (KRd: 3.8%, Rd: 3.3%), ENDEAVOR (Kd: 5.6%, Vd: 3.3%), and A.R.R.O.W. (Kd 20/70 mg/m^2 once-weekly: 3.8%, Kd 20/27 mg/m^2 twice-weekly: 5.5%). Acute renal failure adverse events (all grades) led to discontinuation of any investigational product in ASPIRE (KRd: 0.5%, Rd: 1.0%), ENDEAVOR (Kd: 1.3%, Vd: 0.4%), and A.R.R.O.W. (Kd 20/70 mg/m^2 once-weekly: 2.1%, Kd 20/27 mg/m^2 twice-weekly: 2.1%). Adverse event outcomes were reported for all adverse events in ASPIRE and ENDEAVOR, and reported for serious adverse events only in A.R.R.O.W. In ASPIRE and ENDEAVOR, most of the acute renal failure adverse events (all grades) were resolved (ASPIRE KRd: 6.1%, Rd: 5.7%; ENDEAVOR Kd: 5.6%, Vd: 3.1%) or stabilized/not resolving (ASPIRE KRd: 2.8%, Rd: 1.8%; ENDEAVOR Kd: 4.5%, Vd: 3.1%). One fatal outcome was reported in ASPIRE (KRd: 0%, Rd: 0.3%) and ENDEAVOR (Kd: 0.2%, Vd: 0%). Additionally, resolved with sequelae outcome was reported in ASPIRE (KRd: 0.3%, Rd: 0%); however, this outcome was not collected in ENDEAVOR.

In A.R.R.O.W., all of the acute renal failure serious adverse events were resolved (Kd 20/70 mg/m^2 once-weekly: 3.8%, Kd 20/27 mg/m^2 twice-weekly: 3.8%) or not resolved (Kd 20/70 mg/m^2 once-weekly: 0.8%, Kd 20/27 mg/m^2 twice-weekly: 1.3%). None were reported as fatal or unknown in either treatment group.

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

4. Objectives, Endpoints and Hypotheses

4.1 Objectives and Endpoints

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

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

Objectives	Endpoints
Exploratory	
• Assess the depth of MRD	• Percentage of MRD[-] below the threshold of 10^{-4}, 10^{-5}, and 10^{-6} by NGS-based method at time of suspected CR or better
• Evaluate the correlation between MRD status and PFS	• PFS by depth of MRD response at: 10^{-4}, 10^{-5}, and 10^{-6}
• Evaluate the correlation of PFS in high versus standard risk subject populations	• PFS of high versus standard risk subjects defined by fluorescence in-situ hybridization [FISH; 17p deletion, t(4:14), t(14:16)], and Revised International Staging System (R-ISS)
• Evaluate pharmacokinetics (PK) and pharmacodynamics (PDn) of carfilzomib when administered in combination with pomalidomide and dexamethasone	• carfilzomib PK parameters (maximum observed concentration [C_{max}], area under the concentration-time curve [AUC], half-life [$t_{1/2}$]) • carfilzomib PDn parameters (inhibition of proteasome activity relative to baseline)
• Assess pharmacogenetics in subjects receiving KPd	• CD138 selection of tumor cells at screening and disease progression
• Analyze exploratory biomarkers	• [redacted] levels in peripheral blood at 12 and 24 months (± 4 weeks)

4.2 Hypotheses

The primary hypothesis is that KPd will improve **ORR by** evaluating whether the lower bound of the 90% CI of the **ORR** excludes **60**%. The secondary hypothesis is that KPd will improve **MRD[-]CR rate at 12 months by** evaluating whether the lower bound of the 90% CI of **the MRD[-]CR rate at 12 months** excludes **3**%. The secondary hypothesis

will be assessed only after the primary objective is met. **Both** exact binomial 2-sided 90% and 95% CIs will be generated **around the point estimate for each of these endpoints.**

5. Study Design

5.1 Overall Design

The study is an open-label, phase 2 trial to assess efficacy and safety of carfilzomib, pomalidomide, and dexamethasone (KPd).

Eligible subjects will have relapsed or relapsed and refractory multiple myeloma after receiving 1 or 2 prior treatment regimens. Subjects must be refractory to lenalidomide and may have been previously exposed to an anti-CD38 antibody therapy. Subject is considered refractory if any of the following criteria is met:

- The best response reached during at least 1 regimen containing the drug of interest was stable disease or progressive disease
- The reason that the drug of interest was stopped was progression in at least 1 regimen
- The date of relapse/progression is after start date and within 60 days after stop date of the drug of interest in at least 1 regimen

According to Protocol Amendment 3, Approximately 85 subjects will be enrolled, with approximately one-third of subjects in the first relapse and two-thirds of subjects in second relapse. **In late 2021, enrollment was discontinued after 54 subjects were enrolled.** Subjects may receive treatment until progression. The regimens will be administered per Section 7.1.

All subjects will be assessed for multiple myeloma disease response according to the International Myeloma Working Group Uniform Response Criteria (IMWG-URC) (Section 12.11) every 28 ± 7 days from cycle 1 day 1 through death, confirmed PD, lost to follow-up, withdrawal of full consent (whichever occurs first), or end of study, regardless of cycle duration, dose delays or treatment discontinuation. Subjects who end study drug(s) before confirmed progressive disease (PD) are required to complete disease response assessments and report new antimyeloma treatment every 28 ± 7 days until first subsequent antimyeloma treatment, death, loss to follow-up, withdrawal of full consent, confirmed progress disease (PD), or end of study, whichever occurs first.

The individual subject disease response and disease progression for this study will be independently assessed by an Independent Review Committee (IRC) in accordance with

the IMWG-URC. The membership criteria and operational details of the IRC will be described in the IRC Charter. The IRC will centrally review the disease-related tests and assessments to evaluate disease progressions and responses without the knowledge of the investigator's disease assessments. The IRC assessment will be used for the analysis of the ORR.

Bone marrow aspirates will be collected as clinically indicated to confirm a response of complete response (CR) or stringent complete response (sCR). Subjects with a suspected CR or better will have a bone marrow for MRD assessment at 12 months ± 4 weeks unless a minimal residual disease (MRD) assessment was performed within 4 months prior to the scheduled assessment (eg, coordinated with a bone marrow procedure to confirm CR). Subjects with a MRD[-]CR at the first time point (8 to 12 months from initiation of treatment) should have the subsequent MRD assessment 12 months ± 4 weeks after the earlier assessment (20-24 months after the start of treatment), if subjects have not relapsed nor started new antimyeloma therapy prior to this subsequent MRD assessment.

Subjects who discontinue either carfilzomib or pomalidomide, but not both drugs, will be considered to remain on study treatment.

Safety laboratory studies (complete blood counts and differential, complete metabolic panel) will be collected on day 1 of each cycle, prior to dosing. A Data Review Team (DRT) will convene regularly to independently evaluate safety. Timing and frequency of the DRT meetings will be detailed in the DRT charter. After discontinuation of study treatment, a safety follow-up visit will be scheduled 30 (+3) days after the last dose of study treatment. Subjects who discontinue treatment and either start new antimyeloma treatment or have PD, will enter long-term follow-up every 12 weeks until death or end of study.

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

Subjects in this clinical investigation shall be referred to as "subjects". **According to Protocol Amendment 3,** approximately 85 subjects will be enrolled in the study, with approximately one-third of subjects in first relapse and two-thirds of subjects in second relapse. **In late 2021, enrollment was discontinued after 54 subjects were enrolled.**

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 45 investigative sites globally will be included in the study. Sites that do not enroll subjects within 6 months of site initiation may be closed.

5.3 End of Study

5.3.1 End of Study Definition

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

5.3.2 Study Duration for Subjects

Subjects may be treated until disease progression. There is a 28-day screening window and a safety follow-up 30 (+3) days after the last dose of carfilzomib and long term follow-up visits will be conducted every 12 weeks (± 2 weeks) after the safety follow-up visit until end of study resulting in a maximum duration on study of approximately 61 months.

5.4 Justification for Investigational Product Dose

5.4.1 Carfilzomib/Pomalidomide

Carfilzomib/pomalidomide/dexamethasone has been evaluated in several investigator-sponsored, single arm, phase 2 trials. At the highest dose, 60 subjects with relapsed or refractory multiple myeloma at first relapse received 20/36 mg/m^2 carfilzomib twice-weekly (days 1, 2, 8, 9, 15, and 16) in combination with pomalidomide (4 mg/day days 1-21) and low dose dexamethasone. Patients not previously treated with stem cell transplant (n = 30) received 4 cycles of induction followed by high dose melphalan/autologous stem cell transplant followed by 4 additional cycles of KPd and then Pd to progression. Subjects who had previously received a stem cell transplant were treated with 8 cycles of KPd followed by Pd to progression (Sonneveld et al, 2018). KPd was also investigated in 3 trials using a dose of 27 mg/m^2 twice-weekly in 2 trials (n = 143 total subjects) and 27 mg/m^2 once weekly (n = 47) combined with pomalidomide and dexamethasone. These last 3 trials enrolled subjects with advanced myeloma, most subjects were refractory to lenalidomide and 25% to 70% were dual refractory to both lenalidomide and bortezomib. These preliminary data provide extensive evidence for the efficacy of the KPd regimen in advanced refractory multiple myeloma (Table 5-1). In

patient populations with comparable levels of prior therapy and refractoriness to novel agents as enrolled in earlier trials of pomalidomide plus dexamethasone, KPd resulted in 7 to 10 months mPFS compared to 3.9 to 4.2 months for Pd. The safety profile demonstrates that the adverse events observed with the combination KPd are consistent with the product labels for carfilzomib and pomalidomide (Bringhen et al, 2018; Jakubowiak et al, 2017; Shah et al, 2015).

Table 5-1. Summary of KPd Dose and Trial Results

Study	Characteristics of patient population	Dose/Schedule	Number of subjects	mPFS (mo)	mOS
Bringhen et al, 2018	Relapsed or refractory, refractory to LEN 1-3 prior therapies (2)[a] 100% LEN refractory, 90% dual refractory	27 mg/m^2 Once weekly days 1, 8, 15 C1-8 then days 1, 15 to progression	47	10.2	NE, 67% at 12 mo
Sonneveld et al, 2018	Relapsed or refractory, refractory to LEN and or bortezomib 1 prior therapy	36 mg/m^2 Twice weekly days 1, 2, 8, 9, 15, 16 C1-8 (not transplant) or C1-4 induction and C5-8 after transplant	60	18	NE, 80% at 16.3 mo
Jakubowiak et al, 2017	Relapsed or refractory, refractory to LEN[b] 1+ prior therapies (2)[a] 91% LEN refractory, 25% dual refractory	27 mg/m^2 Twice weekly days 1, 2, 8, 9, 15,16 C1-8 then days 1, 2, 15, 16 to progression	64	16.8	NE, 77% at 24 mo
Shah et al, 2013	Relapse or refractory, refractory to LEN[b] 1+ prior therapies (5)[a] 100% LEN refractory, 90% dual refractory	27 mg/m^2 Twice weekly days 1, 2, 8, 9, 15,16 C1-6 then days 1, 2, 15, 16 to progression	79	9.7	NE, median > 18 mo
Shah et al, 2015	Relapse or refractory, refractory to LEN[b] 2+ prior therapies (6)[a] 100% LEN refractory, 90% dual refractory	27 mg/m^2 Twice weekly days 1, 2, 8, 9, 15,16 C1-6 then days 1, 2, 15, 16 to progression	32	7.2	20.6 mo

KPd = carfilzomib in combination with pomalidomide and dexamethasone; LEN = lenalidomide; mo = months; mOS = median overall survival; mPFS = median progression-free survival; NE = not evaluable
[a] Median number of prior therapies.
[b] Refractory to lenalidomide in any prior line of therapy.

