- TTP
- time to response
- sustained MRD[-]CR (defined as the proportion of subjects that maintain MRD[-]CR for 12 months or more after achieving MRD[-]CR status)
- CRR (defined as the proportion of best overall response of sCR or CR)
- MRD[-] rate
- electronic clinical outcome assessments (eCOAs): quality of life questionnaire – core 30 items (QLQ-C30) Global Health Status/Quality of Life (QoL) measured by European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 version 3 questionnaire
- subject incidence of treatment-emergent adverse events
- safety laboratory values, left ventricular ejection fraction (LVEF), forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio, and vital signs at each scheduled assessment

Study Design: This is a phase 3 multicenter, open-label, randomized study in subjects with relapsed or refractory multiple myeloma (RRMM) who have received 1 to 3 prior therapies.

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

- Arm 1: KdD
- Arm 2: Kd

Randomization will be performed using an interactive voice/web response system (IxRS) and subjects will be stratified based on the following criteria: Original International Staging System (ISS) stage (variables: albumin and beta 2 microglobulin; strata: Stage 1 or 2 vs Stage 3) at screening, prior proteasome inhibitor exposure (yes vs no), number of prior lines of therapy (1 vs ≥ 2), and prior cluster differentiation antigen 38 (CD38) antibody therapy (yes vs no).

Subjects will receive the treatment determined by randomization for a maximum of 4 years or until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or death (whichever occurs first). No crossover between the treatment arms will be allowed. All subjects will be assessed for multiple myeloma disease response according to the IMWG-URC using central laboratory test results every 28 ± 7 days. Disease response assessments will be performed every 28 ± 7 days until confirmed progressive disease (PD).

Following progression or discontinuation of study drug(s), subjects will have 2 follow-up visits (30 days [+ 3] and 8 weeks [± 7 days] after last dose of all study drug[s]) and then remain in long-term follow-up (LTFU) where data on survival status **and subsequent antimyeloma therapy** will be gathered every 12 weeks ± 2 weeks.

For subjects in arm 1 (KdD), local hepatitis B testing will be performed at the next scheduled visit for all subjects being actively treated with daratumumab that do not already have a prior medical history of hepatitis B. In addition, subjects with a clinical history of hepatitis B infection or who test positive for hepatitis B virus (HBV) serologies will be monitored closely for signs and symptoms of hepatitis B and will have local HBV DNA testing performed at their next visit and then every 12 weeks while on treatment with daratumumab and until 6 months after ending treatment.

Sample Size: Approximately 450 subjects will be enrolled (300 in arm 1 and 150 in arm 2).

Summary of Subject Eligibility Criteria:

Key Inclusion Criteria

- male or female subjects ≥ 18 years of age
- relapsed or progressive multiple myeloma after last treatment

occurs, then PK and PDn assessments should be performed on the actual administration day of daratumumab, not on the original scheduled administration day.

Daratumumab can be discontinued in the event of a treatment-related toxicity that, in the opinion of the investigator, warrants discontinuation. The subject will be considered on protocol treatment while receiving either carfilzomib or daratumumab (ie, if either carfilzomib or daratumumab are discontinued or interrupted, the subject is still considered on treatment if still taking the other investigational product).

For subjects who are diagnosed with HBV reactivation while on daratumumab treatment, study treatment should be interrupted until the infection is adequately controlled (See Section 6.7.1).

6.2.2.3 Daratumumab: Management of Infusion-related Reactions

Subjects should be carefully observed during daratumumab infusions. Trained study staff at the clinic should be prepared to intervene in case of any infusion reactions occurring, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at the bedside. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

If an IRR develops, then the infusion should be temporarily interrupted. Subjects who experience adverse events during the infusion must be treated according to the investigator's judgment and best clinical practice. Subjects should be treated with acetaminophen, antihistamine, or corticosteroids, as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or anaphylactic reaction, daratumumab should be discontinued and no additional daratumumab should be administered to the subject.

Infusion-related Reactions of Grade 1 or Grade 2

If the investigator assesses a grade 1 to 2 IRR adverse event to be related to administration of study drug, then the daratumumab administration should be paused. When the subject's condition is stable, daratumumab administration may be restarted at the investigator's discretion.

If the subject experiences a grade 2 or higher event of laryngeal edema, or a grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not

Table 10. Schedule of Assessments

Assessment	Screening	Assessment Cycle Days							Follow-up[a]		LTFU	Notes
		1	2	8	9	15	16	22	Visit 1	Visit 2		
General Assessments (continued)												
ECHO	X	(X)										Screening ECHO may be done within 30 days prior to randomization, if performed as a part of standard of care. Monitored every 6 months (± 2 weeks) from C1D1 (not to be assessed within 4 days of daratumumab infusion).
Pulmonary function tests (PFTs)	X	(X)										Screening PFT measurements may be done within 30 days prior to randomization, if performed as a part of standard of care. Monitored every 6 months (± 2 weeks) from C1D1 (not to be assessed within 4 days of daratumumab infusion).
Clinical outcome assessments		**Every 28 ± 7 days starting from C1D1 through follow-up visit 1.**										These questionnaires must be completed before dosing on study drug administration days **(see Section 7.3.13)**.
Survival											X	Every 12 weeks (± 2 weeks) after last follow-up visit.
Subsequent Antimyeloma Therapies									**X**	**X**	**X**	**Data on subsequent antimyeloma therapy will be collected regardless of whether the subject has progressed (see Section 7.3.15).**
Laboratory Assessments												
Hematology: Screen/Cycle 1	X	X		X		X		X				Screening: Subjects must fast for at least 9 hours. Lab results must be evaluated for potential dose modification assessment prior to dosing. Further details in Section **7.3.16**.
Hematology: Cycles 2+		X							X			
Chemistry: Screen/Cycle 1	X	X		X		X		X				
Chemistry: Cycles 2+		X							X			

(X) = Parentheses indicate that the particular test is situational at that time point, as specified in the respective notes.
Footnotes defined on the last page of the table.

Table 12. Dosing Schedule - Arm 1 (KdD)

Investigational Products and Other Protocol-required Therapies	Dosing Cycle Day							Notes
	1	2	8	9	15	16	22	
IV predose and postdose hydration (for carfilzomib as needed)								
Cycle 1	X	X	X	X	X	X		Not required for days when daratumumab is administered
Dexamethasone IV or PO (40 mg/week)								
All cycles	20	20	20	20	20	20	40	Dexamethasone 40 mg will be taken weekly (20 mg each day when taken on successive days). Cycle 1: All subjects, regardless of age, will receive 20 mg C1D1 and C1D2, followed by 20 mg methylprednisolone on C1D3.
Dexamethasone IV or PO (20 mg/week) – for subjects > 75 years of age								
Cycle 1	20	20	20	8	20	8	20	Cycle 1: All subjects will receive 20 mg C1D1 and C1D2, followed by 20 mg methylprednisolone on C1D3. 20 mg will be given as a preinfusion medication for daratumumab infusion, followed by 8 mg of dexamethasone prior to carfilzomib infusion on C1D9 and C1D16. Cycle 2+: 20 mg must be given as a preinfusion medication for daratumumab infusion (without 8 mg dose on subsequent carfilzomib dosing day), otherwise the 20 mg dose can be split across carfilzomib dosing days (eg, 12/8, 10/10, etc).
Cycle 2	20	-	20	-	20	-	20	
Cycles 3 to 6	20	-	12	8	20	-	20	
Cycles 7+	20	-	12	8	12	8	20	
Carfilzomib IV								
Cycle 1	20	20	56	56	56	56		The dose[a] will be 20 mg/m^2 on C1D1 and C1D2 and 56 mg/m^2 beginning on C1D8 and thereafter.
Cycle 2+	56	56	56	56	56	56		
Daratumumab IV								
Cycle 1	8	8	16		16		16	For pre/post-infusion medication guidance, see Sections 6.2.2.1.1 and 6.2.2.1.2. C1D1 and C1D2: 8 mg/kg in 500 mL NS will be administered each day. Thereafter, daratumumab will be given 16 mg/kg per dose diluted in 500 mL NS. Daratumumab infusions begin after carfilzomib infusions are completed.
Cycle 2	16		16		16		16	
Cycles 3 to 6	16				16			
Cycles 7+	16							

CxDx = cycle X day X; IV = intravenous; KdD = carfilzomib, dexamethasone, and daratumumab; NS = normal saline; PO = by mouth.
[a] For patients with baseline chronic hepatic impairment (mild, moderate), reduce the starting and subsequent doses of carfilzomib by 25% (ie, 15 mg/m^2 day 1 and 2 of cycle 1 and 42 mg/m^2 day 8 cycle 1 and thereafter).

Table 13. Dosing Schedule - Arm 2 (Kd)

Investigational Products and Other Protocol-required Therapies	Dosing Cycle Day							Notes
	1	2	8	9	15	16	22	
IV predose and postdose hydration (for carfilzomib as needed)								
Cycle 1	X	X	X	X	X	X		See Section 6.2.1.1.1 for details.
Dexamethasone IV or PO								
All cycles	20	20	20	20	20	20	40	When multiple doses are required within the same week, split the dose amongst the days for a total of 40 mg/weekly. The dexamethasone dose must be given as IV on C1D1 and C1D2.
Dexamethasone IV or PO – for subjects > 75 years of age								
All cycles	12	8	12	8	12	8	20	When multiple doses are required within the same week, split the dose amongst the days for a total of 20 mg/week (eg, 12/8, 10/10, etc). The dexamethasone dose must be given as IV on C1D1 and C1D2.
Carfilzomib IV								
Cycle 1	20	20	56	56	56	56		The dose[a] will be 20 mg/m^2 on C1D1 and C1D2 and 56 mg/m^2 beginning on C1D8 and thereafter.
Cycle 2+	56	56	56	56	56	56		

CxDx = cycle X day X; IV = intravenous; Kd = carfilzomib and dexamethasone; PO = by mouth.

