Title: A Randomized, Open-label, Phase 3 Study Comparing Carfilzomib, Dexamethasone, and Daratumumab to Carfilzomib and Dexamethasone for the Treatment of Patients With Relapsed or Refractory Multiple Myeloma

CANDOR

Study of Carfilzomib ANd Daratumumab fOr Relapsed myeloma

Amgen Protocol Number (carfilzomib) 20160275

EudraCT number 2016-003554-33

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Amendment 4:	17 May 2019
Amendment 5	02 October 2019
Amendment 6	**17 March 2021**

Investigator's Agreement

I have read the attached protocol entitled A Randomized, Open-label, Phase 3 Study Comparing Carfilzomib, Dexamethasone, and Daratumumab to Carfilzomib and Dexamethasone for the Treatment of Patients With Relapsed or Refractory Multiple Myeloma (CANDOR), dated 17 March 2021, and agree to abide by all provisions set forth therein.

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

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub investigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

Protocol Synopsis

Title: A Randomized, Open-label, Phase 3 Study Comparing Carfilzomib, Dexamethasone, and Daratumumab to Carfilzomib and Dexamethasone for the Treatment of Patients With Relapsed or Refractory Multiple Myeloma (CANDOR)

Study Phase: 3

Indication: Relapsed or Refractory Multiple Myeloma

Primary Objective: The primary objective is to compare carfilzomib, dexamethasone, and daratumumab (KdD) to carfilzomib and dexamethasone (Kd) in terms of progression free survival (PFS) in patients with multiple myeloma who have relapsed after 1 to 3 prior therapies.

Secondary Objective(s): Key secondary objectives are to compare the following between the 2 arms:

- Overall Response Rate (ORR; defined as the proportion of best overall response of stringent complete response [sCR], complete response [CR], very good partial response [VGPR], and partial response [PR])
- rate of minimal residual disease negative-complete response (MRD[-]CR) in bone marrow aspirates at 12 months (± 4 weeks) as determined by Next-Generation sequencing (NGS)
- overall survival (OS)

Additional secondary objectives are to compare the following between the 2 arms:

- safety and tolerability
- duration of response (DOR)
- time to next treatment
- time to progression (TTP)
- time to response
- persistence of MRD[-]CR
- complete response rate (CRR)
- MRD[-] rate
- quality of life

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

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).

Secondary Endpoint(s): Key secondary endpoints include:

- ORR: defined as the proportion of best overall response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR) by IRC
- MRD[-]CR rate, MRD[-]CR defined as achievement of CR by IRC per International Myeloma Working Group-Uniform Response Criteria (IMWG-URC) 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
- 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 $\geq$ 2), and prior cluster differentiation antigen 38 (CD38) antibody therapy (yes vs no).

Subjects will receive the **study** treatment determined by randomization [redacted] 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 $\pm$ 7 days. [redacted] **d**isease response assessments will be performed every 28 $\pm$ 7 days until confirmed progressive disease (PD).

Following progression or discontinuation of study drug(s), subjects will have **1** follow-up visit (30 days [+ 3] after last dose of all study drug[s]). **After disease progression,** data on survival status and subsequent antimyeloma therapy will be gathered **at** [redacted].

Local serology testing for hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody **will be performed** at the next scheduled visit for all subjects that do not already have a **known** medical history of hepatitis B infection or who have not had testing conducted within the previous 12 weeks. In addition, subjects with a **known medical** 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 **deoxyribonucleic acid (**DNA**)** testing performed at their next visit and then every 12 **weeks (± 2 weeks) or more frequently if clinically indicated through follow-up Visit 1. Subjects in arm 1 (KdD) will continue to be**

monitored and tested for 6 months following the last dose of daratumumab. A **hepatitis** specialist should be consulted for all subjects who test positive for HBV serology **or HBV DNA to undergo full assessment and make decisions regarding HBV reactivation treatment and/or confirmation whether HBV reactivation is adequately controlled to resume study drugs**. Subjects who have received Hepatitis B vaccination with only anti-HBs positivity and no clinical signs of hepatitis do not require HBV DNA monitoring.

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
- 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.

Non-investigational Product

Non-Amgen Non-investigational Product Dosage and Administration:

Dexamethasone 40 mg will be taken orally (PO) or by IV infusion weekly. The IV administration of dexamethasone must be given on cycle 1 days 1 and 2. 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. 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.

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.

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

For subjects in arm 1 on cycles 7+ without previous infusion-related reaction (IRR), dexamethasone premedication may be decreased or omitted, if the subject cannot tolerate 20 mg of dexamethasone or equivalent.

Procedures: Written informed consent must be obtained from all subjects or legally acceptable representatives before any study specific screening procedures are performed. The following procedures will occur per the Schedule of Assessments: medical history, complete physical examination, physical measurements, vital signs, Eastern Cooperative Oncology Group performance status (ECOG PS), ECG, echocardiogram (ECHO), pulmonary function tests (PFTs), recording of concomitant medications, review of adverse events and serious adverse events. Electronic clinical outcome assessments **will no longer be collected after protocol Amendment 6.** Imaging studies for bone lesions (all subjects) and soft tissue plasmacytoma evaluation (if clinically indicated). Central laboratory testing will be performed to confirm disease and stage including bone marrow with samples for MRD and fluorescence in-situ hybridization (FISH). Additional central laboratory testing will include hematology, serum chemistry, hepatic and renal function. Local laboratory testing will include coagulation factors, pregnancy testing, blood typing with indirect antiglobulin test (IAT), HBV serologies, and HBV DNA testing. Samples will also be taken to perform pharmacokinetic (PK), pharmacodynamic (PDn), biomarker studies, and anti-daratumumab antibody assessments. Subjects will be assessed for survival status and subsequent antimyeloma therapies will be collected during LTFU.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 11).