In prior Amgen sponsored trials, the maximum tolerated dose of carfilzomib in combination with dexamethasone was found to be 70 mg/m^2 (CHAMPION-1). In an effort to provide a more convenient but safe and efficacious dose and schedule of carfilzomib, this dose was investigated in the phase 3 superiority A.R.R.O.W. trial and found to have superior efficacy with similar safety profile as the 27 mg/m^2 twice-weekly dose (Moreau et al, 2018). Amgen has also investigated twice-weekly and once-weekly carfilzomib schedules in combination with lenalidomide and dexamethasone. The phase 3 ASPIRE trial demonstrated the safety and efficacy of a 27 mg/m^2 twice-weekly dose of KRd (Stewart et al, 2015). An ongoing phase 1b trial has investigated a weekly schedule of carfilzomib at a dose of 56 mg/m^2 (n = 10) or 70 mg/m^2 (n = 46) in combination with lenalidomide and dexamethasone (Study CFZ013; NCT02335983). The safety profile of the weekly carfilzomib doses (56 and 70 mg/m^2) was consistent with the safety profile of KRd from the ASPIRE trial (Biran et al, 2018), see Table 5-2.

Table 5-2. CFZ-013 and Aspire Safety Summary

Grade ≥ 3 TEAEs Incidence % All data pooled	CFZ 013 KRd	Aspire KRd
Median age (years)	64	64
Lines of therapy, median, study N	1-3, 2, 56 10 at 70 mg/m2 and 46 at 56 mg/m2 weekly	1-3, 2, 392
All Cause, SAE	50, 35.7	83.7, 59.7
Neutropenia	17.7	29.6
Thrombocytopenia	17.8	16.6
Anemia	10.6	17.9
Pneumonia/fever neutropenia	7.1/1.8	2.1 / NR
Dyspnea	1.8	2.8
Hypertension	7.1	4.3
Acute Renal Failure	3.6	3.3
Heart Failure	1.8	3.8

KRd = carfilzomib/lenalidomide/dexamethasone; NR = none reported; TEAE = treatment-emergent adverse event.

Based on evidence from the phase 2 studies of KPd, weekly doses up to 72 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 has identified 56 to 70 mg/m^2 weekly carfilzomib combined with Rd to have an acceptable safety profile. These findings provide support to the proposed combination of Pd with weekly carfilzomib at a dose of 56 mg/m^2. The hypothesis of the study is that a weekly KPd regimen will address the patient need for more convenient dosing schedule while retaining robust efficacy.

5.5 Patient Input on Study Design

No patient input was obtained for this study design.

6. Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). This log will be completed and updated via an Interactive Response Technology (IRT).

Eligibility criteria will be evaluated during screening and collected in the case report form (CRF).

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 or procedures.

102 Male or female subjects age ≥ 18 years

103 First or second relapse of multiple myeloma by International Myeloma Working Group (IMWG) criteria (subjects refractory to the most recent line of therapy, excluding carfilzomib, are eligible)

104 Refractory to lenalidomide

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

- IgG multiple myeloma: serum monoclonal protein (M-protein) level ≥ 1.0 g/dL
- IgA, IgD, IgE multiple myeloma: serum M-protein level ≥ 0.5 g/dL
- urine M-protein ≥ 200 mg per 24 hours

- in subjects without measurable serum or urine M-protein, serum-free light chain (SFLC) ≥ 100 mg/L (involved light chain) and an abnormal serum kappa lambda ratio

107 Must have at least a partial response (PR) to at least 1 line of prior therapy

108 Prior therapy with PI is allowed. Subjects receiving prior carfilzomib therapy must have achieved at least a PR, was not removed due to toxicity, did not relapse within 60 days from discontinuation of carfilzomib, and must have at least a 6 month carfilzomib treatment-free interval from their last dose of carfilzomib.

109 Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 2 (see Section 12.9)

6.2 Exclusion Criteria

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

Disease Related

201 Primary refractory multiple myeloma

202 Waldenström macroglobulinemia

203 Multiple myeloma of IgM subtype

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

205 Plasma cell leukemia ($> 2.0 \times 10^9$/L circulating plasma cells by differential). If automated differential shows ≥ 20% of other cells, obtain manual differential to identify other cells.

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

207 Previous diagnosis of amyloidosis associated with myeloma

208 Myelodysplastic syndrome

209 Toxicity requiring discontinuation of lenalidomide therapy

210 Prior treatment with pomalidomide

Other Medical Conditions

211 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% 5-year disease-free survival

212 Active hepatitis B virus (HBV) infection. Subjects with positive hepatitis B surface antigen (HBsAg) or core antibody (anti-HBc) that achieve sustained virologic response (SVR) with antiviral therapy directed at hepatitis B are allowed. Subjects with known history or resolved infection (negative for HBsAg but positive for antibodies to surface antigen, and/or core antigen) must been screened with HBV DNA levels. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA.

213 Known human immunodeficiency virus (HIV) infection, hepatitis C infection (subjects with hepatitis C that achieve a sustained virologic response after antiviral therapy are allowed). Tests to be performed if required per local country regulations.

214 Presence of graft-versus-host disease including continuation of immunosuppressive therapy despite resolution of graft-versus-host disease

215 Known cirrhosis

216 Uncontrolled hypertension, defined as an average systolic blood pressure ≥ 160 mmHg or diastolic ≥ 100 mmHg despite optimal treatment (measured following European Society of Hypertension/European Society of Cardiology 2018 guidelines; Section 12.10). Subjects with controlled hypertension as defined by the guidelines (link available in Section 12.10) are eligible.

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

218 Intolerance to hydration due to pre-existing pulmonary or cardiac impairment

219 History of interstitial lung disease or ongoing interstitial lung disease

220 Active infection within 14 days prior to enrollment requiring systemic antibiotics, antiviral (except antiviral therapy directed at hepatitis B) or antifungal agents. Such infection must be fully resolved prior to initiating study treatment.

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

222 Known pulmonary hypertension

223 Pleural effusions requiring thoracentesis or ascites requiring paracentesis within 14 days prior to enrollment

Prior/Concomitant Therapy

224 Immunotherapy with potential antimyeloma activity within 21 days prior to enrollment

225 Monoclonal antibody therapy within 21 days prior to enrollment

226 Chemotherapy with approved anticancer therapeutic within 21 days prior to enrollment

227 Plasmapheresis within 21 days prior to enrollment

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

229 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 $< 30\%$ of the bone marrow)

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

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

Prior/Concurrent Clinical Study Experience

232 Currently receiving treatment in another investigational device or drug study, or less than 28 days since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

Diagnostic Assessments

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

234 Hepatic dysfunction within 28 days prior to enrollment:

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

235 Left ventricular ejection fraction $< 40\%$ assessed by transthoracic ECHO

236 Absolute neutrophil count (ANC) $< 1 \times 10^9$/L within 28 days prior to enrollment. Screening ANC should be independent of granulocyte- and granulocyte macrophage-colony stimulating factor support for at least 1 week and of pegylated granulocyte stimulating factor for ≥ 2 weeks

237 Hemoglobin < 80 g/L within 28 days prior to enrollment. Subjects should not have received red blood cell (RBC transfusions) for at least 7 days prior to obtaining the screening hemoglobin.

238 Platelet count $< 50 \times 10^9$/L ($\leq 30 \times 10^9$/L if plasma cell percentage in the bone marrow is $\geq 50\%$) within 28 days prior to start of treatment

Subjects should not have received platelet transfusions for at least 7 days prior to obtaining the screening platelet count.

Other Exclusions

239 Pregnant or breastfeeding female subjects or female subjects who are planning to become pregnant or breastfeed during treatment and for an additional 30 days after the last dose of carfilzomib or pomalidomide (whichever occurs latest).

240 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 carfilzomib or pomalidomide (whichever occurs latest). Additionally, subjects unwilling to use contraception at least 28 days prior to initiating treatment. Refer to Section 12.5 for additional contraceptive information.

241 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 unwilling to undergo pregnancy testing weekly during the first 4 weeks of pomalidomide use followed by a pregnancy test every 4 weeks in females with regular menses or every 2 weeks in females with irregular menstrual cycles.

242 Male subjects with a female partner of childbearing potential who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use contraception during treatment (including during dose interruptions) and for an additional 90 days after the last dose of study treatment. 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 latex or synthetic condom (even if they have had a vasectomy with medical confirmation of surgical success) during treatment (including during dose interruptions) and for an additional 90 days after the last dose of study treatment.

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

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

246 Known history of allergy to carfilzomib or Captisol (a cyclodextrin derivative used to solubilize carfilzomib)

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

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

6.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written Institutional Review Board/Independent Ethics

Committee (IRB/IEC) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 12.3).

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

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment 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 form) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned in IRT. 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.

Subjects who have previously received daratumumab or other anti-CD38 antibody therapy are eligible, if they meet all other inclusion criteria.

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 (reasons for screen failure up to 3), eligibility criteria, and any serious adverse events.

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

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

7. Treatments

Study treatment is defined as any investigational product(s) or non-investigational product(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.

7.1 Treatment Procedures

7.1.1 Investigational Products

7.1.1.1 Carfilzomib

7.1.1.1.1 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.

7.1.1.1.2 Dosage, Administration, and Schedule

Each subject's first dose of carfilzomib will be calculated based upon baseline body surface area (BSA) using the Mosteller formula. In subjects with BSA > 2.2 m^2, the dose should be capped based on a BSA of 2.2 m^2. The dose for each subject should not be revised unless the subject experiences a change in body weight of $> 20\%$ in which case the BSA and dose should be recalculated. The recalculated BSA becomes the new baseline. The dose can also be modified in response to toxicity following the dose modification guideline tables.

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

The planned dose (mg/m^2), dose administered (mg), start date/time, stop date/time, reason for change in planned dose, reason for dose change/withheld, reason for dose

delay, reason for dose interruption and package lot number of carfilzomib are to be recorded on each subject's electronic case report form (eCRF).

Carfilzomib will be administered intravenously over 30 ± 5 minutes, on days 1, 8, and 15 (± 2 days) of each 28-day cycle for up to 12 cycles or progression. A dose of 20 mg/m^2 will be administered on day 1 of cycle 1. All subsequent doses will be 56 mg/m^2. The frequency of carfilzomib administration will be reduced to day 1 and 15 per cycle starting with cycle 13 and continued until progression or end of study.