[a] For patients with baseline chronic hepatic impairment (mild, moderate), reduce the starting and subsequent doses of carfilzomib by 25% (ie, 15 mg/m^2 day 1 and 2 of cycle 1 and 42 mg/m^2 day 8 cycle 1 and thereafter).

7.2 General Study Procedures

The procedures performed and timing of each study visit are outlined in the Schedule of Assessments (Table 10 and Table 11). Details regarding each type of procedure are provided in subsequent subsections. Procedures that are part of routine care are not considered study-specific procedures and may be used at screening to determine eligibility.

Refer to the applicable supplemental central laboratory, IxRS, IPIM, and study manuals for detailed collection and handling procedures.

7.2.1 Screening Enrollment and/or Randomization

The following procedures are to be completed during the screening period at time points designated in the Schedule of Assessments (Table 10 and Table 11). Details of these procedures can be found in Section 7.3.

- Confirmation that the ICF has been signed prior to any study-specific screening procedures being performed
- Screening and randomization in IVR/IWR system, as applicable
- Demographic data (including sex, age, race, and ethnicity)
- Medical/surgical history (including multiple myeloma history)
- Multiple myeloma frailty index
- Adverse event reporting (any adverse events that occur following subject signing consent must be reported)
- Concomitant medications
- Physical examination, including examination of cardiovascular and respiratory systems, abdominal exam, and general neurologic exam
- Physical measurements: height, weight, and BSA (Mosteller Formula)
- ECOG performance status
- 12-lead ECG with QTc interval
- Vital signs
- Echocardiogram (ECHO)
- Pulmonary function tests (PFTs)
- Laboratory assessments: hematology, serum chemistries, coagulation tests, quantitative immunoglobulins, β2 microglobulin, pregnancy test (FCBP), blood typing and indirect antiglobulin test (IAT)
- Disease assessments: serum protein electrophoresis (SPEP)/urine protein electrophoresis (UPEP)/immunofixation (IFE), SFLC, bone marrow sample and aspirate for FISH and MRD[-], plasmacytoma evaluation (if clinically indicated), bone lesion assessment

CCI

[redacted]

2. BACKGROUND AND RATIONALE

2.1 Multiple Myeloma

Multiple myeloma, a clonal neoplastic proliferation of plasma cells, is the second most common hematologic malignancy and is responsible for approximately 80 000 annual deaths worldwide (1% of cancer deaths). The estimated incidence of multiple myeloma in 2012 worldwide was 114 000 persons and this represents 0.8% of all cancers. The 5 year prevalence of multiple myeloma worldwide was estimated at 229 000 persons (Ferlay et al, 2015). Multiple myeloma is a disease of older adults, with a median age at diagnosis of 70 years (Howlader et al, 2013).

2.2 Proteasome Background

The proteasome is a multicatalytic proteinase complex that is responsible for degradation of a wide variety of protein substrates within normal and transformed cells. Intracellular proteins targeted for degradation by the proteasome are first ubiquitinated via the ubiquitin conjugation system. Ubiquitinated proteins are cleaved within the proteasome by 1 or more of 3 separate N terminal threonine protease activities: a chymotrypsin like activity, a trypsin like activity, and a caspase like activity.

2.3 Amgen Investigational Product Background

2.3.1 Carfilzomib Background (Nonclinical)

Carfilzomib is a tetrapeptide epoxyketone based inhibitor of the 20S proteasome. Carfilzomib, showed less off target activity when measured against a broad panel of proteases including metallo-, aspartyl-, and serine proteases compared to bortezomib; bortezomib showed off target inhibitory activity in the nanomolar range against several serine proteases (Arastu-Kapur et al, 2009). This selectivity may be responsible for the

carfilzomib dosed at 20/70 mg/m^2 weekly in combination with daratumumab. As of 30 June 2016, there have been 20 subjects treated with KdD in this study with the observed adverse events were consistent with the known individual safety profiles for carfilzomib and daratumumab. The safety profile of carfilzomib dosed at 20/70 mg/m^2 weekly in combination with dexamethasone and daratumumab is consistent with the known safety profiles of carfilzomib and daratumumab independently.

Carfilzomib PKs with the 20/70 mg/m^2 weekly dose showed higher C_{max} (maximum concentration) than that with the 20/56 mg/m^2 twice-a-week dose (2390 ng/mL vs 2079 ng/mL, respectively). Although the area under the curve is higher with 20/56 mg/m^2 twice a week (1896 ng•hr/mL vs 1030 ng•hr/mL per week), it is unlikely that these parameters would be modified by the addition of daratumumab. This assumption is based on the short half-life of carfilzomib (< 1 hour) leading to no accumulation. Additionally, no drug-drug interaction is expected due to the orthogonal MoA of these agents and their different metabolism and elimination routes.

Given these data, this study will evaluate the 20/56 mg/m^2 twice-a-week dose schedule for carfilzomib in combination with daratumumab and low-dose dexamethasone in this phase 3 study to develop a highly efficacious regimen for RRMM patients.

2.6 Clinical Hypothesis

The KdD regimen will provide significant improvement in PFS over the Kd regimen.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 3 multicenter, open-label, randomized study in subjects with RRMM who have received 1 to 3 prior therapies.

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

- Arm 1: KdD using 20/56 mg/m^2 carfilzomib and 16 mg/kg daratumumab
- Arm 2: Kd using 20/56 mg/m^2 carfilzomib

Randomization will be performed using an interactive voice/web response system (IxRS) and subjects will be stratified based on the following criteria:

1. Original International Staging System (ISS) stage (variables: albumin and beta 2 microglobulin; strata: Stage 1 or 2 vs Stage 3) at screening
2. Prior proteasome inhibitor exposure (yes vs no)

3. Number of prior lines of therapy (1 vs ≥ 2)
4. Prior CD38 antibody therapy (yes vs no)

Subjects will receive the treatment determined by randomization for a maximum of 4 years or until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or death (whichever occurs first). No crossover between the treatment arms will be allowed. All subjects will be assessed for multiple myeloma disease response according to the International Myeloma Working Group-Uniform Response Criteria (IMWG-URC) (Appendix M) using central laboratory test results every 28 ± 7 days. Disease response assessments will be performed every 28 ± 7 days until confirmed PD irrespective of cycle duration including dose delays or treatment discontinuation. The disease assessment schedule is independent of treatment schedules.

Following progression or discontinuation of study drug(s), subjects will have 2 follow-up visits (30 days [+ 3] and 8 weeks [± 7 days] after last dose of all study drug(s) and then remain in long-term follow-up (LTFU) where data on survival **and subsequent antimyeloma therapy** will be gathered every 12 weeks ± 2 weeks.

Subjects in arm 1 (KdD) with a known history of HBV infection or those who test positive for HBV serologies will be monitored closely for signs and symptoms of hepatitis B. In addition, for subjects with a known history of HBV infection or those who test positive for HBV serologies, local HBV DNA testing will be performed at the next scheduled visit and then every 12 weeks during daratumumab treatment and for 6 months following the last dose of daratumumab.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

Approximately 120 sites in North America, Australia, Europe, and Asia will participate in this global study. During the conduct of the study, additional sites may be added as necessary.

Sites that do not enroll subjects within 5 months of site initiation may be closed.

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 of greater than 2.2 m^2, the dose should be capped based on a BSA of 2.2 m^2. The dose for each subject should not be revised unless the subject experiences a change in body weight of ≥ 20% in which case the BSA and dose should be recalculated. The dose can also be modified in response to toxicity following the dose modification guideline tables.

The planned dose (mg/m^2), dose (mg), total volume of preparation (mL), total volume administered (mL), 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 is to be recorded on each subject's electronic case report form (eCRF).

6.2.1.1.1 Intravenous Prehydration

Subjects in arm 2 will receive IV prehydration prior to each carfilzomib infusion during cycle 1. For subjects in arm 1, no prehydration for carfilzomib will be required on days of daratumumab administration.

Prehydration will consist of 250 mL normal saline or other appropriate IV fluid.

Thereafter, carfilzomib prehydration should only be administered if the subject's condition and/or risk factors require it. The total volume of prehydration and the reason for prehydration after cycle 1 will be recorded.

6.2.1.2 Carfilzomib: Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

Carfilzomib may be discontinued, temporarily delayed, or dosage temporarily reduced, in the event of a treatment-related toxicity that, in the opinion of the investigator, warrants the discontinuation, temporary delay or dose reduction, as indicated in Table 3 and Table 4. The subject will be considered on protocol treatment while receiving either carfilzomib or daratumumab (ie, if either carfilzomib or daratumumab are discontinued or interrupted, the subject is still considered on treatment if still taking the other investigational product).

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

Each subject's dose will be calculated based on the subject's weight rounded to the nearest kilogram. Dosing calculations do not need to be changed for weight changes that are < 10% from baseline. The pharmacist will calculate the required volume **and number of vials** needed. The daratumumab infusion rate is provided in Table 5.