Statistical Considerations:

The efficacy analyses of PFS and key secondary endpoints will be conducted on the full analysis set. Treatment effects in efficacy endpoints will be evaluated and compared KdD vs Kd. For PFS, response and disease progression will be determined by an IRC in a blinded manner. In addition, response and disease progression outcomes will be determined locally by investigators in an unblinded manner and centrally by the sponsor using a validated computer algorithm (Onyx Response Computer Algorithm [ORCA]) in a blinded manner. The primary analysis of PFS will be based on IRC assessed outcomes; the timing will be event driven and will happen when approximately 188 PFS events are reached. The PFS outcomes assessed by the investigators as well as by ORCA will serve as supportive analyses of PFS.

The primary comparison of PFS will be tested using a log rank test stratified by the randomization stratification factors per IxRS at 1-sided significance level of 0.025.

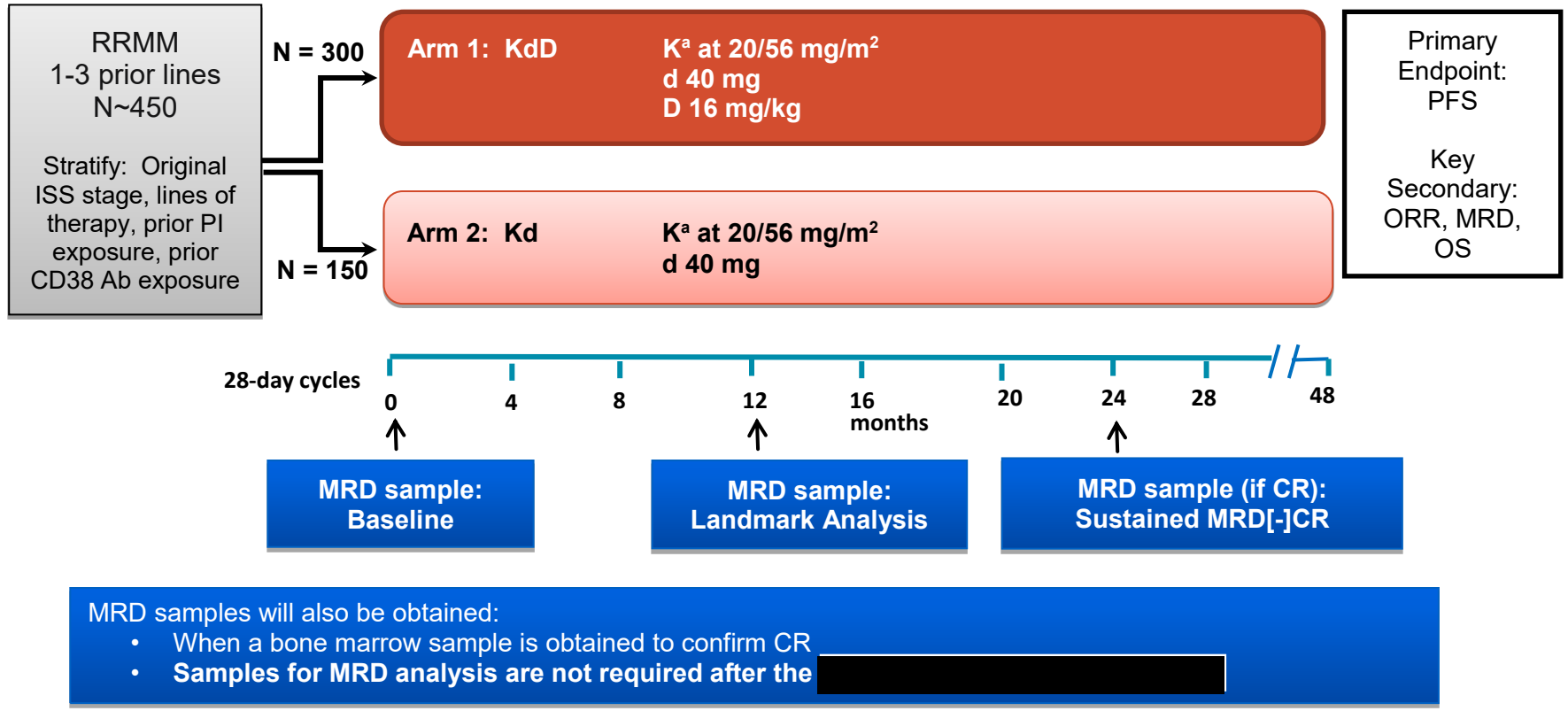
If PFS is significant, the key secondary endpoints will be tested by hierarchical testing in the order of ORR, MRD[-]CR by NGS, and OS. Overall response rate and MRD[-]CR will be tested once at the time when primary analysis of PFS is significant. If PFS, ORR, and MRD[-]CR are all statistically significant at 0.025 significance level, then OS will be tested multiple times with an overall alpha of 0.025. [redacted] Overall response rate and MRD[-]CR will be analyzed using the Cochran-Mantel-Haenszel chi-square test controlling for the randomization stratification factors per IxRS. Overall survival will be analyzed using the same method as described for the PFS endpoints.

Safety data, including laboratory test results, vital signs, treatment-emergent adverse events, serious adverse event and treatment related events, will be summarized by actual treatment received. Analysis on changes on LVEF and PFTs over time will be conducted.

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

Sponsor: Amgen, Inc.
Data Element Standards Version(s)/Date(s): Version 5.0, 20 March 2015

Study Schema



Ab = antibody; CD38 = cluster differentiation antigen 38; CR = complete response; d = dexamethasone; D = daratumumab; **DCO = data cutoff;** ISS = International Staging System; K = carfilzomib; MRD = minimal residual disease; MRD[-]CR = minimal residual disease negative-complete response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PI = proteasome inhibitor; RRMM = relapsed or refractory multiple myeloma.

[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).