7.1.1.1.3 IV Prehydration

Subjects may receive IV pre-hydration (normal saline or other appropriate IV fluid) prior to each carfilzomib infusion during cycle 1. Investigators must consider IV pre-hydration in subjects at high-risk for tumor lysis or renal toxicity. All subjects must be monitored for fluid overload and hydration should be tailored to individual needs. It is recommended to use no more than 750 mL IV fluids as a combination of pre- and post-hydration.

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

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

7.1.1.1.4 Hepatic Insufficiency

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

- 15 mg/m^2 day 1 of cycle 1 and 42 mg/m^2 day 8 of cycle 1 and thereafter.

If hepatic function returns to normal, the dose may be re-escalated to 56 mg/m^2 after the first cycle. For dose modification due to subsequent changes in hepatic function, refer to Section 7.4.1.1.2.

Mild and moderate hepatic dysfunction is defined as:

- Mild: elevated bilirubin > 1.0 but ≤ 1.5 x ULN or normal bilirubin with any elevation of AST
- Moderate: elevated bilirubin > 1.5 but < 3 x ULN

7.1.1.2 Pomalidomide

7.1.1.2.1 Dosage Formulation

Pomalidomide will be manufactured and packaged by Celgene.

Pomalidomide is initially supplied as a 4-mg capsule, and supplied as a 3 mg, 2 mg, or 1 mg capsule if dose modification is required (refer to Pomalyst® Prescribing Information or Imnovid® SmPC for more details).

7.1.1.2.2 Dosage, Administration, and Schedule

Pomalidomide dose will be 4 mg per day orally on days 1 to 21 of each cycle until progression.

The planned dose (mg), dose administered (mg), start date, stop date, reason for dose change/withheld, reason for dose delay, are to be recorded on each subject's eCRF.

7.1.1.2.3 Hepatic Insufficiency

For subjects with mild or moderate hepatic impairment, (Child-Pugh classes A or B), the recommended starting dose is 3 mg daily (25% dose reduction). For subjects with severe hepatic impairment (Child-Pugh class C), the recommended dose is 2 mg (50% dose reduction). See Section 12.12.

7.1.2 Non-investigational Products

7.1.2.1 Dexamethasone: Dosage, Administration, and Schedule

Dexamethasone, a non-Amgen non-investigational product, will also be used in this study (Dexamethasone SmPC and USPI). Dexamethasone will be administered at least 30 minutes, but no more than 4 hours prior to carfilzomib on days of carfilzomib administration.

Dexamethasone will be administered at a dose of 40 mg on days 1, 8, 15, and 22 of each 28-day cycle up to progression during cycles 1 to 12.

Dexamethasone will be administered at a dose of 20 mg on days 1 and 15 of each 28-day cycle up to progression during cycles 13 onward.

For subjects ≥ 75 years of age, the dose will be 20 mg during cycles 1 through 12 and 10 mg from cycles 13 onward.

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

7.1.3 Medical Devices

There are no investigational medical devices being used in this study.
Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

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

7.1.4 Other Protocol-required Therapies

All other protocol-required therapies including, antiviral prophylaxis, and proton pump inhibitor or protocol recommended therapies including thromboprophylaxis, tumor lysis syndrome prophylaxis, bone preserving therapy, prophylaxis for Pneumocystis jiroveci pneumonia, and for at-risk subjects, prophylaxis for Hepatitis B virus reactivation that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies.

7.1.4.1 Antiviral Prophylaxis

An antiviral is a required concomitant medication for the duration of treatment with carfilzomib. Acyclovir, famciclovir, or valacyclovir should be administered per institutional standards, dose adjustments for renal function where appropriate, initiated within 1 week of the first dose of carfilzomib and should continue for the duration of treatment with carfilzomib.

7.1.4.2 Proton-pump Inhibitor

Proton-pump inhibitor (omeprazole or equivalent) is required while on high-dose dexamethasone (40 mg or 20 mg weekly).

7.1.4.3 Thromboprophylaxis

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

7.1.4.4 Tumor Lysis Syndrome Prophylaxis or Therapy

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

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

7.1.4.5 Bone Preserving Therapy / Bone Targeting Agents

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

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

7.1.4.6 Prophylaxis for Pneumocystis Jiroveci

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

7.1.4.7 Prophylaxis for Hepatitis B Virus Reactivation

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

7.1.4.8 Other Permitted Therapies

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

- antivirals
- medications to control hyperglycemia
- medications to prevent constipation (eg, adequate hydration, high-fiber diet, and stool softeners, if needed)
- prophylactic antiemetics, with the exception of corticosteroids
- granulocyte colony stimulating factors (as clinically indicated; may be used prophylactically after cycle 1), erythropoietin, and transfusion of platelets and red blood cells (RBCs)
- 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.

7.1.5 Other Treatment Procedures

No other treatment procedures are required.

7.1.6 Product Complaints

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

This includes any investigational or non-investigational products provisioned and/or repackaged/modified by Amgen.

. carfilzomib

. pomalidomide

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

Product complaints must be reported to Amgen within 24 hours.

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

7.1.7.1 Anticancer Therapeutic or Radiation

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

7.1.7.2 Plasmapheresis

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

7.1.7.3 Corticosteroids

Long-term corticosteroids for nonmalignant conditions (eg, asthma, inflammatory bowel disease) equivalent to a dexamethasone dose $>$ 4 mg/day or prednisone $>$ 20 mg/day are not permitted. Corticosteroids given short-term (up to 2 weeks) for non-malignant conditions are permitted provided that the cumulative dose is less than 40 mg per week dexamethasone equivalent (less than 20 mg dexamethasone equivalent for subjects ≥ 75 years of age). Medical monitor should be contacted if short-term corticosteroid use is required $>$ 2 weeks or at cumulative dose of more than 40 mg dexamethasone equivalent or 20 mg for subjects ≥ 75 years of age.

7.1.7.4 Prohibited Therapies

Use of the treatments listed below is prohibited during the study:

- Subjects may not receive treatment with an investigational drug or device while participating in this study
- During cycle 1, the prophylactic use of hematopoietic growth factors is prohibited
- Other agents that target CD38
- Medications used for other indications that have antimyeloma properties (for example, interferon and clarithromycin (Ghosh et al, 2014)
- Administration of approved or investigational treatments for multiple myeloma (including but not limited to conventional chemotherapies, IMiDs, or proteasome inhibitors other than those agents that are part of the regimen for which the subject was enrolled)
- Concomitant administration of investigational agents is prohibited. Administration of commercially available agents with activity against or under investigation for multiple myeloma are not permitted

Continuation of study drug during or after emergency orthopedic surgery or radiotherapy because of subject benefit may only occur in the absence of disease progression and after consultation with and approval by the sponsor. Such emergency radiotherapy may consist of localized radiotherapy for pain control or for stabilization of an extensive bone lesion at high risk of pathologic fracture or damage to surrounding tissues in a subject in whom delay of systemic therapy is not appropriate. Such radiotherapy is to occur within the first 2 cycles of treatment and the absence of evidence of disease progression is to be reviewed and approved by the sponsor.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

7.2 Method of Treatment Assignment

Subjects who meet eligibility criteria will be treated with KPd.

7.3 Blinding

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

7.4 Dose Modification

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

7.4.1.1 Amgen Investigational Product: Carfilzomib

Carfilzomib will be discontinued, temporarily delayed, or dosage temporarily reduced, in the event of a treatment-related toxicity that, in the opinion of the investigator, warrants the discontinuation, temporary delay or dose reduction as indicated in Table 7-2 and Table 7-3 (refer to Table 7-5 and Table 7-6 for KPd pomalidomide dosage adjustments).

Dose reduction levels of carfilzomib for toxicity management of individual subjects are provided in Table 7-1. Subjects who require a dose level reduction and tolerate the reduced dose for 1 full cycle may at the discretion of the treating physician increase the dose to a prior dose starting with the next cycle except when the dose reduction is due to: pulmonary hypertension, pulmonary toxicity, grade 3 or worse cardiac failure, or drug-induced hepatotoxicity.

Table 7-1. Dose Decrements for Carfilzomib

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

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

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

If day 1 of a cycle is delayed, all subsequent doses within the cycle and day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. However, if a within-cycle dose is delayed, then the dates of the subsequent within-cycle doses should not be adjusted. For within-cycle doses, if administration does not commence within the allowable window of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up. There should be a minimum of 5 days between carfilzomib doses.

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

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

7.4.1.1.1 Carfilzomib: Guidelines for Hematologic Toxicity

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

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

Hematologic toxicity	Recommended Action	
Thrombocytopenia		
When platelets fall to $< 30 \times 10^9/L$ and for each subsequent drop to $< 30 \times 10^9/L$	If platelets 10 to $30 \times 10^9/L$ without evidence of bleeding	• hold • restart at previous dose when platelets $> 30 \times 10^9/L$
	If evidence of bleeding or platelets $< 10 \times 10^9/L$	• hold • restart at 1 dose decrement when platelets

		> 30 x 10^9/L and bleeding is controlled
Neutropenia		
When ANC falls to < 0.75 x 10^9/L and for each subsequent drop to < 0.75 x 10^9/L	If ANC 0.5 to 0.75 x 10^9/L	continue at full dose
	If ANC < 0.5 x 10^9/L	• hold dose • resume at 1 dose decrement when ANC ≥ 0.5 x 10^9/L

ANC = absolute neutrophil count.

7.4.1.1.2 Carfilzomib: Guidelines for Nonhematologic Toxicity

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

Table 7-3. Carfilzomib Modification Guidelines for Nonhematologic Toxicities

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

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Footnotes defined on last page of the table

Table 7-3. Carfilzomib Modification Guidelines for Nonhematologic Toxicities

Symptom/Sign/Investigation	Recommended Action
Other Nonhematologic Toxicities	
Tumor lysis syndrome: 3 or more of the following: increase in creatinine of ≥ 50% from baseline increase in uric acid of ≥ 50% from baseline increase in phosphate of ≥ 50% from baseline increase in potassium of ≥ 30% from baseline decrease in calcium from baseline OR increase in LDH of ≥ 2-fold from baseline	Hold carfilzomib until all abnormalities in serum chemistries have resolved; resume at full dose.
Congestive heart failure	Any subject with congestive heart failure, whether or not drug-related, must have the dose held until resolution or return to baseline. Appropriate medical management should be initiated and continued as clinically indicated. If no resolution after 4 weeks, carfilzomib will be permanently discontinued.
< Grade 3	Once congestive heart failure resolves or returns to baseline, resume at full dose.
≥ Grade 3	Once congestive heart failure resolves or returns to baseline, treatment may continue at 1 dose level reduction.
Infection (grade 3 or 4)	Hold carfilzomib. Once infection is controlled and the subject is without infection-related symptoms, and if ANC > 1.0×10^9/L, resume at full dose. If ANC < 1.0×10^9/L, follow hematologic toxicities dose reduction guidelines.
Hepatitis B reactivation	Hold carfilzomib until infection is adequately controlled (see Section 7.1.4.7 for guidance on Hepatitis B virus reactivation prophylaxis).
Neuropathy (grade 2 with emergent pain, or grade 3)	Hold carfilzomib until resolved to ≤ grade 2 without pain; then resume at 1 dose decrement.
Neuropathy (grade 4)	Permanently discontinue carfilzomib.
Dyspnea (grade ≥ 2)	Hold carfilzomib until resolution to grade 1 or baseline, then resume at 1 dose decrement. Investigate cause and record findings. If caused by another adverse event listed in this table, follow recommendations for that adverse event.