The planned dose (mg/kg), dose (mg), total volume of preparation (mL), total volume administered (mL), 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 daratumumab is to be recorded on each subject's eCRF.

Table 5. Daratumumab Infusion Rate

C1D1 and C1D2 (8 mg/kg)		C1D8 (16 mg/kg)		Subsequent Infusions	
Time (minutes)	mL/hr	Time (minutes)	mL/hr	Time (minutes)	mL/hr
0 - 60	50	0 - 60	50[a]	0 - 60	100[b]
61 - 120	100	61 - 120	100	61 - 120	150
121 - 180	150	121 - 180	150	121 - 180	200
181 - 240	200	181 - 240	200	181-	200
500 mL		500 mL[a]			500 mL

CxDx = cycle X day X; IRR = infusion-related reaction.

[a] If the subject's first 2 infusions of 8 mg/kg daratumumab are well-tolerated (defined as an absence of IRR > grade 1), the first infusion of 16 mg/kg daratumumab will be administered at an initial rate of 50 mL/hour and increased by 50-mL/hour increments at 60-minute intervals, as tolerated, to a maximum rate of 200 mL/hour. If the 8 mg/kg infusions are not well-tolerated (defined as IRR > grade 1), the dose may be split in 2 days (on 500 mL each day).

[b] Modified rates should only be used if at least one 16 mg/kg infusions of daratumumab was well-tolerated as defined by an absence of >grade 1 infusion-related reactions during a final infusion rate of ≥ 100 mL/hr.

See Section 7.3.10 for details on vital sign monitoring during daratumumab and other infusions.

6.2.2.1.1 Pre-infusion Medications for Daratumumab

On daratumumab infusion days, subjects will receive the following medications 1 to 3 hours before daratumumab infusion (and prior to carfilzomib infusion):

1. paracetamol 650 to 1000 mg orally (PO) or IV, and
2. antihistamine (diphenhydramine 25 to 50 mg or equivalent, PO or IV), and
3. leukotriene inhibitor (montelukast 10 mg PO or equivalent) should be given.

Dexamethasone is also required pre-infusion, as well as 1 day after daratumumab infusion. Refer to Section 6.3.1 for additional information on dexamethasone dosing.

For days when dexamethasone is given in the absence of other IV infusion (neither carfilzomib nor daratumumab is scheduled), it may be given within ± 2 days for each scheduled dose. Dexamethasone will be administered at least 30 minutes (but no more than 4 hours) prior to carfilzomib and within 1 to 3 hours from the daratumumab dose.

Additional details regarding dexamethasone is provided in the Investigational Product Information Manual.

6.3.2 Dexamethasone: Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

All dexamethasone administrations must be within the 2 days of the scheduled administration; however, it must be given on days carfilzomib and/or daratumumab will be administered.

The dose, date, and time are to be recorded on each subject's eCRF. The reason for dose change of dexamethasone is also to be recorded on each subject's eCRF.

For conditions that do not require dexamethasone dose reduction, refer to Section 6.4.

For subjects > 75 years of age or subjects whose weekly dexamethasone dose has been reduced to 20 mg/week, 20 mg of dexamethasone will be given as a preinfusion medication for daratumumab infusion, followed by 8 mg of dexamethasone prior to carfilzomib infusion on days 9 and 16 of cycle 1. Starting with cycle 2, 20 mg dexamethasone must be given on days daratumumab is administered (without 8 mg dose on subsequent carfilzomib dosing day), otherwise the 20-mg dose can be split across carfilzomib dosing days (eg, 12/8, 10/10, etc, as shown in Table 12 and Table 13).

When carfilzomib is permanently discontinued, investigators may at their discretion omit dexamethasone on days when given in the absence of daratumumab based on their assessment of the subject's steroid tolerance.

Subjects in arm 1 on cycles 7+ without previous IRR, may decrease or omit dexamethasone premedication, if the subject cannot tolerate 20 mg of dexamethasone or equivalent.

6.3.2.1 Dexamethasone: Dose Reduction Levels

T**hree** dose reduction levels are defined for dexamethasone based on the age of subjects, as shown in Table 7. Dose reductions are permanent, dose must not be increased following a dose reduction.

Table 10. Schedule of Assessments

Assessment	Screening	Assessment Cycle Days							Follow-up[a]		LTFU	Notes
		1	2	8	9	15	16	22	Visit 1	Visit 2		
General Assessments												
Informed consent	X											
Demographics	X											
Medical/surgical history	X											Includes multiple myeloma history
Multiple myeloma frailty index	X											
Review of AEs/SAEs	Continually											Refer to Section 9.2.1.3 for AEs/SAEs that occur > 30 days after last dose of all study drug(s).
Concomitant medications	Continually											
Complete physical examination	X								X	X		
Physical measurements (weight, BSA)	X	X										BSA should be calculated per Mosteller formula and utilized to calculate required study drug doses. Weight can be measured again in case of substantial weight gain/loss.
Physical measurement (height)	X											
ECOG performance status	X								X			
12-lead ECG with QTc interval	X											And as clinically indicated.
ECG: Cycle 1				X								
ECG: Cycle 2		X										
Vital signs	X	X	X	X	X	X	X	(X)	X	X		Checked prior to administration of study drug(s) (K or D) in all cycles. Additional measurements described in Section 7.3.10. Day 22 (arm 1 only): cycles 1 and 2 only.

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(X) = Parentheses indicate that the particular test is situational at that time point, as specified in the respective notes.
Footnotes defined on the last page of the table.

call to subject every 12 weeks (± 2 weeks). Details of these procedures can be found in Section 7.3.

For subjects in arm 1 (KdD) with a known history of HBV infection or who test positive for HBV serologies, local testing for HBV DNA by PCR will be performed at the next scheduled site visit and then every 12 weeks during daratumumab treatment and for 6 months following the last dose of daratumumab (see Section 7.3.16).

7.3 Description of Study Procedures

7.3.1 Demographics

Demographic data 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 PKs of the protocol-required therapies.

7.3.2 Medical History

The investigator or designee will collect a complete medical and surgical history that started within 30 days prior to informed consent. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF. Cardiovascular risk factors which include family history of cardiovascular disease and smoking history will also be required.

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

7.3.3 Multiple Myeloma Frailty Index

Subjects ≥ 65 years of age will have their frailty score assessed at screening only using the Multiple Myeloma Frailty Score (Appendix O; Palumbo et al, 2015).

7.3.4 Review of Safety Events and Current Concomitant Medications

All adverse events, serious adverse events, and changes in concomitant medications must be recorded on the subject's eCRF from informed consent to 30 days following the

last dose of all study drug(s). All adverse events are followed until resolution or stabilization.

Additional information will be collected for selected cardiopulmonary adverse events (including dyspnea, ischemic heart disease or cardiac failure) which will include results of work up performed as clinically indicated and/or investigator assessment of etiology.

7.3.5 Concomitant and Prior Medications

All concomitant medications must be recorded in the designated eCRF from informed consent to 30 days following the last dose of all study drug(s). Prior medications are to be included if taken 30 days prior to informed consent. All prior medications that continue after the informed consent are to be recorded as concomitant medications.

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

7.3.6 Physical Examination

A complete physical examination is to include examination of cardiovascular and respiratory systems, abdominal examination, and general neurologic examination. Clinically significant abnormal physical examination findings identified prior to the signing of informed consent should be reported as part of medical history, not as adverse events.

7.3.7 Physical Measurements

Weight (in kilograms) and height (in centimeters) will be measured (height will be measured only at the screening physical examination). Body surface area will be determined using the Mosteller Formula (Mosteller, 1987):

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

7.3.8 ECOG Performance Status

The subject's performance status will be assessed using the ECOG performance scale (see Appendix D) at intervals identified in the Schedule of Assessments (Table 10).

7.3.9 Echocardiogram

All subjects will have a baseline transthoracic ECHO (TTE) during screening, including assessments of systolic and diastolic left ventricular function and right ventricular function. Screening ECHO may be done within 30 days prior to randomization, if performed as a part of standard of care. Echocardiograms are to be repeated approximately every 6 months (± 2 weeks) from cycle 1 day 1, until end of treatment, or

if clinically indicated. Routine ECHO (every 6 months) should not be assessed within 4 days after daratumumab infusion. However, ECHO should be performed within 72 hours of cardiac failure event initiation, regardless of the timing in relation to infusion.

7.3.10 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Vital sign measurements are performed prior to administration of study drug(s) in all cycles.

Subjects must be in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. The position selected for a subject should be the same that is used throughout the study and documented in the medical record and on the vital sign CRF. Take at least 2 blood pressure measurements spaced 1 to 2 minutes apart and additional measurements if the first 2 are quite different (Appendix F). Record the average blood pressure on the vital sign CRF.

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

Record all measurements on the vital signs CRF.

Additional Vital Sign Measurements

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

Vital signs are to be monitored extensively on cycle 1 day 1 for the first infusion of daratumumab, as described below:

- before the start of daratumumab infusion;
- at 0.5, 1, 1.5, 2, and 3.5 hours after the start of the infusion;
- at end of infusion; and
- 0.5 and 1 hour after the end of infusion

For all other daratumumab infusion days, vital signs are also to be measured at the end of the infusion.

7.3.11 Electrocardiogram

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.

7.3.15 Subsequent Antimyeloma Therapies

All subjects will be followed by telephone contact or other method to collect subsequent antimyeloma therapies approximately every 12 weeks (± 2 weeks) after the last follow-up visit until the subject has withdrawn consent for further participation, is lost to follow-up, has died, end of study, or the study is closed, whichever is earliest.