Study Glossary

Abbreviation or Term	Definition/Explanation
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
AST	aspartate aminotransferase
BSA	body surface area
CD38	cluster differentiation antigen 38
CDC	complement dependent cytotoxicity
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRR	complete response rate
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DCO	**data cutoff**
DLCO	diffusing capacity of the lungs for carbon monoxide
DMC	Data Monitoring Committee
DNA	**deoxyribonucleic acid**
DOR	duration of response
DTT	dithiothreitol
ECG	electrocardiogram
ECHO	echocardiogram
eCOA	electronic clinical outcome assessment
ECOG	Eastern Cooperative Oncology Group
eCRF	**electronic case report form**
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
End of Study	defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit)

Abbreviation or Term	Definition/Explanation
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
EORTC	European Organisation for Research and Treatment of Cancer
[redacted]	
ESC	European Society of Cardiology
ESH	European Society of Hypertension
FC	flow cytometry
FCBP	females of childbearing potential
FcR	Fc receptor
FDG-PET	fluorodeoxyglucose-positron emission tomography
FEV1	forced expiratory volume in 1 second
FISH	fluorescence in-situ hybridization
FSH	follicle stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
gDNA	genomic DNA
HBsAg	**hepatitis B surface antigen**
HBV	**hepatitis B virus**
Heart rate	number of cardiac cycles per unit of time
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IFE	immunofixation
Ig	**immunoglobulin**
IMiD	**immunomodulatory drug**
IMWG-URC	**International Myeloma Working Group-Uniform Response Criteria**
INR	international normalized ratio
Interactive Voice Response (IVR)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
Interactive Web Response (IWR)	web based technology that is linked to a central computer in real time as an interface to collect and process information.
IRB/IEC	**institutional review board/independent ethics committee**

Abbreviation or Term	Definition/Explanation
IRC	Independent Review Committee
IRR	infusion-related reaction
ISS	International Staging System
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
IV	intravenous
IxRS	interactive voice/web response system
Kd	**20/56 mg/m^2 twice weekly carfilzomib and dexamethasone**
KdD	20/56 mg/m^2 twice weekly carfilzomib, dexamethasone, and daratumumab
K-M	Kaplan-Meier
KRd	carfilzomib, lenalidomide, and dexamethasone
LDH	**lactate dehydrogenase**
LD WBCT	low-dose whole body computed tomography
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
MDSC	myeloid-derived suppressor cells
MoA	mechanisms of action
MR	minimal response
MRD	minimal residual disease
MRD[-]CR	minimal residual disease negative-complete response; defined as achievement of CR (includes sCR) per International Myeloma Working Group-Uniform Response Criteria (IMWG-URC) and MRD[-] status as assessed by NGS (at a 10^{-5} level, pending analytical validation)
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NE	not evaluable
NGS	Next-Generation sequencing
NK	**natural killer**
NT-proBNP	N-terminal of the prohormone brain natriuretic peptide
NYHA	New York Heart Association
ORCA	Onyx Response Computer Algorithm
ORR	overall response rate
OS	overall survival
PBMCs	peripheral blood mononuclear cells
PD	progressive disease
PDn	pharmacodynamics

Abbreviation or Term	Definition/Explanation
PET	positron emission tomography
PFS	**progression free survival**
PFT	pulmonary function test
PJP	pneumocystis jirovenci pneumonia
PK	**pharmacokinetic**
PO	orally
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes
POR	proof of receipts
PR	partial response
Primary Completion	**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**
PR interval	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG
PS	performance status
PSA	prostate specific antigen
QLQ-C30	quality of life questionnaire – core 30 items
[redacted]	
QoL	quality of life
QRS interval	QRS interval the interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles
QTc interval	**QT interval corrected for heart rate using accepted methodology**
QT interval	QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG
RBC	red blood cell
R-ISS	Revised International Staging System
RRMM	relapsed or refractory multiple myeloma
SAP	statistical analysis plan
SBECD	sulfobutylether beta-cyclodextrim sodium
sCD38	soluble cluster differentiation antigen 38
sCR	stringent complete response
SD	stable disease

Abbreviation or Term	Definition/Explanation
SFLC	serum free light chain
SIFE	serum immunofixation
[redacted]	[redacted]
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline (E6)). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
SPEP	serum protein electrophoresis
sWFI	sterile water for injection
TCR	T-cell receptor
TLS	tumor lysis syndrome
TTE	transthoracic echocardiogram
UIFE	urine immunofixation
ULN	upper limit of normal
UPEP	urine protein electrophoresis
US FDA	United States Food and Drug Administration's
Vd	bortezomib with dexamethasone
VGPR	very good partial response

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1. OBJECTIVES

1.1 Primary

The primary objective is to compare carfilzomib, dexamethasone, and daratumumab (KdD) to carfilzomib and dexamethasone (Kd) in terms of progression free survival (PFS) in patients with multiple myeloma who have relapsed after 1 to 3 prior therapies.

1.2 Secondary

Key secondary objectives are to compare the following between the 2 arms:

- Overall Response Rate (ORR; defined as the proportion of best overall response of stringent complete response [sCR], complete response [CR], very good partial response [VGPR], and partial response [PR])
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- safety and tolerability
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- time to progression (TTP)
- time to response
- persistence of MRD[-]CR
- complete response rate (CRR)
- MRD[-] rate
- quality of life

1.3 Exploratory

[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 80000 annual deaths worldwide (1% of cancer deaths). The estimated incidence of multiple myeloma in 2012 worldwide was 114000 persons and this represents 0.8% of all cancers. The 5 year prevalence of multiple myeloma worldwide was estimated at 229000 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 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 2 phase 3 trials: PX 171-009 ASPIRE and 2011-003 ENDEAVOR. Following these approvals, Kyprolis in combination with either lenalidomide and dexamethasone or dexamethasone alone is indicated for 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 20**20**, an estimated **4361** subjects (**3976.4** 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. CD38 is an enzyme that catalyzes the metabolism of cyclic adenine dinucleotide phosphate ribose and nicotinic acid to adenine dinucleotide phosphate which functions in regulation of intracellular calcium stores. Various preclinical experiments with multiple myeloma cell lines, purified multiple myeloma cells, and mononuclear cell suspensions have demonstrated that daratumumab triggers lysis of multiple myeloma cells by a variety of mechanisms. The binding of the antibody to CD38 positions of the Fc receptor (FcR) in a way that optimizes interaction with complement resulting in strong complement dependent lysis (de Weers et al, 2011).