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Footnotes defined on last page of the table

Table 7-3. Carfilzomib Modification Guidelines for Nonhematologic Toxicities

Symptom/Sign/Investigation	Recommended Action
Hypertension (SBP > 140 and/or DBP > 90, measured per Section 12.10)	
< Grade 3	Continue at same dose and initiate appropriate treatment to control hypertension (see Section 12.10 for link to guidance).
≥ Grade 3	Hold carfilzomib until resolution to normal or baseline. Initiate appropriate antihypertensive therapy prior to resuming carfilzomib at 1 dose decrement.
Pulmonary toxicity: Non-infectious interstitial lung disease, acute respiratory failure, ARDS (≥ grade 3)	Hold carfilzomib until resolution to grade 1 or baseline and restart at 1 dose decrement.
Pulmonary hypertension (grade ≥ 3)	Hold carfilzomib until resolution to grade 1 or baseline and restart at 1 dose decrement
Posterior reversible encephalopathy syndrome: Headaches, altered mental status, seizures, visual loss, and hypertension	If PRES is suspected, hold carfilzomib. Consider evaluation with neuroradiological imaging, specifically MRI, for onset of visual or neurological symptoms suggestive of PRES. If PRES is confirmed, permanently discontinue carfilzomib. If the diagnosis of PRES is excluded, carfilzomib administration may resume at same dose, if clinically appropriate.
Progressive multifocal leukoencephalopathy	Patients should be monitored for any new or worsening neurologic, cognitive or behavioral signs, or symptoms that may be suggestive of PML as part of the differential diagnosis of CNS disorders. If PML is suspected, withhold administration of carfilzomib; patients should be promptly referred to a specialist and appropriate diagnostic testing should be initiated. Discontinue carfilzomib if PML diagnosis is confirmed.
Thrombotic microangiopathy: Fever, microangiopathic hemolytic anemia, renal failure, thrombocytopenia, neurological manifestations	If the diagnosis is suspected, hold carfilzomib and manage per standard of care including plasma exchange as clinically appropriate. If TMA is confirmed, permanently discontinue carfilzomib. If the diagnosis is excluded, carfilzomib can be restarted
Venous thrombosis (≥ grade 3)	Hold carfilzomib and adjust anticoagulation regimen; resume at full dose once anticoagulation has been optimized per treating investigator's discretion.
Any other drug-related nonhematologic toxicity ≥ grade 3[b]	For carfilzomib attribution, hold dose. Resume at 1 dose decrement when toxicity has resolved to grade 1 or less or to baseline grade.

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ALT = alanine aminotransferase; ANC = absolute neutrophil count; ARDS = acute respiratory distress syndrome; AST = aspartate aminotransferase; CNS = central nervous system; CrCl = creatinine clearance; DBP = diastolic blood pressure; KRD = carfilzomib in combination with lenalidomide and dexamethasone; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; PML = Progressive multifocal leukoencephalopathy; PRES = Posterior Reversible Encephalopathy Syndrome; SBP = systolic blood pressure; TMA = thrombotic microangiopathy; ULN = upper limit of normal.

Table 7-3. Carfilzomib Modification Guidelines for Nonhematologic Toxicities

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[a] For a rapid fall from baseline in CrCl or an absolute fall of ≥ 60 mL/min, contact the medical monitor.
[b] In the event of a possible drug-related nonhematologic toxicity, the investigator should, to the best of his/her ability, assess its relationship to pomalidomide (P), carfilzomib (K), dexamethasone (d), or the combination of K**P**d to the extent possible.

7.4.1.1.3 Conditions Not Requiring Carfilzomib Dose Reduction

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

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

7.4.1.2 Non-Amgen Investigational Product: Pomalidomide

Dose reduction levels of pomalidomide for toxicity management of individual subjects are provided in Table 7-4.

Table 7-4. Dose Decrements for Pomalidomide

	Reduced Pomalidomide Doses (mg/m^2)		
Nominal Dose[a]	Dose -1	Dose -2	Dose -3
4 mg	3 mg	2 mg	1 mg

Pomalidomide will be discontinued, temporarily delayed, or dosage temporarily reduced, in the event of a treatment-related toxicity that, in the opinion of the investigator, warrants the discontinuation, temporary delay or dose reduction as indicated in Table 7-5 and Table 7-6.

Table 7-5. Pomalidomide Modification Guidelines for Thrombocytopenia and Neutropenia

	Recommended Action
	Pomalidomide
Neutropenia	
ANC < 500 per mcL or ANC < 1000 per µL with fever ≥ 38.5°C	Interrupt pomalidomide treatment, follow complete blood count (CBC) weekly, administer myeloid growth factor

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Footnotes defined on last page of the table

Table 7-5. Pomalidomide Modification Guidelines for Thrombocytopenia and Neutropenia

	Recommended Action
	Pomalidomide
Neutropenia (continued)	
ANC return to ≥ 500 per µL	Resume pomalidomide at 3 mg daily
For each additional drop < 500 per µL	Interrupt pomalidomide treatment
Return to ≥ 500 per µL	Resume pomalidomide at 1 mg less than the previous dose
Thrombocytopenia	
Platelets < 25 000 per µL	Interrupt pomalidomide treatment, follow CBC weekly
Platelets return to > 50 000 per µL	Resume pomalidomide at 3 mg daily
For each additional drop < 25 000 per µL	Interrupt pomalidomide treatment
Return to ≥ 50 000 per mcL	Resume pomalidomide at 1 mg less than the previous dose

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ANC = absolute neutrophil count; CBC = complete blood count

Table 7-6. Pomalidomide Modification Guidelines for Nonhematologic Toxicities

	Recommended Action
Symptom/Sign/Investigation	**Pomalidomide**
Rash = grade 3	**Interrupt pomalidomide. Decrease by one dose level when dosing is resumed at next cycle (rash must be resolved or improved to ≤ grade 1 before dose resumption.**
Rash = grade 4 or blistering (including angioedema, anaphylactic reactions, exfoliative or bullous rash or if Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected.	**Permanently discontinue study treatment**
Venous Thromboembolic events (VTE) ≥ grade 3	**Interrupt dose and initiate anticoagulation treatment. Maintain dose levels when dosing resumed at next cycle at discretion of treating physicians.**
Other ≥ grade 3 pomalidomide-related adverse events	**Interrupt pomalidomide. If dose reduction is appropriate, interrupt pomalidomide for the remainder of the cycle. Start the reduced dose on day 1 of the next cycle. Adverse event should be resolved or improved to ≤ grade 2 before restarting treatment.**

7.4.1.3 Non-Amgen Non-Investigational Product: Dexamethasone

Dexamethasone may be discontinued, temporarily delayed, or dosage temporarily reduced, in the event of a treatment-related toxicity that, in the opinion of the investigator, warrants the discontinuation, temporary delay or dose reduction. Investigators are advised to consult the approved regional labeling for dexamethasone for additional details.

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

7.4.2 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 7.4.1 for stopping and rechallenging requirements when subjects have abnormal hepatic laboratory values (ie, AST, ALT, total bilirubin) and/or signs/symptoms of hepatitis. Carfilzomib should be discontinued for drug-induced hepatotoxicity attributable to carfilzomib.

7.5 Preparation/Handling/Storage/Accountability

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

7.6 Treatment Compliance

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

7.7 Treatment of Overdose

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

7.8 Prior and Concomitant Treatment

7.8.1 Prior Treatment

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

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

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

Prior therapies for non-multiple myeloma conditions that were being taken/used from 30 days prior to signing of the ICF will be collected on the Concomitant Medications eCRF. Collect therapy name, indication, dose, unit, frequency, start and stop dates.

7.8.2 Concomitant Treatment

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

Concomitant therapies are to be collected from informed consent through the 30 days after the last dose of all study drug(s). For all concomitant therapies, collect therapy name, indication, dose, unit, frequency, start and stop dates and record on Concomitant Medications eCRF.

It is recommended to follow the Eighth Joint National Committee 2014 and 2018 ESC/ESH evidence-based guidelines for the management of high blood pressure in adults (Williams et al, 2018; James et al, 2014; and Section 12.10).

8. Discontinuation Criteria

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

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

8.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the

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

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- decision by investigator or sponsor
- lost to follow-up
- death
- ineligibility determined
- protocol deviation
- non-compliance
- adverse event
- subject request
- disease progression
- pregnancy

8.2 Discontinuation From the Study

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

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

to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

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

Not applicable.

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

8.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study 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 IRT and screen the subject in order to assess eligibility for participation. The screening window is up to 28 days from date of consent until enrollment.

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

9.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 2-1). Subjects assessed as eligible for the study will be enrolled and must start study treatment within 3 days of enrollment. On-study visits may be completed within 3 days. The date of the first dose of protocol-required therapies is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Administration of protocol-required therapies is to be administered last during each visit that it is required, unless otherwise indicated in the Schedule of Activities.

After discontinuation from study treatment, subjects who do not have confirmed PD are required to continue disease response assessments and report new antimyeloma treatment and will be followed every 28 ± 7 days until first subsequent antimyeloma

treatment, death, loss to follow-up, withdrawal of full consent, confirmed PD, or end of study, whichever comes first.

9.1.3 Safety Follow-up

Upon discontinuation from the study treatment for any reason, a safety follow-up visit will be performed approximately 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.

9.1.4 Long-term Follow-up

After discontinuation from study treatment and the subject either starts new antimyeloma treatment or has PD, they enter long-term follow-up. Survival information will be collected as indicated in the Schedule of Activities (Table 2-1). Long-term follow-up may continue until end of study.

9.1.4.1.1 End of Study

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

The end of study visit will occur for all subjects who have not discontinued from the study 4 years after last subject enrolled. This could either be a safety follow-up visit 30 (+3) days after last dose of study drug(s) or a final long-term follow-up survival assessment.

9.2 Description of General Study Assessments and Procedures

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

9.2.1 General Assessments

All of the assessments below and in the Schedule of Activities (Table 2-1) will be recorded on the eCRF.

9.2.1.1 Informed Consent

All subjects must sign and personally date the IRB/IEC 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.

Additionally, demographic data will be used to study the impact on biomarker variability and PK of the protocol-required therapies.

9.2.1.3 Medical History

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

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

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).

9.2.1.5 Physical Measurements

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

Body surface area should be calculated using the Mosteller Formula (Mosteller, 1987):

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

9.2.1.6 Substance Abuse History

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

9.2.1.7 Performance Status

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

9.2.2 Efficacy Assessments

Disease assessments will be based on local laboratory data and local imaging obtained in accordance with the IMWG-Uniform Response Criteria (IMWG-URC) (Section 12.11) until confirmed PD (Section 9.2.2.6) irrespective of cycle duration including dose delays and treatment discontinuation as indicated in the Schedule of Activities (Table 2-1). After discontinuation from study treatment, subjects who do not have confirmed PD are required to continue disease response assessments and report new antimyeloma

treatment and will be followed every 28 ± 7 days until first subsequent antimyeloma treatment, death, loss to follow-up, withdrawal of full consent, confirmed PD, or end of study, whichever comes first.