7.3.16 Laboratory Assessments

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

For cycle 1 day 1, hematology and serum chemistry panel from screening may be used if within 14 days of day 1. For subsequent visits in cycle 1, hematology and chemistry may be completed up to 72 hours prior to scheduled dose weekly for cycle 1. Starting in cycle 2, only day 1 is required.

As of Protocol Amendment 4, all subjects being actively treated with daratumumab who do not have a prior medical history of hepatitis B will be tested locally for HBsAg, anti-HBs, and anti-HBc at their next visit.

Subjects with a known history of HBV infection or who test positive for serologies (anti HBc and/or anti-HBs with exception of serologic findings suggestive of HBV vaccination [anti-HBs positivity as the only serologic marker] and a known history of prior HBV vaccination) who are enrolled in arm 1 (KdD) will be closely monitored for clinical signs of active HBV infection. Local testing for HBV DNA by PCR will be performed for subjects with a known history of HBV infection or those who test positive for HBV serologies at the next scheduled site visit and

then every 12 weeks during daratumumab treatment and for 6 months following the last dose of daratumumab.

Table 14 below outlines the specific analytes that will be assessed during the study.

Table 14. Laboratory Analyte Listing

Central Laboratory: Chemistry	**Central Laboratory: Hematology**	**Central Laboratory: Disease Assessments**	**Central Laboratory: Other Labs**
Sodium Potassium Chloride Bicarbonate Albumin Calcium Adjusted calcium Glucose BUN or Urea Creatinine Total bilirubin Direct bilirubin Alk phosphatase AST (SGOT) ALT (SGPT) **Magnesium** **Phosphorous** *Screening only:* *NT-proBNP* *LDH* *Uric acid* *Amylase* *Lipase* *Fasting lipid panel:* • *Total cholesterol* • *HDL* • *LDL* • *Triglycerides*	RBC Hemoglobin Hematocrit Platelets WBC Differential Neutrophils Bands/stabs Segs Eosinophils Basophils Lymphocytes Monocytes Plasma cell count: • plasma cell percent *Screening only:* *HbA1c* **Local Laboratory: Coagulation** PT/INR PTT	MRD assessment by NGS (bone marrow aspirate) FISH (bone marrow aspirate) SPEP Serum Immunofixation UPEP Urine immunofixation SFLC	Quantitative immunoglobulins (serum): • IgA, IgD, IgE, IgG, IgM β2-microglobulin (serum) Exploratory serum biomarker Exploratory plasma biomarker Exploratory pharmacogenomic (germline saliva sample) DIRA Pharmacokinetics **Local Laboratory: Other Labs** Serum pregnancy Urine pregnancy Blood typing with indirect antiglobulin test **Hepatitis B serologies (HBsAg, anti-HBs, and anti-HBc)[a]** **HBV DNA testing by PCR[b]**

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; DIRA = daratumumab immunofixation electrophoresis reflex assay; FISH = fluorescence in-situ hybridization; HbA1c = hemoglobin A1c; **anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus;** HDL = high-density lipoproteins; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoproteins; MRD = minimal residual disease; NGS = next generation sequencing; NT-proBNP = N-terminal of the prohormone brain natriuretic peptide; **PCR = polymerase chain reaction;** PT = prothrombin time; PTT = partial prothrombin time; RBC = red blood cells; Segs = segmented neutrophils; SFLC = serum free light chain; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamate-pyruvate transaminase; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; WBC = white blood cells.

[a] **Hepatitis B serology testing is only required for subjects in arm 1 (KdD) who do not have a prior medical history of HBV.**

[b] **Serial testing for HBV DNA by PCR is only required for subjects in arm 1 (KdD) who have a prior medical history of HBV or who test positive for HBV serologies.**

Uncrossmatched, ABO/RhD compatible RBC units should be administered if transfusion is needed emergently as per local blood bank practice.

Despite daratumumab binding to CD38 on erythrocytes, no indication of clinically significant hemolysis has been observed in daratumumab studies. For additional details, refer to the Daratumumab IB.

7.3.19 Pharmacokinetic Samples

7.3.19.1 Pharmacokinetic Samples: Carfilzomib

Blood samples for PK are outlined in the Schedule of Assessments (Table 10). PK sampling will be obtained from all subjects on cycle 1 day 8 and cycle 3 day 1 at the following time points:

- within 2 minutes prior to the end of infusion
- within 15 minutes post end of infusion
- within 30 minutes to 2 hours post end of infusion

Actual PK collection time will be recorded and be used in the population PK analysis.

7.3.19.2 Pharmacokinetic Samples: Daratumumab

Samples to assess the serum concentration (pharmacokinetics) of daratumumab will be obtained from all subjects in arm 1 according to the Schedule of Assessments (Table 10) and analyzed using validated immunoassay methods. PK samples will be obtained predose on day 1 of cycles 1, 3, 7, and 12; and at the end of the daratumumab infusion on cycle 3 day 1. Additionally, samples will be obtained 30 days and 8 weeks after the last daratumumab dose during the follow-up visits.

All these samples assessments will be performed in subjects randomized to receive daratumumab. On dosing days, predose samples may be obtained up to 2 hours prior to start of infusion. End of infusion samples may be drawn up to 2 hours after the end of the infusion. The exact dates and times of blood sampling must be recorded. Refer to the Laboratory Manual or equivalent document for sample collection requirements. Collected samples must be stored under the specified and controlled conditions for the temperatures indicated in the laboratory manual.

7.3.20 Pharmacodynamics (Optional): Carfilzomib

Blood samples for the optional PDn substudy are outlined in the Schedule of Assessments (Table 10) with a total of 45 patients from arm 1 and 25 patients from arm 2 to be enrolled. Samples will be collected at the following time points:
cycle 1 day 1 collected 15 min pre-infusion and at 1 hour (± 15 min) post end of infusion;

screening (prior to dosing at cycle 1 day 1) includes MRD NGS, FISH, cytomorphology, pharmacogenetics, and biomarker bone marrow aspirate. All other bone marrow aspirate assessments include MRD NGS, cytomorphology, and pharmacogenetics.

Additional bone marrow biopsy or aspirate slides will be obtained as clinically indicated to confirm a response of CR or sCR. **In addition,** a bone marrow aspirate will be obtained for MRD assessment at all of the following time points:

- at a fixed, landmark analysis at 12 months (± **4** weeks)
  - **12 months calculated from baseline (cycle 1 day 1)**
  - **this sample is collected from subjects who have not had confirmed disease progression**
  - **if subject reached CR prior to the 12 month landmark and the CR sample was taken within 4 months, no additional sample is required, unless clinically indicated**
- when a subject reaches CR and did not have a **bone marrow aspirate sample taken for MRD** analysis within the past 4 months, unless there is a clinical reason to repeat the assessment
  - **this sample may be collected/saved at the same time when the cytomorphology sample is collected for the confirmation of CR (per IMWG-URC criteria described in protocol Appendix M)**
- **at 12 months after confirmed CR (per IMWG-URC criteria described in protocol Appendix M) and subject did not have an MRD analysis within the past 4 months, unless there is a clinical reason to repeat the assessment**
- at 24 months (± **4** weeks) for all subjects that have reached a CR and have not have an MRD assessment within the past 4 months, unless there is a clinical reason to repeat the assessment
  - **24 months is calculated from baseline (cycle 1 day 1)**
  - **this sample is collected from all subjects who reached CR at any point during the study participation and are still receiving treatment or have not progressed and still attend site for disease assessment visits**

Samples for MRD analysis are not collected from subjects who have PD confirmed or have withdrawn consent related to this study assessment.

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

Skeletal survey will include lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. Low-dose whole body computed tomography (LD WBCT) or fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) may be used in place of skeletal survey. Bone lesion assessment (all subjects) will be conducted at screening (may be within 30 days prior to randomization)

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected, and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse 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 **(grade 1 to 4)** on the Events eCRF. **Record a grade 5 adverse event as a separate event with a 1 day duration.**

For situations when an adverse event or serious adverse event is due to multiple myeloma report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, multiple myeloma).

Note: The term “disease progression” should not be used to describe the disease-related event or adverse event.

The investigator’s clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject’s legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.2 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization (exceptions: hospitalized due to long infusion time of study drugs or if hospitalized overnight only for observation as described in Section 6.2.2.1.2)
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury, or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Safety Event Reporting Procedures

9.2.1 Adverse Events

9.2.1.1 Reporting Procedures for Adverse Events That Do Not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after signing of ICF through 30 days after the last dose of study treatment or the follow-up visit (whichever is later) are reported using the Event CRF.

The investigator must assign the following adverse event attributes:

- adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- dates of onset and resolution (if resolved),
- severity (and/or toxicity per protocol),
- assessment of relatedness to investigational product(s) or other protocol-required therapies, and
- action taken.

The adverse event grading scale used will be the Amgen adverse event standard grading score; Common Terminology Criteria for Adverse Events (CTCAE). The grading scale used in this study is described in Appendix A.

The investigator must assess whether the adverse event is possibly related to the investigational product(s). This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product(s)?