Antibody dependent lysis with daratumumab has been demonstrated in complement free cell suspensions of multiple myeloma cells and cell lines with peripheral blood mononuclear cells (PBMCs) enriched for natural killer (NK) cells using both normal and patient PBMCs. Other mechanisms of action (MoA) including antibody-dependent cellular phagocytosis (ADCP) and apoptosis triggered by FcR-crosslinking have been demonstrated with daratumumab (van der Veer et al, 2011b). Analysis from clinical trials of daratumumab revealed an immunomodulatory role of daratumumab that leads to the induction of clonal T cell expansion and reduction of immune suppressive cell populations $CD38^+$ myeloid-derived suppressor cells (MDSC), $CD38^+$ TReg, and $CD38^+$ BReg cells (Krejcik et al, 2016).

Clinical activity of daratumumab was first studied in phase 1/2 Gen 501 and phase 2 SIRIUS trials. A recent summary of the pooled results of these trials was reported (Usmani et al, 2016). The patient population was RRMM with 2 or more prior lines of therapy, 76% of patients received more than 3 lines of therapy (median 5, range 2 to 14 lines). A total of 148 patients were treated at the 16 mg/kg dose, 86.5% of patients were double refractory to both IMiD and proteasome inhibitors. The ORR was 31% and DOR 7.6 months with a median PFS of 4 months. Only 4% of patients discontinued therapy due to adverse events. Most adverse events were due to infusion reactions with approximately 50% with reactions to first infusion dropping to approximately 10% with second infusion and rare with subsequent infusions. Of interest, patients achieving only stable disease/minimal response (SD/MR) also appeared to benefit with a median OS of 18 months compared to 20 months for responders and 3 months for those with not evaluable/progressive disease (NE/PD). The highly significant activity of daratumumab in RRMM, novel non-overlapping mechanism or

toxicity with regard to bortezomib and lenalidomide predict high tolerability and efficacy of KdD combination therapy in treatment of relapsed multiple myeloma.

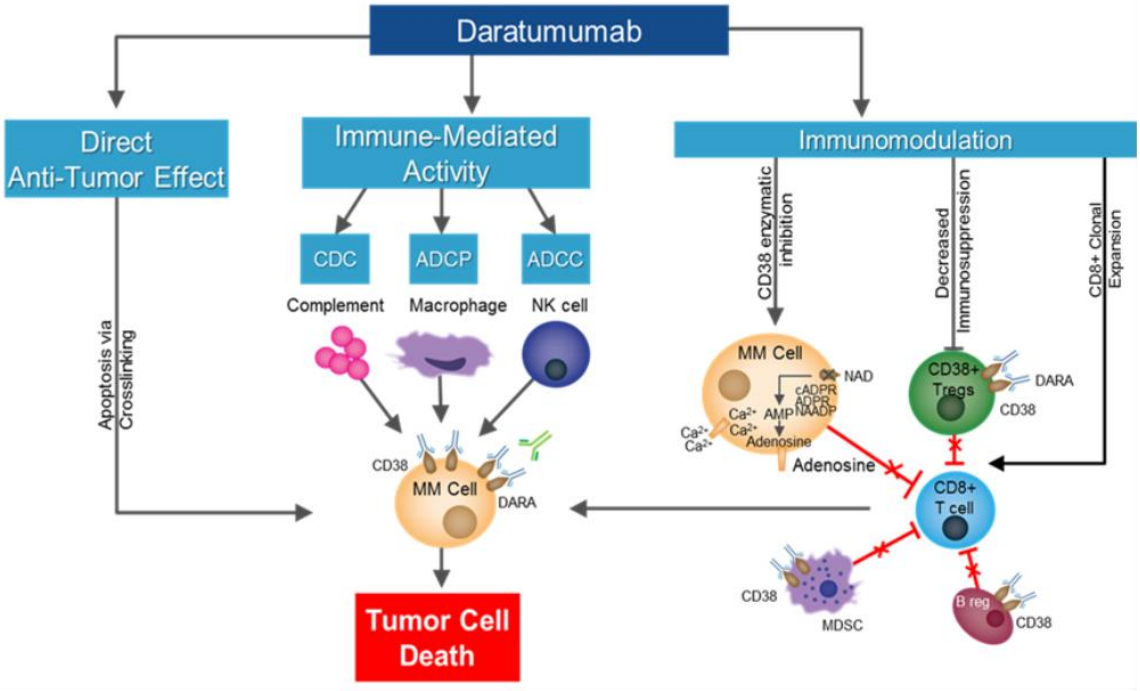
2.4.2 Daratumumab Mechanism of Action

Daratumumab is a targeted immunotherapy that binds to CD38, a transmembrane glycoprotein that is overexpressed in multiple myeloma plasma cells. Multiple MoA have been observed for daratumumab, including complement dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), induction of apoptosis by Fc gamma receptor mediated crosslinking of tumor bound monoclonal antibodies, and ADCP.