Disease response and progression assessments include: serum and urine protein electrophoresis (SPEP, urine protein electrophoresis [UPEP], respectively), SFLC, serum and urine immunofixation (SIFE, UIFE, respectively) (Section 9.2.2.1), quantitative IgA, IgD, or IgE (for subjects with IgA/IgD/IgE myeloma), bone marrow sample evaluation (Section 9.2.2.2), serum calcium, bone lesion assessment (Section 9.2.2.3) and extramedullary plasmacytoma evaluation (Section 9.2.2.5).

9.2.2.1 SPEP, UPEP, SFLC, SIFE, and UIFE

Serum protein electrophoresis, UPEP, SIFE, UIFE, and SFLC will all be conducted at the local laboratory. Samples will be collected every 28 ± 7 days (starting from cycle 1 day 1) irrespective of cycle duration including dose delays and treatment discontinuation. Blood will be obtained for SFLC, SPEP, and SIFE. Twenty-four-hour urine samples will be obtained for UPEP and UIFE. Results for SPEP, UPEP, or SFLC must be available at screening and before enrollment. Serum protein electrophoresis, UPEP, and SFLC will be repeated on cycle 1 day 1 (unless screening values are within 14 days of cycle 1 day 1). Post cycle 1 day 1, UPEP and UIFE will be measured every disease assessment as well as SPEP and SIFE. Subjects with IgA, IgD, or IgE myeloma must have a quantitative IgA, IgD, or IgE (as appropriate) with each response assessment.

Subjects will be evaluated for disease response and progression according to the IMWG response criteria in Section 12.11 (Kumar et al, 2016). Disease status categories include sCR, CR, VGPR, PR, SD, and PD.

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

* Every effort should be made to obtain 2 consecutive samples at any time prior to initiation of any new therapy. If not possible to obtain the second consecutive assessment to confirm disease progression before initiation of any new therapy, this confirmatory sample for disease progression may be obtained after the new therapy is initiated.

- all response categories require 2 consecutive assessments made at any time before initiation of any new therapy
- all categories other than progression also require no known evidence of progression including new bone lesions if radiographic studies were performed
- confirmation of CR or better requires bone marrow assessment (aspirate or biopsy per IMWG-URC guidelines)

- extramedullary plasmacytoma evaluation (if present at screening)
- a second assessment is not required for radiographic and bone marrow assessments

Disease parameters needed to determine disease response, progression, and IRC adjudication will be collected via patient eCRFs and reviewed by the IRC.

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

A baseline bone marrow aspirate sample will be collected at screening, or prior to dosing at cycle 1 day 1. A bone marrow sample obtained as standard of care may be used as the baseline sample if taken within 45 days prior to enrollment for FISH and MRD testing. The first sample obtained for baseline bone marrow aspirate will be for tumor specific sequence identification for MRD measurement by next-generation sequencing (NGS) at the central lab.

After screening, bone marrow aspirate will be obtained:

- at time of suspected CR or better. Depending on when this procedure occurs, an additional aliquot of bone marrow aspirate will be frozen and saved at the central lab for MRD testing to be performed at a later time.
- at time of MRD assessment. MRD will be conducted in subjects with suspected CR or better at 12 months ($\pm$ 4 weeks) but may be performed as early as 8 months after start of treatment in subjects with suspected CR or better. Subjects with a MRD[-]CR response at the first time point should have the subsequent MRD assessment 12 months $\pm$ 4 weeks after the earlier assessment, if subjects have not relapsed nor started new antimyeloma therapy prior to this subsequent MRD assessment.

If the bone marrow aspirate sample taken is found to be of insufficient quantity or quality for testing, the site may be contacted to request provision of a suitable archival bone marrow aspirate sample.

9.2.2.3 Bone Lesion Assessment (Skeletal Survey, Computed Tomography [CT], or Positron Emission Tomography/CT [PET/CT])

Skeletal survey will include lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. Low-dose whole body computed tomography or fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) may be used in place of skeletal survey. Bone lesion assessment at screening (all subjects) may be done within 28 days prior to enrollment, if performed as a part of standard of care. It should be repeated if worsening clinical symptoms suggest PD or as clinically indicated. The same method of

assessment used at baseline will be used throughout the study. These imaging studies will be read locally.

9.2.2.4 Quantitative Immunoglobulin

Quantitative immunoglobulins IgG, IgM, and IgA will be performed at screening for all subjects. If IgD or IgE type of myeloma, IgD or IgE will be performed as well.

After screening, quantitative IgA, IgD, and IgE will be assessed every 28 days (± 7 days) in subjects with IgA, IgD, or IgE myeloma, respectively.

Quantitative immunoglobulins (IgG, IgM, IgA) will be repeated every 12 months ± 2 weeks from cycle 1 day 1 in subjects with PR or better, or if applicable, may be done at time of MRD assessment. Immunoglobulins may also be obtained more frequently as clinically indicated.

9.2.2.5 Extramedullary Plasmacytoma

Extramedullary plasmacytoma evaluation will be conducted at screening only if a lesion is suspected clinically. The evaluation may be done within 28 days prior to enrollment, if performed as a part of standard of care. If a measurable extramedullary plasmacytoma is detected during screening, evaluation will be repeated during treatment to confirm a response of PR or better, or to confirm PD, or as clinically indicated. Plasmacytomas identified by physical examination during screening should be monitored by physical examination locally every 28 (± 7) days until undetectable and then as clinically indicated. If assessment can only be performed radiologically, then evaluation of extramedullary plasmacytomas should be done every 12 weeks ± 2 weeks until a plateau or CR. Radiographical assessment may be done as clinically indicated and at the time of suspected disease progression. The same technique, which may include clinical evaluation by palpation, ultrasound, CT scan, magnetic resonance imaging (MRI), or positron emission tomography/computed tomography (PET/CT) should be employed for each measurement of plasmacytoma dimensions as clinically appropriate (refer to Section 12.11). Bidimensional lesion measurements must be performed and recorded in the designated eCRF.

9.2.2.6 Progressive Disease Assessment

Confirmation of PD requires 2 consecutive assessments made at any time before the initiation of any new therapy*, as well as no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to

satisfy these response requirements. Bone marrow, plasmacytoma, and skeletal survey assessments are not required to be confirmed by repeat testing.

* Every effort should be made to obtain 2 consecutive samples at any time prior to initiation of any new therapy. If not possible to obtain the second consecutive assessment to confirm disease progression before initiation of any new therapy, this confirmatory sample for disease progression may be obtained after the new therapy is initiated.

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

9.2.3 Safety Assessments

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

9.2.4 Adverse Events and Serious Adverse Events

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.

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

9.2.4.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) version 5 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 informed consent through 30 days after the last dose of study drugs (carfilzomib, pomalidomide, and dexamethasone) are reported using the Events CRF.

9.2.4.1.2 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 informed consent through the end of long-term follow-up or 30 days after the last dose of study drugs (carfilzomib, pomalidomide, and dexamethasone), whichever comes later, are reported using the Events CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours of the investigator's awareness of the event, 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.

Since the criteria in the CTCAE grading scale differs from the regulatory criteria for serious adverse events**, if adverse events correspond to grade 4 CTCAE toxicity grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life-threatening status), it will be** left to the investigator's judgment to **also** report these abnormalities as serious adverse events**. For any adverse event that applies to this situation, comprehensive documentation of the event's severity must be recorded in the subject medical records**.

9.2.4.1.3 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 (as defined in Section 9.2.4.1.2) or after end of study. However, these serious adverse events should be reported to Amgen (regardless of causality) if the investigator becomes aware of them. 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 awareness of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product. **If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.**

9.2.4.2 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.

9.2.4.3 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 awareness 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 Events CRF.

9.2.4.4 Regulatory Reporting Requirements for Serious Adverse Events

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

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

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

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

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

9.2.4.5 Safety Monitoring Plan

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

9.2.4.6 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 after last dose of study drugs for female subjects and 90 days after last dose of study treatment for male subjects.

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.

9.2.4.7 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, temperature, and, if available, respiratory rate and oxygen saturation in the event of a cardiac and/or pulmonary adverse events.

Subject must be in a sitting 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 sitting position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital signs eCRF. Take 2 blood pressure measurements spaced 1 to 2 minutes apart and additional measurements if the first 2 are more than 10 mmHg apart for either systolic or diastolic blood pressure.

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

9.2.4.8 Electrocardiograms (ECGs)

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The ECG must include the following measurements: heart rate, QRS, QT, QTc, and PR intervals. The principal investigator or (eg, designated site physician) will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

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

9.2.4.9 Vital Status

Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued study visits with or without withdrawing consent and should include interrogation of public databases, if necessary. If deceased, the date and reported cause of death should be obtained.

9.2.4.10 Other Safety

9.2.4.10.1 Echocardiogram

All subjects will have a baseline complete ECHO, not simply clearance of left ventricular ejection fraction (LVEF), including assessments of systolic and diastolic left ventricular function and right ventricular function and valvular stenosis or insufficiency. Screening ECHO may be done within 28 days prior to enrollment, if performed as a part of standard of care. Echocardiogram is to be repeated approximately every 6 months (± 2 weeks) from cycle 1 day 1 until safety follow-up visit, or more often if clinically indicated. An ECHO must be performed within 72 hours of the onset of a suspected cardiac failure event. Real-time blood pressure at time of ECHO will be collected on the CRF.

9.2.4.10.2 Pulmonary Function Tests (PFTs)

Pulmonary function tests include spirometry to measure FEV1, %FEV1, FEV1/forced vital capacity, forced vital capacity, and diffusing capacity of the lungs for carbon monoxide (DLCO) assessment. Screening PFT measurements may be done within 28 days prior to enrollment, if performed as a part of standard of care. All subjects will have PFTs assessed approximately every 6 months (± 2 weeks) from cycle 1 day 1, until safety follow-up visit, or more often if clinically indicated. Serial measurements should be performed with the same equipment and comparable procedure.

9.2.4.10.3 Hepatitis B

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

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

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

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

9.2.5 Clinical Laboratory Assessments

Refer to 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 Events 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 laboratory manual and the Schedule of Activities (Table 2-1).

9.2.5.1 Pregnancy Testing

A high sensitive (urine or serum) pregnancy test should be completed 14 days prior to first dose of study drug and again 24 hours prior to first dose of study drug for females of childbearing potential.

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 be performed weekly during the first 4 weeks of pomalidomide use followed by a pregnancy test every 4 weeks in females with regular menses or every 2 weeks in females with irregular menstrual cycle, and approximately 30 days after the last dose of study drugs.

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

9.2.6 Pharmacokinetic Assessments

Approximately 20 subjects will be invited to participate in an optional pharmacokinetic (PK) substudy.

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

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

9.2.7 Pharmacodynamic Assessments

Approximately 20 subjects will be invited to participate in an optional PDn substudy.

Venous blood samples of approximately 6 mL will be collected for measurement of proteasome inhibition as specified in the Schedule of Activities (Table 2-1).