The investigator must assess whether the adverse event is possibly related to any study-mandated activity (eg, administration of investigational product, protocol-required therapies, use of medical device(s) and/or procedure (including any screening procedure(s)). This relationship is indicated by a "yes" or "no" response to the question:

"Is there a reasonable possibility that the event may have been caused by a study activity (eg, administration of investigational product, protocol-required therapies, use of medical device(s)), and/or procedure"?

The Investigator is expected to follow reported adverse events until stabilization or reversibility.

9.2.1.2 Reporting Procedures for 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 the subject signing of the informed consent through 30 days after the last dose of the investigational product are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Event CRF.

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic Serious Adverse Event Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the electronic Serious Adverse Event Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the eSerious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

The investigator must assess whether the serious adverse event is possibly related to the investigational product(s). This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product(s)? Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records.

Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

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

9.2.1.3 Reporting Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union [EU] member states), 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 has to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

9.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is taking carfilzomib report the pregnancy to Amgen Global Patient Safety as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur 30 days after the last dose of carfilzomib or 3 months after the cessation of daratumumab treatment. For male subjects, investigators should report pregnancies that occur during treatment and for an additional 90 days after the last dose of carfilzomib and/or daratumumab (whichever was given last).

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a female subject becomes pregnant during the study or within 30 days after the last dose of carfilzomib or within 3 months after the last dose of daratumumab, the investigator should attempt to obtain information regarding the birth outcome and health of the infant.

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.

If a female breastfeeds while taking protocol-required therapies report the lactation case to Amgen as specified below. In addition to reporting a lactation case during the study, investigators should report lactation cases that occur 30 days after the last dose of carfilzomib or 3 months after the last dose of daratumumab.

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a male subject's female partner becomes pregnant while taking protocol-required therapies or within 90 days after the last dose of carfilzomib and/or daratumumab (whichever was given last), the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

PFS defined as time from randomization until disease progression or death from any cause. Response and disease progression determined by a blinded Independent Review Committee (IRC).

10.1.1.2 Secondary Endpoint(s)

Key secondary endpoints include:

- ORR: defined as the proportion of best overall response of sCR, CR, VGPR, and PR by IRC
- MRD[-]CR rate, MRD[-]CR defined as achievement of CR by IRC per IMWG-URC (see Appendix M) and MRD[-] status as assessed by NGS (at a 10^{-5} level, pending analytical validation) at 12 months
- OS

Additional secondary endpoints:

- DOR
- time to next treatment

- TTP
- time to response
- sustained MRD[-]CR (defined as the proportion of subjects that maintain MRD[-]CR for 12 months or more after achieving MRD[-]CR status)
- CRR (defined as the proportion of best overall response of sCR or CR)
- MRD [-] rate
- EORTC QLQ-C30- Global Health Status/QoL scale
- subject incidence of treatment-emergent adverse events
- safety laboratory values, LVEF, FEV1/FVC ratio, and vital signs at each scheduled assessment

10.1.1.3 Exploratory Endpoint(s)

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[redacted]

10.1.2 Analysis Sets

10.1.2.1 Full Analysis Set

The full analysis set will include all randomized subjects. All subjects will be analyzed according to treatment to which they are randomized. Full analysis set will be used for the primary and key secondary endpoints.

10.1.2.2 Safety Analysis Set

The safety population will include all randomized subjects who received at least 1 dose of any study treatment (ie, carfilzomib, dexamethasone, or daratumumab). Subjects in the analyses based on the safety analysis set will be analyzed according to the treatment group corresponding to the actual treatment received.

10.1.2.3 Per Protocol Analysis Set

The per protocol analysis set is a subset of the full analysis set which includes subjects who do not have important protocol deviations that are considered to have an effect on efficacy outcomes. The list of important protocol deviations is maintained by the sponsor on an ongoing basis and will be finalized before the primary analysis of the study.

10.1.3 Covariates and Subgroups

In addition to the stratification factors for randomization, original ISS stage (Stage 1 or 2 versus Stage 3) at screening, prior proteasome inhibitor exposure (yes vs no), number of prior lines of therapy (1 vs ≥ 2), and prior CD38 antibody therapy (yes vs no) the following covariates will be used to examine primary and selected secondary endpoints in subgroups as appropriate:

- baseline demographics and characteristics:
  - age
  - sex
  - race
  - region
- baseline organ function and comorbid conditions:
  - ECOG PS
  - baseline CrCl
  - baseline hypertension history
  - baseline history of ischemic heart disease
- baseline disease characteristics:
  - revised ISS stage
  - IgG vs non-IgG
  - determination of measurable disease at baseline
  - β2-microglobulin level
  - risk group as determined by FISH
  - presence of soft tissue plasmacytoma
  - prior lenalidomide exposure
  - refractory to lenalidomide

10.1.4 Handling of Missing and Incomplete Data

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

The inferential comparison between treatment groups for both the ORR and MRD[-]CR will be made using the Cochran-Mantel-Haenszel chi-square test controlling for the randomization stratification factors per IxRS. An estimate of the common odds ratio (95% CI) will be provided as a measure of the relative treatment effect. The primary analysis of ORR will be based on IRC assessed outcomes. The analyses based on investigator-assessed and ORCA will serve as supportive analyses. Similarly, the CR portion of the MRD[-]CR endpoint will be based on IRC assessments.

Overall survival will be analyzed using the same method as described for the PFS endpoints after PFS, ORR, MRD[-]CR all reach statistical significance. CCI

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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. 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 is to be documented in the subject's medical records, and the ICF 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. The original signed ICF is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject or legally acceptable representative.

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

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed ICF, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. 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.

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 is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB/IEC approval [IRBs only]/renewal [IRBs and IECs] throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen.

AMGEN Study # 20160275 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

Appendix G. NHLBI Table of Asthma Severity

Components of Severity		Intermittent			Persistent								
					Mild			Moderate			Severe		
		Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years
Impairment	Symptoms	≤2 days/week			>2 days/week but not daily			Daily			Throughout the day		
	Nighttime awakenings	0	≤2x/month		1–2x/month	3–4x/month		3–4x/month	>1x/week but not nightly		>1x/week	Often 7x/week	
	SABA* use for symptom control (not to prevent EIB*)	≤2 days/week			>2 days/week but not daily	>2 days/week but not daily and not more than once on any day		Daily			Several times per day		
	Interference with normal activity	None			Minor limitation			Some limitation			Extremely limited		
	Lung function												
	➔ FEV_1* (% predicted)	Not applicable	>80%	>80%	Not applicable	>80%	>80%	Not applicable	60–80%	60–80%	Not applicable	<60%	<60%
	➔ FEV_1/FVC*		>85%	Normal†		>80%	Normal†		75–80%	Reduced 5%†		<75%	Reduced >5%†
Risk	Asthma exacerbations requiring oral systemic corticosteroids‡	0–1/year			≥2 exacerb. in 6 months, or wheezing ≥4x per year lasting >1 day AND risk factors for persistent asthma	≥2/year		*Generally, more frequent and intense events indicate greater severity.*					
		*Consider severity and interval since last asthma exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.**											
Recommended Step for Initiating Therapy *(See "Stepwise Approach for Managing Asthma Long Term," page 7)* *The stepwise approach is meant to help, not replace, the clinical decisionmaking needed to meet individual patient needs.*		Step 1			Step 2			Step 3	Step 3 medium-dose ICS* option	Step 3	Step 3	Step 3 medium-dose ICS* option or Step 4	Step 4 or 5
								Consider short course of oral systemic corticosteroids.					
		In 2–6 weeks, depending on severity, assess level of asthma control achieved and adjust therapy as needed. For children 0–4 years old, if no clear benefit is observed in 4–6 weeks, consider adjusting therapy or alternate diagnoses.											

* **Abbreviations:** EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; SABA, short-acting $beta_2$-agonist.

† Normal FEV_1/FVC by age: 8–19 years, 85%; 20–39 years, 80%; 40–59 years, 75%; 60–80 years, 70%.

‡ Data are insufficient to link frequencies of exacerbations with different levels of asthma severity. Generally, more frequent and intense exacerbations (e.g., requiring urgent care, hospital or intensive care admission, and/or oral corticosteroids) indicate greater underlying disease severity. For treatment purposes, patients with ≥2 exacerbations may be considered to have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

- received at least 1 but not more than 3 prior lines of therapy for multiple myeloma (induction therapy followed by stem cell transplant and consolidation/maintenance therapy will be considered as 1 line of therapy; see Appendix E for guidance)
- prior therapy with carfilzomib is allowed as long as the patient had at least a PR to most recent therapy with carfilzomib, was not removed due to toxicity, did not relapse within 60 days from discontinuation of carfilzomib, and will have at least a 6-month carfilzomib treatment-free interval from last dose received until first study treatment. (Patients may receive maintenance therapy with drugs that are not proteasome inhibitors or CD38 antibodies during this 6-month carfilzomib treatment free interval)
- prior therapy with anti-CD38 antibodies is allowed as long as the patient had at least a PR to most recent therapy with CD38 antibody, was not removed due to toxicity, did not relapse within 60 days from intensive treatment (at least every other week) of CD38 antibody therapy, and will have at least a 6-month CD38 antibody treatment-free interval from last dose received until first study treatment.

Key Exclusion Criteria

- prior participation in a Janssen daratumumab phase 3 study (with exception of subjects in control arm that have withdrawn consent from study participation)
- known moderate or severe persistent asthma within the past 2 years
- known chronic obstructive pulmonary disease (COPD) with a FEV1 < 50% of predicted normal
- active congestive heart failure (New York Heart Association [NYHA] Class III to IV), symptomatic ischemia, uncontrolled arrhythmias, clinically significant electrocardiogram (ECG) abnormalities, screening ECG with corrected QT interval (QTc) of > 470 msec, pericardial disease, or myocardial infarction within 4 months prior to randomization

For a full list of eligibility criteria, please refer to Section 4.