Translational biomarker studies of samples from patients treated in daratumumab phase 1 and phase 2 studies (Studies GEN501 and MMY2002, respectively) have revealed previously unknown immunomodulatory effects of daratumumab (Krejcik et al, 2016). Detailed analysis by flow cytometry (FC) of changes in circulating immune cells demonstrated that daratumumab was able to induce large increases in $CD8^+$ T numbers. Next generation T-cell receptor (TCR) sequencing was utilized to evaluate changes in T cell clonality. Interestingly, in patients who responded to daratumumab, both the maximal individual increase in a T cell clone, as well as the sum of expanded T cell clones, were significantly increased suggesting that T cell expansion may have a role in eliminating the myeloma cells. In order to assess the potential mechanism by which daratumumab could lead to these increases in T cell clones, additional analysis revealed that there was a rapid and sustained elimination of highly immunosuppressive subsets of $CD38^+$ Tregs, $CD38^+$ MDSCs, and $CD38^+$ Bregs in patients treated with daratumumab. The $CD38^+$ Tregs identified is a novel population of Tregs that are more immunosuppressive than $CD38^-$ Tregs. In addition, it has also been shown that daratumumab can modulate the enzymatic activity of CD38 and potentially lead to a reduction in immunosuppressive adenosine levels in the tumor microenvironment (Horenstein et al, 2013).

Some of daratumumab's most differentiating attributes are the depth of response achieved in responders and the drug's multifaceted MoA. Based upon these new findings, it is hypothesized that daratumumab's deep and durable responses in patients with multiple myeloma are induced, in part, by the immunomodulatory activity that removes immune suppressive functions of $CD38^+$ MDSC, $CD38^+$ TReg, and $CD38^+$ BReg cells and increases T cell clonality. A figure summarizing daratumumab's novel, converging MoA is presented in Figure 1.

Figure 1. Daratumumab Mechanisms of Action



ADCC = antibody dependent cellular cytotoxicity; ADCP = antibody dependent cellular phagocytosis; ADPR = adenosine diphosphate ribose; AMP = adenosine monophosphate; Ca^{2+} = calcium ion; cADPR = cyclic adenosine diphosphoribose; CD38 = cluster differentiation antigen 38; $CD8^{+}$ = cluster of differentiation 8; CDC = complement-dependent cytotoxicity; DARA = daratumumab; MM = multiple myeloma; MDSC = myeloid-derived suppressor cell; NAADP = nicotinic acid adenine dinucleotide phosphate; NAD = nicotinamide adenine dinucleotide; NK = natural killer.

Previously reported to kill tumor cells by immune-mediated mechanisms, such as ADCC, ADCP, and CDC, as well as by programmed cell death via cross linking of the antibody on the cell surface, it is now known that daratumumab also induces immunomodulatory effects via several different pathways that contribute to killing of $CD38^{+}$ immune cells that modulate T cell activity, namely MDSC, TReg, and BReg. This is a novel mechanism previously unreported that is hypothesized to drive development of multiple opportunities for daratumumab beyond $CD38^{+}$ myeloma and other heme malignancies.

2.4.3 Dexamethasone (Non-Amgen Non-investigational Product)

Dexamethasone is commercially available. Details regarding the description, supply, and storage instructions for dexamethasone are found in the prescribing information. Sites are advised to refer to the prescribing information for information that is specific to the brand or formulation of the drug product in use.

2.5 Rationale

2.5.1 Study Rationale

Relapsed or refractory multiple myeloma treatment has evolved rapidly in recent years. ASPIRE was the first phase 3 randomized study demonstrating that a triplet using non-conventional chemotherapy agents had significant improvement in outcomes when compared with a duplet. In this study, KRd reduced the risk of progression by 31% when compared to lenalidomide and dexamethasone (hazard ratio [HR] = 0.69, P < 0.0001; Stewart et al, 2015) which translated in a median PFS of 26.3 months in the KRd arm with consistent benefit in subgroup analyses. These positive results were despite limiting carfilzomib treatment to the first 18 cycles of therapy. Soon after, the concept of superior outcomes with novel agent-based triplets as treatment of early relapsed multiple myeloma (1 to 3 prior lines) was confirmed with other combinations (Table 1). More recently, interim data from 2 phase 3 trials with daratumumab has shown improvement of outcomes when added to either bortezomib and dexamethasone or lenalidomide and dexamethasone backbones. Compared to lenalidomide and dexamethasone for patients with RRMM with a median of 1 prior line of therapy, the addition of daratumumab reduced the risk of progression by 63% (HR = 0.37, P < 0.0001; Dimopoulos et al, 2016). Compared to bortezomib and dexamethasone, the addition of daratumumab reduced the risk of progression by 61% in patients with RRMM with a median of 2 prior lines of therapy (HR = 0.39, P < 0.0001; Palumbo et al, 2016).

Among the phase 3 studies in relapsed multiple myeloma, the results achieved with carfilzomib and daratumumab based combinations suggest that these 2 agents are likely the most potent in their respective classes. They both have demonstrated high rates of overall responses and significant increment of CRRs (Table 1). Moreover, pre-clinical and clinical studies combining daratumumab to proteasome inhibitors have demonstrated synergy (Palumbo et al, 2016; van der Veer et al, 2011a). Therefore, it is expected that the combination of both agents, carfilzomib and daratumumab, would provide a highly efficacious treatment option for patients with relapsed disease.

A number of ongoing phase 3 studies in newly diagnosed transplant ineligible patients are evaluating lenalidomide-based triplets with planned treatment to continue until progression (NCT01335399, NCT01850524, NCT02252172, and NCT02579863). Moreover, a recent meta-analysis has demonstrated OS advantage on the use of lenalidomide maintenance after autologous stem cell transplant (McCarthy et al, 2016). This information points to an increase in the number of subjects that have been exposed

to lenalidomide in first line. Developing lenalidomide-sparing options is expected to address a significant unmet need in the near future for the treatment of relapsed myeloma.