9.2.8 Pharmacogenetic Assessments

If the subject consents to the optional pharmacogenetics portion of this study, bone marrow aspirate (1 – 2 mL in EDTA) will be collected and sent to the central laboratory for CD138 selection of tumor cells. The bone marrow samples will be collected from consenting subjects during screening and at disease progression if a bone marrow biopsy is performed to confirm. These optional pharmacogenetics analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help the investigation of and/or to identify subjects who may have positive or negative response to the therapies administered in this study.

9.2.9 Biomarker Samples

If the subject consents to the optional biomarker portion of this study, 2 to 5 mL of peripheral blood in EDTA will be collected at screening and at the time of bone marrow evaluation for determination of MRD. Samples will be frozen and stored for later use in exploring methods for MRD detection of [redacted] in peripheral blood. The levels of [redacted] will be compared to results from screening peripheral blood and MRD measurements in the bone marrow from the 12- and 24-month assessments ± 4 weeks.

10. Statistical Considerations

10.1 Sample Size Determination

The sample size was determined based on feasibility and the intent to optimize the power for testing the primary hypothesis at 1-sided alpha of 0.05. With 85 subjects, the power for testing the primary hypothesis and secondary hypothesis at 1-sided alpha of 0.05 is expected to be more than 85%. As these estimates are based on recent data available in the study population (eg, sub-populations within clinical trials CANDOR and A.R.R.O.W.), additional scenarios, **including those based on the actual number of subjects who received at least one dose of carfilzomib (52 subjects)**, for the experimental arm and power are included in Table 10-1.

Table 10-1. Power and Hypothesized Treatment Effect

Hypothesis	Sample Size	H0	H1	Power
Primary	**85**	**ORR ≤ 60%**	**ORR ≥ 75%**	**90.4%**
	85	**ORR ≤ 60%**	**ORR ≥ 80%**	**99.3%**
	52	**ORR ≤ 60%**	**ORR ≥ 75%**	**69.2%**
	52	**ORR ≤ 60%**	**ORR ≥ 80%**	**91.8%**
Secondary	85	MRD[-]CR rate at 12 months ≤ 3%	MRD[-]CR rate at 12 months ≥ 10%	86.4%
	85	MRD[-]CR rate at 12 months ≤ 3%	MRD[-]CR rate at 12 months ≥ 12%	95.1%
	52	**MRD[-]CR rate at 12 months ≤ 3%**	**MRD[-]CR rate at 12 months ≥ 10%**	**60.5%**
	52	**MRD[-]CR rate at 12 months ≤ 3%**	**MRD[-]CR rate at 12 months ≥ 12%**	**76.3%**

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

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

Safety Analysis Set

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

MRD Evaluable Analysis Set

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

Pharmacokinetic Analysis Set

The PK Analysis Set will include a subset of up to 20 evaluable subjects in Safety Analysis Set, who have participated in the PK assessment. Evaluable subjects are defined as those subjects providing sufficient PK samples to permit estimation of PK parameters on cycle 2 day 1.

10.2.2 Covariates

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

10.2.3 Subgroups

Primary endpoints will be examined for the below subgroup analysis, if appropriate:

- prior carfilzomib exposure (yes vs no)
- number of prior lines of therapy (1 vs 2)
- timing of lenalidomide refractoriness (during maintenance: yes vs no)

10.2.4 Handling of Missing and Incomplete Data

Subjects may have missing data points for various reasons and the impact on the analysis might differ from 1 endpoint to another. The general rules for accommodating the missing or incomplete data may be refined during the review of the data, and they will be described in detail in the statistical analysis plan (SAP). Sensitivity analyses might be needed to evaluate the robustness of the primary analysis results in case of significant missing data. Incomplete dates for the start of adverse event, concomitant medications, and death will be imputed and the detailed rules will be specified in the SAP.

10.3 Adaptive Design

Adaptive design is not applicable for this study.

10.4 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.

10.4.1 Planned Analyses

10.4.1.1 Primary Analysis

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

10.4.1.2 Sustained MRD Analysis

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

10.4.1.3 Final Analysis

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

10.4.2 Methods of Analyses

10.4.2.1 General Considerations

The analyses of efficacy and safety will be based on the safety analysis set defined in Section 10.2.1.

In principle, continuous variables will be summarized by the non-missing sample size (n), mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by the n and percentage in each category. Time to event endpoints will be summarized with KM curves, KM proportions at select time points, KM quartiles (when estimable), the number of subjects with events, the number of subjects censored, and censoring reasons. Duration of follow-up for time to event endpoints will be estimated using the reverse Kaplan Meier method (Schemper and Smith, 1996). Point estimates for efficacy endpoints will be accompanied by 2-sided 90% and 95% CIs including estimates of KM quartiles (Klein and Moeschberger, 1997), KM proportions (Kalbfleisch and Prentice, 1980), and binomial proportions (Clopper and Pearson, 1934). **The evaluation of whether the key secondary objective was met will follow a**

fixed-sequence approach using the 90% exact confidence interval: the key secondary objective is met only after the primary objective is met.

10.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	**Overall Response Rate** **Overall Response Rate (ORR)** is defined as the proportion of subjects **that** reach **the overall response** among all subjects who received at least 1 dose of **the** carfilzomib. **It** will be calculated along with the associated 90% and 95% exact binomial CIs that will be estimated using the Clopper-Pearson method. **The** lower bound of the 90% exact binomial CI is **evaluated whether it is larger** than the reference **ORR. If that happens, then** the primary objective is met.
Key Secondary	**MRD[-]CR at 12 months at a sensitivity of 10^{-5} using NGS-based method in the bone marrow** **MRD[-]CR rate at 12 months landmark** is defined as the proportion of subjects **who** reach **MRD[-]CR at 12 months landmark assessment** among all subjects who received at least 1 dose of carfilzomib. **The rate** will be calculated along with the associated 90% and 95% exact binomial CIs that will be estimated using the Clopper-Pearson method. **If the primary objective is met, then** the lower bound of the 90% exact binomial CI is evaluated whether it is **greater** than the reference **MRD[-]CR rate.** If that happens, the key secondary objective is met. **The primary analyses for the key secondary endpoint will be based on the safety analysis set, while the sensitivity analyses will be performed on the MRD-evaluable analysis set.** **The data for the key secondary endpoint will include the MRD results from bone marrow samples obtained from subjects with suspected CR or better obtained no earlier than 8 months and no later than 12 months (+ 4 weeks) after enrollment.**
Secondary	MRD[-] response at a sensitivity of 10^{-5} using NGS based method in the bone marrow at any time during therapy MRD[-] rate at any time during therapy is defined as the proportion of subjects who reach MRD[-] at any time during therapy among all subjects who received at least 1 dose of carfilzomib. It will be analyzed using the same method as described for the **key secondary** endpoint. The data will include the MRD results from bone marrow samples obtained from the subjects with a response of VGPR or better at any time during therapy. Sustained MRD[-]CR Sustained MRD[-]CR rate is defined as the proportion of subjects that maintain MRD[-]CR for 12 months or more after achieving MRD[-]CR status among the subjects who reach the MRD[-]CR status at their first MRD assessment. It will be calculated along with the associated 90% and 95% exact binomial CIs that will be estimated using the Clopper-Pearson method. The 12 month

	period of maintaining MRD[-]CR can have a window of ± 4 weeks, ie maintaining MRD[-]CR for at least 12 months (- 4 weeks) is considered as sustained. Sustained MRD[-]CR at 24 months ± 4 weeks Sustained MRD[-]CR rate at 24 months ± 4 weeks is defined as the proportion of subjects that maintain MRD[-]CR for 12 months or more after achieving MRD[-]CR status at their first MRD assessment at 12 months landmark. It will be calculated along with the associated 90% and 95% exact binomial CIs that will be estimated using the Clopper-Pearson method. The 12 month period of maintaining MRD[-]CR can have a window of ± 4 weeks, ie, maintaining MRD[-]CR for at least 12 months (- 4 weeks) is considered as sustained. Duration of Response (DOR) Duration of response will be calculated for subjects who achieve sCR, CR, VGPR, or PR from the first date of PR or better to the date of disease progression or death due to any cause. If a subject is alive or lost to follow-up without experiencing documented disease progression by the data cutoff date, the DOR for the subject will be censored at the date of last valid disease and response assessment. The distribution of DOR including the median will be characterized using the Kaplan-Meier method based on the subjects who achieve best overall response of sCR, CR, VGPR or PR. Time to Response Time to response will be summarized with the non-missing sample size (n), mean, standard deviation, median, minimum, and maximum for responders, ie, subjects who achieve best overall response of sCR, CR, VGPR, or PR. Progression Free Survival (PFS) Progression Free Survival will be calculated from the time of start of treatment until disease progression or death due to any cause, whichever occurs first. If a subject is alive or lost to follow-up without experiencing documented disease progression by the data cutoff date, the PFS data for the subject will be censored at the date of last valid disease and response assessment. Detailed PFS data censoring rule will be described in the SAP. The distribution of PFS, including median, will be estimated using the Kaplan-Meier method. PFS rate at the selected time points (12 months and 24 months) will be reported. The 90% and 95% CIs for the median and other percentiles of PFS will be constructed using the method of Klein and Moeschberger (1997) with log-log transformation. The 90% and 95% CIs for PFS rates will be estimated using the methods by Kalbfleisch and Prentice (1980) with log-log transformation. Overall Survival (OS) Overall survival will be calculated from date of start of treatment until death due to any cause. Subjects still alive will be censored at the date last known to be alive. OS will be analyzed using the same method as described for the PFS endpoints. Complete Response or better rate (CR) The CR will be analyzed using the same methods as described for ORR.
Exploratory	Will be described in the statistical analysis plan finalized before database lock

10.4.2.3 Safety Analyses

10.4.2.3.1 Analyses of Primary Safety Endpoint(s)

Not applicable.

10.4.2.3.2 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, grade 3 and above adverse events, and adverse events leading to withdrawal from investigational product or other protocol-required therapies will also be provided. More details will be included in the SAP.

10.4.2.3.3 Laboratory Test Results

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

10.4.2.3.4 Vital Signs

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

10.4.2.3.5 Physical Measurements

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

10.4.2.3.6 Electrocardiogram

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

10.4.2.3.7 Exposure to Investigational Product

The extent of exposure to study treatments will be evaluated with respect to treatment duration number of cycles started, total dose received, number of doses administered, dose intensity. The reasons for dose modification, or discontinuation from any study treatment will be summarized separately. More details will be included in the SAP.

10.4.2.3.8 Exposure to Other Protocol-required Therapy

Not applicable.