Investigational Product

Amgen Investigational Product Dosage and Administration:

Carfilzomib will be administered as an intravenous (IV) infusion. On days when more than 1 investigational product is administered, the required order of administration is as follows: dexamethasone, pre-infusion medications for daratumumab, carfilzomib, daratumumab, and post-infusion medications for daratumumab.

Carfilzomib will be dosed twice weekly over 30 ± 5 minutes, on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. The administration may be within ± 2 days for each scheduled dose. The dose will be 20 mg/m^2 on cycle 1 days 1 and 2 and 56 mg/m^2 beginning on cycle 1 day 8 and thereafter.

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 of greater than 2.2 m^2, the dose should be capped based on a BSA of 2.2 m^2. The dose for each subject should not be revised unless the subject experiences a change in body weight of ≥ 20% in which case the BSA and dose should be recalculated. The dose can also be modified in response to toxicity following the dose modification guideline tables.

Non-Amgen Investigational Product Dosage and Administration:

Daratumumab will be administered as an IV infusion. On days 1 and 2 of cycle 1, daratumumab will be administered at 8 mg/kg in 500 mL normal saline each day. The dose of 16 mg/kg in 500 mL normal saline will be given once weekly as a single infusion for the remaining doses of the first 2 cycles (ie, days 8, 15, and 22 of cycle 1; and days 1, 8, 15, and 22 of cycle 2), then every 2 weeks for 4 cycles (cycles 3 to 6), and then every 4 weeks for the remaining cycles or until disease progression. The administration may be within ± 2 days for each scheduled dose.

resolve within 6 hours from onset, then the subject must be withdrawn from daratumumab treatment.

Infusion-related Reactions of Grade 3 or Higher

For IRR adverse events (other than laryngeal edema or bronchospasm) that are grade 3, the daratumumab administration must be stopped and the subject must be observed carefully until resolution of the adverse event or until the intensity of the event decreases to grade 1, at which point the daratumumab administration may be restarted at the investigator's discretion. If the intensity of the adverse event returns to grade 3 after restart of the daratumumab administration, then the subject must be withdrawn from daratumumab treatment.

For IRR adverse events that are grade 4, the daratumumab administration must be stopped and the subject withdrawn from daratumumab treatment.

Recurrent Infusion-related Reactions

If a grade 3 IRR (or grade 2 or higher event of laryngeal edema, or a grade 2 or higher event of bronchospasm) recurs during or within 24 hours after a subsequent daratumumab administration, the daratumumab treatment must be discontinued.

6.3 Non-Amgen Non-investigational Product: Dexamethasone

6.3.1 Dexamethasone: Dosage, Administration, and Schedule

Dexamethasone, a non-Amgen non-investigational product, will also be used in this study. On days when more than 1 investigational product is administered, the required order of administration is as follows: dexamethasone, pre-infusion medications for daratumumab, carfilzomib, daratumumab, and post-infusion medications for daratumumab.

Dexamethasone 40 mg will be taken orally or by IV infusion weekly. Dexamethasone must be given intravenously on cycle 1 days 1 and 2. See Table 12 and Table 13 to review the arm 1 and arm 2, dosing schedules, respectively. Dexamethasone IV or PO will be given on successive days, at 20 mg each treatment day on weeks with carfilzomib and/or daratumumab infusions. All subjects, regardless of age, will be required to receive 20 mg of dexamethasone on days 1 and 2 of cycle 1 (as a preinfusion medication for daratumumab infusion) followed by 20 mg of methylprednisolone or equivalent on the third day (see Appendix N for corticosteroid dose equivalents).

Table 10. Schedule of Assessments

Assessment	Screening	Assessment Cycle Days							Follow-up[a]		LTFU	Notes
		1	2	8	9	15	16	22	Visit 1	Visit 2		
Laboratory Assessments (continued)												
Coagulation tests	X											
Quantitative immunoglobulins	X											Repeated only in case of clinical need, such as recurrent infections.
Beta 2 microglobulin	X											
Pregnancy test (FCBP)	X	X							X			More frequent pregnancy tests may be conducted if required per local regulations.
Blood typing and IAT: arm 1 subjects only	X											A card with the results should be provided and subject should carry it throughout the treatment period and for at least 6 months after treatment ends
Carfilzomib PK: Cycle 1				X								See Section **7.3.19.1** for timing details.
Carfilzomib PK: Cycle 3		X										
Daratumumab PK: Cycles: 1, 3, 7, 12 (and follow-up visits)		(X)							X	X		Arm 1 only. See Section **7.3.19.2** for timing details.
Anti-daratumumab antibodies: Cycles: 1, 7, 12 (and follow-up visits)		(X)							X	X		Arm 1 only. Scheduled samples are taken from PK sample. The subjects who test positive for ADA will be followed until ADA levels return to baseline and antibody titers and neutralizing antibodies will be measured for these subjects.
HBV DNA testing	**X**	**At the next scheduled site visit and every 12 weeks during daratumumab treatment and for 6 months after the last dose of daratumumab.**										**Subjects in arm 1 who test positive for HBV serologies or have a known a history of HBV infection only. See Section 7.3.16 for more details.**

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(X) = Parentheses indicate that the particular test is situational at that time point, as specified in the respective notes.
Footnotes defined on the last page of the table.

7.2.2 Rescreening

Subjects who are determined not eligible after screening must be screen-failed in the IxRS and the reason for the screen-failure provided. Subjects who are determined to be not eligible after screening may be rescreened once at the discretion of the investigator. Subjects who are determined not eligible for randomization after rescreening must be screen-failed in the IxRS and the reason for the screen-failure provided.

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 rescreening within 21 days of the signing of the original informed consent only need to repeat the assessment(s) that did not originally meet the eligibility criteria; all other initial screening assessments do not need to be repeated. Subjects rescreening greater than 21 days from the signing of the original informed consent must be re-consented and repeat all screening procedures.

In cases of technical failure, central lab samples can be retested during screening and subject will not be considered a screen failure.

7.2.3 Treatment Period

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments (Table 10 and Table 11). Details of these procedures can be found in Section 7.3.

Administration of protocol-required therapies is to occur after all other protocol-required assessments in each visit:

- Adverse event/serious adverse event reporting
- Concomitant medications
- Physical measurements: weight and BSA (Mosteller Formula)
- **electronic clinical outcomes assessments (**eCOAs**)**
- ECG
- Vital signs
- ECHO
- PFTs
- Laboratory assessments: hematology, serum chemistries, pregnancy test (FCBP)**, HBV DNA testing (subjects with a history of HBV or who test positive for HBV serologies in arm 1 only)**
- Disease assessments (every 28 ± 7 days): SPEP/UPEP/IFE, SFLC

reductions in myelosuppression and neuropathy observed in studies comparing carfilzomib with bortezomib.

Incubation of hematologic tumor cell lines with carfilzomib for as little as 1 hour led to rapid inhibition of proteasome activity followed by accumulation of polyubiquitinated proteins and induction of apoptotic cell death (Suzuki et al, 2011; Kuhn et al, 2007).

Carfilzomib has also been administered to rats and monkeys for 6 and 9 months, respectively (twice weekly for 3 weeks on a 28-day cycle). Carfilzomib was well tolerated at doses resulting in more than 80% proteasome inhibition, with no behavioral or histological evidence of peripheral neuropathy (PN) and no neutropenia (Onyx data on file and Carfilzomib Investigator's Brochure [IB]).

2.3.2 Carfilzomib Background (Clinical)

Carfilzomib entered clinical studies in September 2005. On 20 July 2012, Kyprolis® (Carfilzomib for Injection) was approved under the United States Food and Drug Administration's (US FDA) accelerated approval program for the treatment of patients with multiple myeloma who have received at least 2 prior therapies, including bortezomib and an immunomodulatory drug (IMiD), and have demonstrated disease progression on or within 60 days of completion of the last therapy. The initial accelerated approval was based on the results of the phase 2 PX-171-003-A1 study in the United States. Subsequent full approval in the United States and globally were based on two phase 3 trials: PX 171-009 ASPIRE and 2011-003 ENDEAVOR. Following these approvals, Kyprolis in combination with either lenalidomide and dexamethasone or dexamethasone alone is indicated for treatment of relapsed or refractory multiple myeloma (RRMM). The exact indication wording varies by region. Additional data is summarized in the IB.

As of 19 July 2016, an estimated 3373 subjects (2711 subject-years) have been exposed to carfilzomib in company-sponsored clinical trials since the beginning of the development program.

Refer to Section 4 of the Carfilzomib IB for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s).

2.4 Non-Amgen Medicinal Product Background

2.4.1 Daratumumab Background (Non-Amgen Investigational Product)

Daratumumab is a first in class human anti-cluster differentiation antigen 38 (CD38) immunoglobulin (Ig) G1 (kappa) monoclonal antibody. CD38 is differentially expressed during B-cell development with greatest expression on terminally differentiated B-cells.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”. Approximately 450 subjects will be enrolled (300 in arm 1 and 150 in arm 2). Amgen may choose to increase sample size upon observation of slower than expected PFS event rate.

Please refer to Section 10.2 for sample size considerations.