Table 1. Response Rates and Progression Free Survival in Recent Relapsed Multiple Myeloma Phase 3 Clinical Trials

Trial	Arm	ORR (%)	CR (%)	PFS (mo)
ENDEAVOR	Kd	77%	13%	18.7
	Vd	63%	6%	9.4
ASPIRE	KRd	87%	31.8%	26.3
	Rd	67%	9%	17.6
CASTOR	DVd	83%	19%	NR
	Vd	63%	9%	7.3
POLLUX	DRd	93%	43%	NR
	Rd	76%	19%	18.4
ELOQUENT-II	Elotuzumab Rd	79%	4%	19.4
	Rd	66%	7%	14.9
TOURMALINE-II	Ixazomib Rd	78%	11.7%	20.6
	Rd	71.5%	6.6%	14.7

CR = complete response; d = dexamethasone; D = daratumumab; K = carfilzomib; mo = month; NR = not reached; ORR = overall response rate; PFS = median progression-free survival; R = lenalidomide; V = bortezomib.

2.5.2 Rationale for Daratumumab Dose

Dosing of daratumumab in subjects with multiple myeloma is recommended at 16 mg/kg (weekly for 8 weeks, then every 2 weeks for 16 weeks, then every 4 weeks thereafter) administered via intravenous (IV) until disease progression or unacceptable toxicity. The dose selection was based on an acceptable safety profile, maximal clinical activity, and PKs consistent with saturation of the target. The data supporting the selection of a 16 mg/kg dose for the treatment of multiple myeloma are as follows:

- Safety: Clinical safety data demonstrated that daratumumab is well-tolerated, with clinically manageable side effects, highlighted by the fact that no subject treated with 16 mg/kg daratumumab monotherapy discontinued treatment as a result of a daratumumab related adverse event.
  - For doses above 4 mg/kg, there was no dose dependent toxicity pattern observed.

- Clinical efficacy: Clinical response data derived from Study GEN501 and Study MMY2002 show robust activity among subjects treated at 16 mg/kg with ORRs of 36% and 29%, respectively.
  - The response rates were consistently and significantly higher and deeper at the 16 mg/kg dose level as compared to various schedules at the 8 mg/kg dose level.
- Pharmacokinetics: Daratumumab exhibits target-mediated drug disposition. Daratumumab binds to CD38 receptors in the body and the complex with daratumumab is rapidly cleared. As the dose is increased or after repeated administration, CD38 becomes saturated, and the impact of target binding clearance is minimized and PK data can indicate target saturation.
  - Population PK and exposure-response analyses suggested that 16 mg/kg is the lowest tested dose at which the majority (approximately 80%) of subjects achieved serum concentrations above the model-predicted 99% target saturation threshold and 90% of the maximum effect on ORR threshold.
  - Lowering the dose would likely result in reduced efficacy, whereas increasing the dose may not provide further improvement of the benefit-risk profile.
  - The initial weekly dosing schedule rapidly established efficacious concentrations. The every 2 week and every 4 week dosing frequencies were sufficient to produce serum concentration levels that maintained target saturation; thus reducing the risk of disease progression.

2.5.3 Rationale for the Combination

The rationale for combining daratumumab with a proteasome inhibitor is supported by the results obtained in the CASTOR study as described above. This study was conducted with bortezomib, a reversible inhibitor of the proteasome which was also evaluated head-to-head against carfilzomib and dexamethasone in the ENDEAVOR study with a similar patient population. The results of this comparison suggest superior outcomes with carfilzomib with a 47% reduction in the risk of progression or death (HR = 0.53, P < 0.0001; Dimopoulos et al, 2016) and are the basis for the labeled dose in RRMM. Given the orthogonal MoA of daratumumab, the addition to the carfilzomib and dexamethasone regimen is hypothesized to be highly efficacious and possibly result in a longer duration of PFS compared to the experimental arm in the CASTOR study. An ongoing phase 1b study is evaluating the safety of the addition of daratumumab to carfilzomib and dexamethasone (NCT01998971). As of 30 June 2016, 20 subjects have been treated with KdD in the ongoing Study MMY1001. The most frequently reported grade 3 or 4 adverse events were laboratory-related and included thrombocytopenia (35%), neutropenia (25%), and anemia (15%). Cardiac disorders were reported in 4 subjects and were grade 1 and 2 tachycardia (2 subjects), atrial fibrillation (1 subject), and cardiac failure (1 subject). No grade ≥ 3 cardiac disorder adverse events were

reported. The subject with grade 2 cardiac failure recovered from the event and continued on investigational product, receiving a reduced dose of carfilzomib. Based on these preliminary data, the combination of KdD is well tolerated with a safety profile that is consistent with the known safety profile of daratumumab or Kd.

For the combination of these 2 agents, the initial daratumumab infusion and any subsequent infusions that would otherwise require a large volume (eg, 1 liter); will be divided in 2 days to minimize the risk of volume overload given that new or worsening cardiac failure has occurred following the administration of carfilzomib.

2.5.4 Rationale for the Carfilzomib Dose Schedule

The dose schedule in the KdD arm is based on the objective of evaluating the effect of the addition of daratumumab to a well characterized carfilzomib dexamethasone regimen. The safety and efficacy of 20/56 mg/m^2 twice-a-week carfilzomib combined with dexamethasone has been defined in a randomized phase 3 trial (ENDEAVOR; Dimopoulos et al, 2016). In ENDEAVOR, Kd was compared to bortezomib with dexamethasone (Vd) in a similar patient population proposed in this phase 3 trial (Study 20160275). The carfilzomib arm proved superior at the first interim analysis for efficacy reducing the risk of progression or death by 47% (median PFS [Kd vs Vd]: 18.7 months vs 9.4 months). The median follow up for the Kd arm was 11.9 months at the time of the first interim analysis. A pre-planned interim analysis for OS demonstrated a 21% reduction in the risk of death (median OS [Kd vs Vd] 47.6 vs 40 months). The median number of weeks of carfilzomib received per subject was 48.0 in the Kd group (Dimopoulos et al, 2017). At the time of this analysis, there were 212 subjects who have received over 1 year of therapy, 89 with more than 2 years, and 31 with more than 3 years. The incidence of grade 3 treatment-emergent adverse events has decreased over the years, from 74.1% in the first 12 months, to 52.8% between 12 and 24 months, 44.9% between 24 and 36 months, and 29.0% in subjects with more than 36 months. Similarly, the rate of serious adverse events shows a decrease from 47.9% in the first 12 months, 32.5% between 12 to 24 months, 24.7% between 24 to 36 months, and 3.2% in subjects exposed more than 36 months (data on file). The data to-date are supportive of at least 3 years exposure of carfilzomib and low-dose dexamethasone as done in the ENDEAVOR trial.