10.4.2.3.9 Exposure to Concomitant Medication

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

10.4.2.4 Other Analyses

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

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

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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
ALP	alkaline phosphatase
ANC	absolute neutrophil count
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BNP	b-type natriuretic peptide
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CD38	cluster of differentiation 38
CFR	US Code of Federal Regulations
CHF	congestive heart failure
C_{max}	maximum observed concentration
CR	complete response
CrCl	creatinine clearance
CRF	case report form
C_{trough}	maximum trough concentrations
CTCAE	Common Terminology Criteria for Adverse Events
CT	computed tomography
[redacted]	
D	dexamethasone
DBP	diastolic blood pressure
DLCO	diffusing capacity of the lungs for carbon monoxide
DRT	Data Review Team
ECG	electrocardiogram
Echo	echocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
EMA	European Medical Agency

Abbreviation or Term	Definition/Explanation
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
FDG-PET/CT	fluorodeoxyglucose-positron emission tomography/computed tomography
FEV	forced expiratory volume
FISH	fluorescence in situ hybridization
FSH	follicle stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GHS	global health status
HbA1c	hemoglobin A1c
HBc	hepatitis B core antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HR	hazard ratio
HRQOL	health-related quality-of-life
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IFE	immunofixation
Ig, IgA, IgD, IgE, IgM	immunoglobulin, immunoglobulin A, immunoglobulin D, immunoglobulin E, immunoglobulin M
IMiD	immunomodulatory imide drug
IMWG	International Myeloma Working Group
IMWG-URC	International Myeloma Working Group Uniform Response Criteria
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion-related reactions
IRT	Interactive Response Technology

Abbreviation or Term	Definition/Explanation
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
IV	intravenous
K	carfilzomib
Kd	carfilzomib and dexamethasone
KPd	carfilzomib in combination with pomalidomide and dexamethasone
KRd	carfilzomib in combination with lenalidomide and dexamethasone
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LTFU	long-term follow-up
mAb	monoclonal antibody
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MRD	minimal residual disease
MRD[-]	minimal residual disease negative
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NK	natural killer
NT-proBNP	N-terminal pro b-type natriuretic peptide
OR	odds ratio
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
Pd	pomalidomide and low-dose dexamethasone
PD	progressive disease
PDn	pharmacodynamics
PET/CT	positron emission tomography/computed tomography
PFS	progression-free survival
PFT	pulmonary function tests
PG	pharmacogenetic
PI	proteasome inhibitor
PK	pharmacokinetics
PO	by mouth

Abbreviation or Term	Definition/Explanation
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes
PR	partial response
PRES	Posterior reversible encephalopathy syndrome
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
QOL	quality of life
QTc	corrected QT interval
R	lenalidomide
RBC	red blood cell
Rd	lenalidomide with dexamethasone
RDW	red cell distribution width
REMS	Risk Evaluation and Mitigation Strategy
R-ISS	Revised International Staging System
RT-PCR	real-time polymerase chain reaction
SAP	statistical analysis plan
SBP	systolic blood pressure
sCR	stringent complete response
SCR	screening
SFLC	serum-free light chain
SFU	safety follow-up
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SIFE	serum immunofixation
SmPC	Summary of Product Characteristics
SOC	standard of care
SPEP	serum protein electrophoresis
SVR	sustained virologic response
$t_{1/2}$	half-life
TLS	tumor lysis syndrome
TMA	thrombotic microangiopathy
TTP	time to progression
TTR	time to response
UIFE	urine immunofixation
UPEP	urine protein electrophoresis
ULN	upper limit of normal

Abbreviation or Term	Definition/Explanation
US	United States
USPI	United States Prescribing Information
Vd	bortezomib with dexamethasone
VGPR	very good partial response
WBC	white blood cell

12.2 Appendix 2. Clinical Laboratory Tests

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

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

Subjects must fast for at least 9 hours before screening fasting lipid panel and glucose. 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

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

ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; FISH = fluorescent in situ hybridization; HbA1C = hemoglobin A1c; HDL = high density lipoprotein; IgA = immunoglobulin A; IgD = immunoglobulin D; IgE = immunoglobulin E; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MRD = minimal residual disease; NGS = next generation sequencing; NT -proBNP = N-terminal pro b-type natriuretic peptide; PDn = pharmacodynamics; PG = pharmacogenetics; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell count; RDW = Red cell distribution width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; SIFE = serum immunofixation; SFLC = serum free light chains; SPEP = serum protein electrophoresis; UIFE = urine immunofixation; UPEP = urine protein electrophoresis; WBC = white blood cell count

12.3 Appendix 3. Study Governance Considerations

Data Monitoring Committees and Independent Review Committees

Data Review Team

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

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

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

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

Data Protection/Subject Confidentiality

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

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

On the Case Report Form (CRF) demographics page, in addition to the unique subject identification number, include the age (year of birth only) 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 Amgen, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

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

Publication Policy

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

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

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

Investigator Signatory Obligations

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

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

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

Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

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

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

Source Documents

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

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

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the Interactive Response Technology (IRT) (if used, such as subject ID and enrollment 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/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts, Investigational Product Accountability Record(s), Return of Investigational Product

for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable

- Non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable

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

Study and Site Closure

Amgen or its designee may stop the study or study 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/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

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

Compensation

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

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

Definition of Adverse Event

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

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, 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 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.

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
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 Events case report form (CRF). • The investigator must assign the following adverse event attributes: – Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms); – Dates of onset and resolution (if resolved); – Did the event start prior to first dose of investigational product – Assessment of seriousness; – Severity (or toxicity defined below); – Assessment of relatedness to investigational product (carfilzomib and/or pomalidomide), or other protocol-required therapies; – Action taken; and – Outcome of event • If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the highest grade (Grades 1 to 4) on the Events CRF. Record a Grade 5 adverse event as a separate event with a 1-day duration. • It is not acceptable for the investigator to send photocopies of the subject's medical records to Amgen in lieu of completion of the Events 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 5 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 (carfilzomib and pomalidomide), protocol-required therapies, and/or study-mandated procedures 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.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed Events 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.
- If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using a paper-based Serious Adverse Event Contingency Report Form (also referred to as the electronic Serious Adverse Event [eSAE] Contingency Report Form) (see Figure 12-1) within 24 hours of the investigator's awareness 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 system has been taken off-line, then the site can report this information on the paper-based Serious Adverse Event Contingency Report Form (see Figure 12-1).
- Once the study has ended, serious adverse event(s) should be reported to Amgen (regardless of causality) if the investigator becomes aware of a serious adverse

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

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Form (paper-based form)

A Study # 20180117 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 ☐F ☐M	Race	If applicable, provide End of Study date

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? carfilzomib No✓ Yes✓ / pomalidomide No✓ Yes✓ / <Device> No✓ Yes✓ / <Device> No✓ 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	03 Required/prolonged hospitalization	05 Congenital anomaly / birth defect
	02 Immediately life-threatening	04 Persistent or significant disability /incapacity	06 Other medically important serious event

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

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

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A **Study # 20180117** 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 # 20180117 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 subjects and female subjects of childbearing potential are outlined in Section 6.2. Contraceptive use and methods should be consistent with local regulations for subjects participating in clinical studies.

Female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant during treatment and for an additional 30 days after the last dose of carfilzomib or pomalidomide.

Male subjects must receive pregnancy prevention counseling and be advised of the risk to the fetus if they father a child during treatment and for additional 90 days after the last dose of study treatment.

Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use another highly effective or effective method 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 documented hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Females with documented permanent infertility due to an alternate medical cause (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), can be considered not of childbearing potential.

Note: Bilateral tubal ligation/occlusion is not considered a permanent sterilization method.

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.

- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine hormonal-releasing system (IUS)
- Bilateral tubal ligation/occlusion
- Vasectomized partner whom also uses a condom with spermicide, even with a successful vasectomy per medical assessment (provided that partner is the sole sexual partner of the female subject of childbearing potential)
- 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 latex or synthetic condom with spermicide, even after successful vasectomy, during treatment and for an additional 90 days after the last dose of study treatment

The female partner should consider using an acceptable method of effective contraception such as: IUS, 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]).

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 an additional 30 days after the last dose of carfilzomib or pomalidomide.
- Information will be recorded on the Pregnancy Notification Form (see Figure 12-2). The form must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through an additional 30 days after the last dose of carfilzomib or pomalidomide. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an adverse event or serious adverse event. Abnormal pregnancy outcomes (eg, spontaneous abortions, stillbirth, fetal death, congenital anomalies) will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject 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 must discontinue study treatment (see Section 8.1 for details).

Male Subjects With Partners Who Become Pregnant after Enrollment

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

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through an additional 30 days after the last dose of carfilzomib or pomalidomide.
- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's awareness of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 239.
- 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 an additional 30 days after the last dose of carfilzomib or pomalidomide.

Figure 12-2. Pregnancy and Lactation Notification Worksheet

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: 20180117

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:** _____

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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: 20180117

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

12.6 Appendix 6. Sample Storage and Destruction

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

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

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

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

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

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as

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

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

Hepatotoxicity stopping rules are described in Section 7.4.1.

12.8 Appendix 8. Guidelines for Documenting Prior Treatment

Patients must have documented relapse after at least 1, but no more than 2 prior treatment regimens or lines of therapy for multiple myeloma. When documenting prior treatments for multiple myeloma, the following guidelines should be used:

- A new line of therapy is considered to start when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of lack of adequate response, progressive disease (PD) (even if the level of progression has not yet met International Myeloma Working Group-Uniform Response Criteria [IMWG-URC] for PD), relapse, or toxicity.
- An increase in dose of therapy, with the intention of recapturing response in a subject who has evidence of progression on that therapy, is considered a new therapy.
- A new line of therapy is also considered to start when a planned period of observation of therapy is interrupted by a need for additional treatment for the disease.
- Examples of 1 line of therapy include:
  - Induction therapy and stem cell transplant followed by planned maintenance therapy (provided there is no intervening PD)
  - Induction therapy followed by maintenance therapy (provided there is no intervening PD)
- Documentation of at least partial response (PR) to at least 1 prior therapy

For patients with prior carfilzomib therapy, documentation of response (≥ PR) must be available for the most recent previous carfilzomib therapy as well as stop date. Documentation that the subject was not removed from carfilzomib therapy due to toxicity must also be available. For patients with prior therapy with either carfilzomib, the start of the 6-month treatment-free interval is when either carfilzomib is discontinued even if other portions of the regimen are continued.

12.9 Appendix 9. ECOG Performance Status

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

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

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

Patients should be seated comfortably in a quiet environment for 5 min before beginning BP measurements.
Three BP measurements should be recorded, 1–2 min apart, and additional measurements only if the first two readings differ by > 10 mmHg. BP is recorded as the average of the last two BP readings.
Additional measurements may have to be performed in patients with unstable BP values due to arrhythmias, such as in patients with AF, in whom manual auscultatory methods should be used as most automated devices have not been validated for BP measurement in patients with AF.
Use a standard bladder cuff (12–13 cm wide and 35 cm long) for most patients, but have larger and smaller cuffs available for larger (arm circumference > 32 cm) and thinner arms, respectively.
The cuff should be positioned at the level of the heart with the back and arm supported, to avoid muscle contraction and isometric-exercise dependent increases in BP.
When using auscultatory methods, use phase I and V (sudden reduction/disappearance) Korotkoff sounds to identify SBP and DBP, respectively.
Measure BP in both arms at the first visit to detect possible between-arm differences. Use the arm with the higher value as the reference.
Measure BP 1 min and 3 min after standing from seated position in all patients at the first measurement to exclude orthostatic hypotension. Lying and standing BP measurements should also be considered in subsequent visits in older people, in people with diabetes, and in other conditions in which orthostatic hypotension may frequently occur.
Record heart rate and use pulse palpation to exclude arrhythmia.