3.4 Replacement of Subjects

Subjects who are enrolled and then withdrawn (or removed from treatment or the study) will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The duration of screening is up to 21 days. Subject accrual is estimated as 11 months.

The duration of treatment for an individual subject is anticipated to be a median of 25 months but subjects may be treated up to a maximum of 4 years if the subject has not yet experienced disease progression. There are 2 follow-up visits that occur 30 days (+ 3) and 8 weeks (± 7 days) after the last dose of all study drug(s). After the second follow-up visit, subjects will enter LTFU.

Subjects will be followed for survival up through 48 months after the last subject has been enrolled.

Total study duration for an individual subject is estimated to be 4 years.

3.5.2 End of Study

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early. Primary completion is anticipated to occur when approximately 188 PFS events occur which is expected to be 27 months after the first subject is enrolled.

The primary completion date is the date when data for the primary endpoint are last collected for the purposes of conducting the primary analysis.

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

dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up.

Carfilzomib must be discontinued permanently if a delay of more than 6 weeks is required due to unresolved toxicity.

6.2.1.3 Carfilzomib: Dose Reduction Levels

Dose reduction levels of carfilzomib for toxicity management of individual subjects are provided in Table 2. Subjects that require a dose level reduction and tolerate the reduced dose for 1 full cycle, may at the discretion of the treating physician increase the dose to a prior dose starting with the next cycle except when the dose reduction is due to: pulmonary hypertension, pulmonary toxicity, grade 3 or worse cardiac failure, and drug-induced hepatotoxicity.

Table 2. Dose Decrements for Carfilzomib

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

CxDx = cycle X day X

[a] If dose reduction of carfilzomib is required on C1D1 or C1D2, the investigator should contact the medical monitor to discuss the situation, before any additional doses of carfilzomib are administered.

[b] For patients with baseline chronic hepatic impairment (mild, moderate), reduce the starting and subsequent doses of carfilzomib by 25% (ie, 15 mg/m^2 day 1 and 2 of cycle 1 and 42 mg/m^2 day 8 cycle 1 and thereafter).

6.2.1.4 Carfilzomib: Guidelines for Hematologic Toxicity

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

6.2.2.1.2 Post-infusion Medications for Daratumumab

Any post-infusion medication will be administered after the infusion has completed.

For the prevention of delayed IRR, all subjects will receive long- or intermediate-acting corticosteroid (see Section 6.2.2.1.1).

In the absence of infusion-related adverse events after the first 3 infusions, post-infusion corticosteroids should be administered per investigator discretion.

For subjects with a higher risk of respiratory complications (eg, subjects with mild asthma or subjects with COPD who have an FEV1 < 80% at screening or developed FEV1 < 80% during the study without any medical history) the following post-infusion medications must be administered:

- antihistamine (diphenhydramine or equivalent)
- leukotriene inhibitor (montelukast or equivalent)
- short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for subjects with COPD)

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after an infusion. If subjects are hospitalized, then their spirometry test (FEV1) should be performed and documented before discharge. If these subjects are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours after all infusions. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, the hospitalization should not be reported as a serious adverse event. Investigators may prescribe bronchodilators, H1-antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic. If an at-risk subject experiences no major IRRs, then these post-infusion medications may be waived after 4 doses at the investigator's discretion.

Any post-infusion medication will be administered after the infusion has completed.

6.2.2.2 Daratumumab: Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

Individual dose modification of daratumumab is not permitted, but dose delay is the primary method for managing daratumumab-related toxicities.

Table 7. Dose Decrements for Dexamethasone

Subject Age	Nominal Dose (mg)	Reduced Weekly Dexamethasone Doses (mg)		
		Dose -1	Dose -2	**Dose -3**
≤ 75 years	40	20	12[a]	**8[b]**
> 75 years	20	12[a]	8	**-**

[a] If the dose needs to be divided over 2 days, administer 8 mg on the first day and 4 mg on the second day.
[b] **The third dose reduction is for subjects 75 years old or younger with steroid intolerance.**

6.3.2.2 Dexamethasone: Guidelines for Dexamethasone-related Toxicity

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

Guidelines for dexamethasone-related toxicities are summarized in Table 8.

Table 8. Treatment Guidelines for Dexamethasone-related Toxicity

Symptom	Findings	Recommended Action
Cardiovascular	Edema > grade 3 (anasarca or limiting function and unresponsive to therapy)	• Diuretics as needed, and restart dexamethasone at 1 dose decrement; if edema persists despite above measures, decrease dose by another dose decrement. • Discontinue dexamethasone permanently if symptoms persist despite second reduction.
Gastrointestinal Toxicity	Dyspepsia, gastric or duodenal ulcer, or gastritis grade 1 or 2 (requiring medical management)	• Continue dexamethasone at same dose and treat with therapeutic doses of histamine 2 (H2) blockers, or proton pump inhibitor. • Consider adding sucralfate or other antiulcer treatment as clinically indicated. • If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
	Dyspepsia, gastric or duodenal ulcer, or gastritis ≥ grade 3 (requiring hospitalization or surgery)	• Hold dexamethasone until symptoms return to baseline. • Restart dexamethasone at 1 dose decrement along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. • If symptoms persist despite above measures, discontinue dexamethasone permanently.
	Acute pancreatitis	• Discontinue dexamethasone permanently.

The ECG must include the following measurements: heart rate, QRS, QT, QTc, and PR intervals.

The primary investigator 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. ECG monitoring is required on cycle 1 day 8 and cycle 2 day 1 at the end of the carfilzomib infusion, and as clinically indicated.

7.3.12 Pulmonary Function Tests (PFTs)

Pulmonary function tests include spirometry to measure FEV1, %FEV1, FEV1/FVC, FVC, diffusing capacity of the lungs for carbon monoxide (DLCO) assessment. Screening PFT measurements may be done within 30 days prior to randomization, 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 end of treatment with carfilzomib, or if clinically indicated. Serial measurements should be performed with the same equipment and comparable procedure. Avoid performing this assessment within 4 days after daratumumab infusion.

7.3.13 Clinical Outcome Assessment

Clinical outcome assessments will be measured using the EORTC QLQ-C30, EORTC QLQ-MY20, and EQ-5D-5L. The questionnaires are provided in Appendix J through Appendix L. These questionnaires will be completed **during treatment** per the Schedule of Assessments **through follow-up visit 1**. They must always be completed prior to dosing when conducted on study drug administration days. For subjects who do not complete the cycle 1 day 1 eCOAs, no subsequent eCOA data will be collected due to the inability to measure change from baseline.

7.3.14 Survival

All subjects will be followed by telephone contact or other method approximately every 12 weeks (± 2 weeks) after the last follow-up visit until the subject has withdrawn consent for further participation, is lost to follow-up, has died, end of study, or the study is closed, whichever is earliest. 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.

7.3.17 Pregnancy Evaluation

For FCBP, a serum pregnancy test that is confirmed negative within 15 days prior to first dose of study drug and a negative urine pregnancy test within the 24 hours prior to first dose is required for eligibility determination and is to be performed at the local laboratory. In addition to the pregnancy test conducted for eligibility, a urine or serum pregnancy test must be locally confirmed negative on day 1 of each cycle prior to dosing and at end of treatment. More frequent pregnancy tests may be conducted if required per local regulations.

7.3.18 Blood Typing and IAT

Blood type, Rh, and IAT should be done before the first dose of daratumumab. Subject RBC phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to first daratumumab infusion.

Daratumumab interferes with the IAT, which is a routine pre-transfusion test performed to identify a patient's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a patient identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab IAT interference with IAT by treating reagent RBCs with dithiothreitol (DTT; Chapuy et al, 2015).

Possible methods for blood banks to provide safe RBCs for transfusion to subjects receiving daratumumab include:

- Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping) or genotypically matched units
- Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using DTT-treated reagent RBCs

cycle 1 (days 2 and 8) and cycle 3 (days 1 and 8) collected only at 1 hour (± 15 min) post end of carfilzomib infusion.

7.3.21 Antibody Testing Procedures

Serum from venous blood samples collected from all subjects in arm 1 will be assessed for the generation of antibodies to daratumumab (immunogenicity) on day 1 of cycles 1, 7, and 12; as well as both follow-up visits, according to Table 10. The subjects who test positive for anti-drug antibody will be followed until anti-drug antibody levels return to baseline; antibody titers and neutralizing antibodies will be measured for these subjects. Serum samples will be screened for antibodies binding to daratumumab and serum titer will also be determined from confirmed positive samples using validated immunoassay methods. Other immunogenicity analyses (eg, assessment of neutralizing capabilities) may be performed to further characterize the immune responses that are generated. Daratumumab concentration will be evaluated at all immunogenicity time points to ensure appropriate interpretation of immunogenicity data. When both daratumumab serum concentration and immunogenicity analyses are specified, they will be performed on aliquots from the same blood draw and no additional sampling is required. Procedures for sample collection, preparation, identification, storage, and shipment will be provided in the Laboratory Manual or equivalent document.

7.3.22 Tumor Response and Multiple Myeloma Disease Assessment

Disease assessments will be based on central laboratory data obtained every 28 ± 7 days until confirmed PD (Section 7.3.22.5) irrespective of cycle duration including dose delays and treatment discontinuation. For subjects who do not progress during treatment, disease assessments will continue to be measured (by the central laboratory) until PD.