Daratumumab has been successfully combined with a range of anti-myeloma therapies, including recently released data on successful combination with a proteasome inhibitor in the CASTOR study in a similar patient population. An ongoing phase 1b study

evaluating the addition of daratumumab to several standards of care includes an arm of 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 $\geq$ 2)

4. Prior CD38 antibody therapy (yes vs no)

Subjects will receive the **study** treatment determined by randomization [redacted], 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. [redacted], **d**isease response assessments will be performed every 28 ± 7 days until confirmed PD irrespective of cycle duration including dose delays or treatment discontinuation. [redacted].

Following progression or discontinuation of study drug(s), subjects will have **1** follow-up visit **30 days (+3)** after last dose of all study drug(s)**. After disease progression,** data on survival **status** and subsequent antimyeloma therapy will be gathered at [redacted].

Local **serology testing for** hepatitis B testing (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [anti-HBs], and hepatitis B core antibody [anti-HBc]) will be performed at the next scheduled visit for all subjects that do not already have a **known** medical history of hepatitis B infection or who have not had testing conducted within the previous 12 weeks. In addition, subjects with a **known medical** 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 (± 2 weeks) or more frequently if clinically indicated through follow-up visit 1. Subjects in arm 1 (KdD) will continue to be monitored and tested for 6 months following the last dose of daratumumab. A **hepatitis** specialist should be consulted for all subjects who test positive for HBV serology **or HBV DNA to undergo full assessment and make decisions regarding HBV reactivation treatment and/or confirmation whether HBV reactivation is adequately controlled to resume study drugs**. Subjects who have received Hepatitis B vaccination with only anti-HBs positivity and no clinical signs of hepatitis do not require HBV DNA monitoring.

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.

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

Subject accrual is estimated as 11 months.

Subjects may be treated **until** disease progression**, but not longer than** up to [redacted]. There **is a 21-day screening window and a** follow-up **visit 30 (+3) days** after the last dose of all study drug(s).

For subjects who discontinue treatment before disease progression, follow-up **visits** will be **conducted** for **disease response assessments every 28 ± 7 days until PD ([redacted]) or locally per Schedule of Assessments ([redacted]). After disease progression,** [redacted]. **Subjects in arm 1 (KdD) with a known history of HBV infection or with positive serology testing will continue to be monitored and tested for HBV reactivation for a maximum of 6 months following the last study dose of daratumumab.**

Total study duration for an individual subject is estimated to be **approximately 5** 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.

End of Study: The end of study date is defined as the date when the last subject in **a**rm 1**, with a known history of HBV infection or who tested positive for HBV serology,** is assessed or receives an intervention for evaluation **of HBV reactivation or when the last patient on the study has an assessment or intervention for the final data collection, whatever** occurs **later.** End of study is anticipated to occur approximately [redacted]**. At the end of study, all data will be reported.**

4. SUBJECT ELIGIBILITY

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

Before any study-specific activities/procedure, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion Criteria

101 Relapsed or progressive multiple myeloma after last treatment

102 Males or females ≥ 18 years of age

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

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

104 Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 2 (see Appendix D)

105 Patients must have at least PR to at least 1 line of prior therapy

106 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)

107 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)

108 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.

109 Left ventricular ejection fraction $\geq 40\%$ as assessed by transthoracic echocardiogram (TTE)

110 Adequate hepatic function within 21 days prior to randomization:

- bilirubin < 1.5 times the upper limit of normal (ULN)
- aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5 times the ULN

111 Absolute neutrophil count (ANC) $\geq 1 \times 10^9$/L within 21 days prior to randomization. Screening ANC should be independent of granulocyte- and granulocyte macrophage-colony stimulating factor support for at least 1 week and of pegylated granulocyte stimulating factor for ≥ 2 weeks.

112 Hemoglobin ≥ 80 g/L within 21 days prior to randomization. Patients should not have received red blood cell (RBC) transfusions for at least 7 days prior to obtaining the screening hemoglobin.

113 Platelet count $\geq 75 \times 10^9$/L ($\geq 50 \times 10^9$/L if myeloma involvement in the bone marrow is $\geq 50\%$) within 21 days prior to randomization. Patients should not have received platelet transfusions for at least 7 days prior to obtaining the screening platelet count.

114 Calculated or measured creatinine clearance (CrCl) of ≥ 20 mL/min within 21 days prior to randomization based on standard formula such as the Cockcroft and Gault. (Subjects on dialysis are excluded)

115 Females of childbearing potential (FCBP) must have a negative serum pregnancy test within 15 days prior to first dose of study drug and a negative urine pregnancy test within the 24 hours prior to first dose

116 FCBP must agree to use highly effective method(s) of contraception, during the study and for 30 days following the last dose of carfilzomib administration or 3 months following the last dose of daratumumab administration, whichever is

later for subjects in the KdD arm; and 30 days following the last dose of carfilzomib administration for the Kd arm.