ESC = European Society of Cardiology; ESH = European Society for Hypertension

For additional antihypertensive guidance and recommendations for blood pressure goals, please refer to the 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology.

https://journals.lww.com/jhypertension/Fulltext/2019/02000/2018_Practice_Guidelines_for_the_management_of.37.aspx

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

Response Subcategory	Multiple Myeloma Response Criteria
sCR	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow aspirate and • Normal SFLC ratio and • Absence of clonal cells in bone marrow biopsy by immunohistochemistry (kappa/lambda ratio ≤ 4:1 or ≥ 2:1 for kappa and lambda subjects 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 subjects with baseline measurable disease only by SFLC, normal SFLC ratio
VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-protein with urine M-protein < 100 mg per 24 hours • In subjects with baseline measurable disease only by SFLC, a decrease ≥ 90% in the difference between involved and uninvolved FLC levels • In subjects achieving a VGPR by other criteria, a soft tissue plasmacytoma must decrease by more than 90% in the SPD compared with baseline
PR	• ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours • In subjects with measurable disease only by SFLC, a decrease ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • In addition to these criteria, if present at baseline, a ≥ 50% reduction in the size (SPD) of soft tissue plasmacytomas is also required

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Footnotes defined on the next page

Response Subcategory	Multiple Myeloma Response Criteria
SD	• Not meeting criteria for CR, VGPR, PR, or PD
PD	• Increase of 25% from lowest confirmed response value in 1 or more of the following: – Serum M-component (absolute increase must be ≥ 0.5 g/dL if the lowest M-component was < 5 g/dL) – Urine M-component (absolute increase must be ≥ 200 mg per 24 hours) – Only in subjects without measurable serum and urine M protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) • Increase of serum M-component of ≥ 1 g/dL if the lowest M-component was ≥ 5 g/dL • Appearance of new lesion(s), ≥ 50% increase from nadir in SPD of > 1 lesion, or ≥ 50% increase in longest diameter of a previous lesion > 1 cm in short axis • ≥ 50% increase in circulating plasma cells (minimum of 200 cells per µL) if this is the only measure of disease

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

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

For sCR: presence/absence of clonal cells is based upon the kappa/lambda (κ/λ) ratio in aspirate. "Measurable" disease is defined by at least 1 of serum protein electrophoresis (SPEP) ≥ 0.5 g/dL, urine protein electrophoresis (UPEP) ≥ 200 mg per 24 hours, or in subjects without measurable serum or urine M-protein, serum free light chains (SFLC) > 100 mg/L (involved light chain) and an abnormal SFLC κ/λ ratio.

Determination of 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.

* Every effort should be made to obtain 2 consecutive samples at any time prior to initiation of any new therapy. If not possible to obtain the second consecutive assessment to confirm disease progression before initiation of any new therapy, this confirmatory sample for disease progression may be obtained after the new therapy is initiated.

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

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

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

12.12 Appendix 12. Child-Pugh Score

Factor	1 point	2 points	3 points
Total bilirubin (μmol/L)	< 34	34 - 50	> 50
Serum albumin (g/L)	> 35	28 - 35	< 28
PT INR	< 1.7	1.7 - 2.3	> 2.3
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)
	Class A	**Class B**	**Class C**
Total Points	5 - 6	7 - 9	10 - 15

Amendment 4

Protocol Title: An Open-label, Phase 2 Study Treating Subjects with First or Second Relapse of Multiple Myeloma with Carfilzomib, Pomalidomide, and Dexamethasone (KPd)

Amgen Protocol Number: 20180117

Amendment Date: 16 May 2022

Rationale:

This protocol is being amended to change the primary endpoint to overall response rate (ORR), and move minimal residual disease negative complete response [MRD(-)CR] rate to secondary endpoint. The Sponsor made the decision to evaluate the primary endpoint of ORR, a recognized endpoint in trials of relapsed or refractory multiple myeloma, in place of MRD(-) CR rate, whose relationship to standard endpoints in clinical trials of relapsed and refractory myeloma is not established (Anderson, 2021).

Changes made in this amendment include:

- To change primary endpoint to ORR, and move MRD(-) CR rate to secondary endpoint in objectives, endpoints and statistical sections
- To update the hypothesis and statistical consideration sections to align with updated endpoints shown above
- To update pomalidomide modification guidelines for nonhematologic toxicities, to align with the current pomalidomide IB

- To add statements on discontinuation of recruitment after 54 subjected enrolled. This decision was made because of challenges to enrollment in part due to evolving changes in multiple myeloma treatment landscape
- To update Figure 12.1; Sample Electronic Serious Adverse Event Contingency Form (paper-based form) based on latest template
- Typographical, formatting, and editorial changes were done throughout the protocol

Superseding Amendment 3

Protocol Title: An Open-label, Phase 2 Study Treating Subjects with First or Second Relapse of Multiple Myeloma with Carfilzomib, Pomalidomide, and Dexamethasone (KPd)

Amgen Protocol Number Carfilzomib 20180117

EudraCT Number: 2019-001169-34

NCT Number: NCT04191616

Amendment Date: 27 April 2021

Rationale:

This purpose of this superseding protocol amendment 3 is:

- To make administrative changes to align with previous Superseding Protocol Amendment 02.

Amendment 3

Protocol Title: An Open-label, Phase 2 Study Treating Subjects with First or Second Relapse of Multiple Myeloma with Carfilzomib, Pomalidomide, and Dexamethasone (KPd)

Amgen Protocol Number Carfilzomib 20180117

EudraCT Number: 2019-001169-34

NCT Number: NCT04191616

Amendment Date: 26 March 2021

Rationale:

The purpose of this protocol amendment 3 is:

- To remove the requirement of daratumumab exposure, which better aligns with the current myeloma population experiencing first or second relapse
- To update the ORR as a key secondary endpoint to further designate this endpoint as clinically important and pre-specify the order for analysis
- To update the number of sites from 35 to 45
- To update the carfilzomib dose modification guidelines for nonhematologic toxicities
- To update the statistical considerations, given newly available data that includes outcomes of subjects who are refractory to lenalidomide
- To update the safety reporting and birth control requirements as per the current protocol template.

Superseding Amendment 2

Protocol Title: An Open-label, Phase 2 Study Treating Subjects with First or Second Relapse of Multiple Myeloma with Carfilzomib, Pomalidomide, and Dexamethasone (KPd)

Amgen Protocol Number Carfilzomib 20180117

Amendment Date: 13 May 2020

Rationale:

This protocol is being amended to:

- Add prophylaxis for Hepatitis B virus reactivation to other protocol-required therapies
- Add Hep B dose modification to the Table for "Dose Modification Guidelines for Nonhematologic Toxicities"
- Change minimal residual disease negative (MRD) assessments with a ± 2-week window, to a ± 4-week window, to align better with clinical practice and maintain consistency with other Amgen protocols
- Update the primary objective from estimating the efficacy by rate of MRD(-) response of Carfilzomib, Pomalidomide, and Dexamethasone (KPd) to estimating the rate of MRD(-) complete response (CR). As per the US Food and Drug Administration (FDA) guidance "Hematological Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment, MRD negativity should be tested in CR patients only for the primary endpoint". Edits were made throughout the protocol to correspond to this change
- Updated screening regarding fetal toxicity "Due to embryo-fetal toxicity, females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable contraception, beginning 4 weeks prior to initiating treatment with pomalidomide." to

accommodate for females of reproductive potential with a 28 days screening window

- Clarifications made to progression free survival (PFS), overall survival (OS), and complete response (CR) in efficacy analyses
- Dose modification in abnormalities from tumor lysis syndrome in Dose Modification Guidelines for Nonhematologic Toxicities
- Extend window for radiological plasmacytoma assessments from every 12 weeks to every 12 weeks ± 2 weeks
- For consistency in the protocol, screening evaluations for disease specific assessments, measurable disease, rescreening, echocardiograms, pulmonary function tests, bone lesions, and plasmacytomas changed from 30 to 28 days
- In Appendix 5, two contraceptive methods were removed to align with the Summary of Product Characteristics for pomalidomide: (1) intrauterine devices and (2) combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
- Remove reporting requirement for start and stop time of Pomalidomide administration.
- Administrative and editorial updates were made throughout

Amendment 2

Protocol Title: An Open-label, Phase 2 Study Treating Subjects with First or Second Relapse of Multiple Myeloma with Carfilzomib, Pomalidomide, and Dexamethasone (KPd)

Amgen Protocol Number Carfilzomib 20180117

Amendment Date: 30 March 2020

Rationale:

This protocol is being amended to:

- Add prophylaxis for Hepatitis B virus reactivation to other protocol-required therapies
- Add Hep B dose modification to the Table for "Dose Modification Guidelines for Nonhematologic Toxicities"
- Change minimal residual disease negative (MRD) assessments with a ± 2-week window, to a ± 4-week window, to align better with clinical practice and maintain consistency with other protocols, namely ARROW 2 carfilzomib in combination with lenalidomide and dexamethasone (KRd) once weekly vs KRd twice weekly, which is for registrational intent.
- Update the primary objective from estimating the efficacy by rate of MRD(-) response of KPd to estimating the rate of MRD(-) complete response. As per the guidance "Hematological Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment, MRD negativity should be tested in complete response (CR) patients only for the primary endpoint".
- Updated screening regarding fetal toxicity "Due to embryo-fetal toxicity, females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable contraception, beginning 4 weeks prior to initiating treatment with pomalidomide." to

accommodate for females of reproductive potential with a 28 days screening window.

- Clarifications made to PFS, OS, CR in Efficacy analysis.
- Dose modification in abnormalities from tumor lysis syndrome in Dose Modification Guidelines for Nonhematologic Toxicities.
- Change in plasmacytoma assessments to ± 2 weeks
- For consistency in the protocol, screening evaluations for disease specific assessments, measurable disease, rescreening, echocardiograms, pulmonary function tests, bone lesions and plasmacytomas changed from 30 to 28 days.
- Administrative and editorial updates

Amendment 1

Protocol Title: An Open-label, Phase 2 Study Treating Subjects With First or Second Relapse of Multiple Myeloma with Carfilzomib, Pomalidomide, and Dexamethasone (KPd)

Amgen Protocol Number Carfilzomib 20180117

Amendment Date: 17 September 2019

Rationale:

This protocol is being amended to:

- Remove cohort 1: Carfilzomib, Daratumumab, and Dexamethasone (KDd), remove all references to Daratumumab
- Add Hepatic Insufficiency for pomalidomide
- Add secondary endpoint of frequency of sustained minimum residual disease (MRD) response
- Update statistical analysis section to include 12 month landmark
- Clarify objectives and endpoints
- Add NGS-based method for evaluating MRD
- Update title of protocol to include second relapse
- Add Independent Review Committee (IRC)
- Update number of subjects and number of sites
- Update study rationale and benefit/risk sections with updated data.
- Add bone targeting agents to recommended therapies
- Administrative and editorial updates