Disease response and progression assessments include: SPEP, UPEP, SFLC, serum and urine immunofixation (SIFE, UIFE, respectively) (Section 7.3.22.1), bone marrow sample evaluation (Section 7.3.22.2), serum calcium, bone lesion evaluation (Section 7.3.22.3), and plasmacytoma evaluation (Section 7.3.22.4).

7.3.22.1 SPEP, UPEP, SFLC, SIFE, and UIFE

Serum protein electrophoresis, UPEP, SIFE, UIFE, and SFLC will all be conducted at the central laboratory 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

and will 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.

7.3.22.4 Extramedullary Plasmacytoma

Extramedullary plasmacytoma evaluation will be conducted at screening only if a lesion is suspected clinically. The evaluation may be done within 30 days prior to randomization, if performed as a part of standard of care. If an extramedullary plasmacytoma is detected, evaluation will be repeated during treatment only to confirm a response of PR or better, or to confirm PD or as clinically indicated. Assessment of measurable sites of extramedullary disease will be performed and evaluated locally every 28 days (for physical examination) for subjects with a history of plasmacytomas or as clinically indicated during treatment for other subjects until confirmed CR or confirmed disease progression. If assessment can only be performed radiologically, then evaluation of extramedullary plasmacytomas may be done every 12 weeks. The same technique (which may include clinical evaluation by palpation, ultrasound, CT scan, magnetic resonance imaging (MRI), or PET/CT should be employed for each measurement of plasmacytoma dimensions as clinically appropriate (refer to Appendix M). Bidimensional lesion measurements must be performed and recorded in the designated eCRF.

7.3.22.5 Progressive Disease Assessment

Progressive disease (including PD due to development of hypercalcemia attributed solely to recurrence/progression of multiple myeloma) must be based on central laboratory evaluation. Confirmation of PD (using 2 consecutive assessments) will be required only when it is determined by central laboratory evaluations and not if identified via imaging as per IMWG-URC criteria, if progression is defined by such lab evaluations. Local laboratory evaluation will not be accepted. The assessments outlined in Appendix M are required for PD. Patients will be considered to have progressive disease if they meet the criteria for progression by a variable that was not considered measurable at baseline; however, for patients who had a measurable serum or urine M-spike at baseline, progression cannot be defined by increases in SFLC alone (Kumar et al, 2016).

7.4 Biomarker Development

Minimal residual disease in bone marrow is a mandatory biomarker measurement in this study. Minimal residual disease will be measured by a NGS based assay. Bone marrow

Incomplete adverse event start dates, concomitant medications start or stop dates, and death date will be imputed and the detailed rules will be specified in statistical analysis plan (SAP). No imputation will be done for the primary analysis of the primary and key secondary endpoints. The frequency of missing disease assessments and deviation of the actual disease assessment times from the scheduled assessment times will be summarized by treatment arms. Sensitivity analyses will be performed to assess the impact on the analysis of PFS due to any missing data/assessment, and any lost to follow-up or discontinuation of assessment of PFS not due to an event. Similar analysis will be performed for QoL endpoints.

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

10.2 Sample Size Considerations

One hundred eighty-eight PFS events are required to have at least 90% power to demonstrate superiority at an alternative HR of 0.6 (arm 1 vs arm 2), using a log rank test at 1-sided overall significance level of 0.025. CCI [redacted]. With 450 subjects randomized (300 in arm 1 vs 150 in arm 2), it is anticipated that 188 events will be accrued at approximately 27 months after the first subject is randomized assuming events follow an exponential distribution. CCI [redacted] The description of sample size calculation for log-rank test factoring in accrual and dropout can be found in Lachin and Foulkes, 1986; Lakatos, 1988; and Chow et al, 2003. The actual timing of primary analysis will be determined by actual enrollment rate, dropout rate, and PFS event rate; hence, it is subject to change as these factors may vary in the study. The minimum detectable PFS HR is approximately 0.738 (corresponding to about 36% improvement in PFS) at the primary analysis. Amgen may choose to increase sample size upon observation of slower than expected PFS event rate.

CCI [redacted] It is

In the case that the PFS results are not statistically significant at the primary PFS analysis, the sponsor may stop the study and if so, the subjects will not be followed for OS any further.

For subgroups listed in Section 10.1.3, odds ratio (with 95% CI) will be provided for ORR and MRD[-]CR rate between the treatment groups. A treatment-by-subgroup interaction test will be provided as appropriate.

Subgroup analysis for OS will be performed using the same method described for PFS, as appropriate.

10.4.4 Safety Endpoints

The analysis of safety endpoints will be based on the safety analysis set. The number and percentage of subjects experiencing at least 1 adverse event will be summarized by treatment group, relationship of adverse event to study treatment, and severity. Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Laboratory parameters will be summarized using descriptive statistics, by postdose shifts relative to baseline, and a summary of subject incidence of clinically significant values. Vital signs will be summarized by changes from baseline values for each treatment group using descriptive statistics. The LVEF and FEV1/FVC endpoints will be summarized by changes from baseline values for each treatment group using descriptive statistics. Drug exposure including duration and intensity will be summarized descriptively for each treatment group.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample ICF is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Manager to the investigator. The written ICF is to be prepared in the languages of the potential patient population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

11.3 Subject Confidentiality

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

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the eCRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.
- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, ICFs) are to be kept in confidence by the investigator, except as described below.

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

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center 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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. After Amgen amends the protocol, the investigator is to return the signed Investigator's Signature page confirming agreement to continue participation in the study according to the amendment. The IRB/IEC must be informed of all amendments and give approval. The investigator must send a copy of

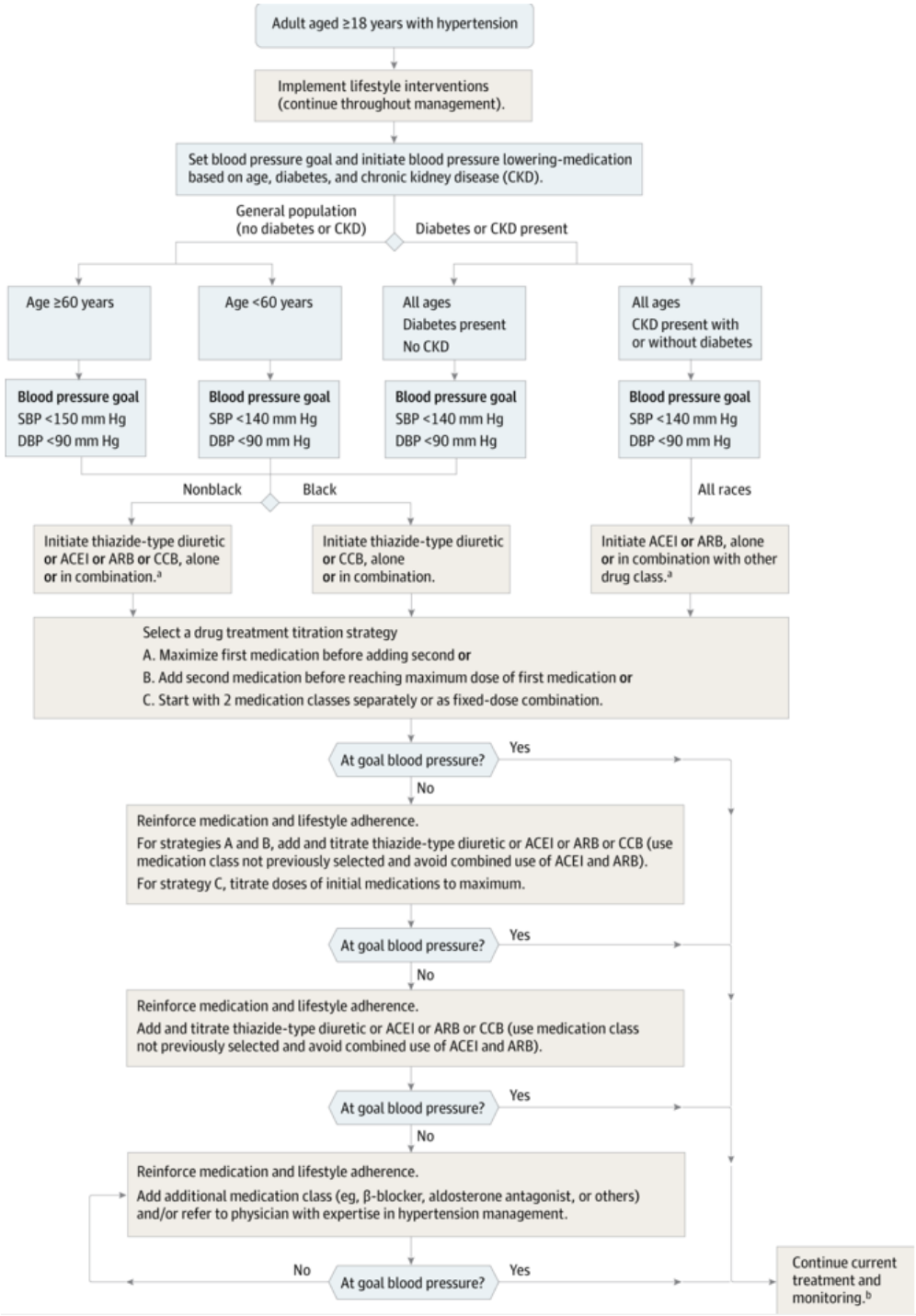
AMGEN Study # 20160275 carfilzomib	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

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

Appendix H. 2014 Antihypertensive Management by 8JNC



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