117 Male subjects who are sexually active with an FCBP must agree to use condoms (unless they have had a vasectomy with medical confirmation of surgical success) during carfilzomib and/or daratumumab treatment and for additional 90 days following the last carfilzomib and/or daratumumab administration.

118 Male subjects must agree to not donate sperm, during treatment and for an additional 90 days following the last carfilzomib and/or daratumumab administration

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

4.2 Exclusion Criteria

201 Waldenström macroglobulinemia

202 Multiple myeloma of IgM subtype

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

204 Plasma cell leukemia ($> 2.0 \times 10^9$/L circulating plasma cells by standard differential)

205 Myelodysplastic syndrome

206 History of other malignancy within the past 5 years except:

- Adequately treated carcinoma in situ of the cervix without evidence of disease
- Prostate cancer with a Gleason score < 6 with undetectable prostate specific antigen (PSA) over 12 months
- Ductal breast carcinoma in situ with full surgical resection (ie, negative margins) and without evidence of disease
- Treated medullary or papillary thyroid cancer
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ
- Similar neoplastic conditions with an expectation of $> 95\%$ 5-year disease-free survival
- Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before randomization and felt to be at low risk for recurrence by the treating physician

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

208 Immunotherapy with potential anti-myeloma activity within 21 days prior to randomization

209 Chemotherapy with approved or investigational anticancer therapeutic within 21 days prior to randomization

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

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

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

213 Contraindication to dexamethasone

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

215 Contraindication to use daratumumab or any of its components: allergies, hypersensitivity, or intolerance to mannitol, monoclonal antibodies or human proteins or excipients (refer to Daratumumab's IB), or known sensitivity to mammalian-derived products.

216 Prior participation in a Janssen daratumumab phase 3 study (with exception of subjects in control arm that have withdrawn consent from study participation)

217 Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to antiviral drugs

218 Intolerance to hydration due to preexisting pulmonary or cardiac impairment

219 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

220 Infiltrative pulmonary disease, known pulmonary hypertension

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

222 Pleural effusions requiring thoracentesis within 14 days prior to randomization

223 Ascites requiring paracentesis within 14 days prior to randomization

224 Uncontrolled hypertension, defined as an average systolic blood pressure $>$ 159 mmHg or diastolic $>$ 99 mmHg despite optimal treatment (measured following European Society of Hypertension/European Society of Cardiology [ESH/ESC] 2013 guidelines; Appendix F)

225 Known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) < 50% of predicted normal.

226 Subjects with confirmed FEV1 < 50% of predicted.

227 Known moderate or severe persistent asthma within the past 2 years (see Appendix G), or currently has uncontrolled asthma of any classification or at time of screening has an FEV1 of < 50%. (Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).

228 Known cirrhosis

229 Known human immunodeficiency virus (HIV) infection, hepatitis C infection (subjects with hepatitis C that achieve a sustained virologic response following antiviral therapy are allowed), or hepatitis B infection (subjects with HBsAg or core antibody that achieve sustained virologic response with antiviral therapy directed at hepatitis B are allowed)

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

231 Pregnant or breastfeeding women, or women who are planning to become pregnant or breastfeed during treatment and for an additional 30 days after discontinuing treatment.

232 Ongoing graft-versus-host disease

233 Autologous stem cell transplant less than 90 days prior to randomization

234 Vaccination with live attenuated vaccines within 4 weeks prior to randomization

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

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

237 Subjects with grade 3 or worse neuropathy within 14 days prior to randomization

238 Allogeneic stem cell transplant less than 100 days prior to randomization

239 Patients on any immunosuppressive therapy for graft versus host disease, even if it has resolved

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics

committee (IRB/IEC) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects or legally acceptable representatives must personally sign and date the IRB/IEC approved ICF before commencement of study-specific activities/procedures.

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

Each subject who enters into the screening period for the study (up to 21 days before cycle 1 day 1) will receive a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by the IxRS. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

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 after re-screening must be screen-failed in the IxRS and the reason for the screen-failure provided.

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.

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 may only be randomized once into this study.

5.1 Randomization/Treatment Assignment

Approximately 450 subjects will be randomized in a 2:1 ratio to 1 of 2 arms (as described in Section 3.1).

Randomization will be performed using an IxRS and subjects will be stratified based on the following criteria:

1. Original ISS stage (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)

The randomization date is to be documented in the subject's medical record and on the enrollment CRF. Subjects must receive their first dose of study treatment within 3 days of randomization.

A randomization number will be assigned to each subject by IxRS and appear on the IxRS randomization confirmation document. The randomization number is different than the subject identification number and will not be utilized by the site as a subject identifier.

6. TREATMENT PROCEDURES

6.1 Classification of Products

The Amgen investigational product used in this study includes: carfilzomib.

The non-Amgen investigational product used in this study includes: daratumumab.

The non-Amgen non-investigational product used in this study includes: dexamethasone.

6.2 Investigational Products

6.2.1 Amgen Investigational Product: Carfilzomib

Carfilzomib will be provided by Amgen Inc.

Carfilzomib is supplied as a sterile, lyophilized, white to off-white powder, ready for reconstitution. It is supplied for single use in 50 mL Type 1 glass vials containing 60 mg of carfilzomib drug product with an elastomeric stopper and flip-off lid. Upon reconstitution with [redacted] mL of preservative-free sterile water for injection (sWFI), the reconstituted solution contains 2 mg/mL carfilzomib, [redacted] mg/mL sulfobutylether beta-cyclodextrim sodium (SBECD), and [redacted] mg/mL citrate buffer, at pH [redacted] to [redacted]

Carfilzomib is supplied in labelled cartons containing 4 single use vials per carton. Carfilzomib must be stored between [redacted]°C to [redacted]°C and remain protected from light.

6.2.1.1 Carfilzomib: Dosage, Administration, and Schedule

Carfilzomib will be administered as an 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. Subjects in arm 1 do not require prehydration, however, prehydration can be administered at investigator's

discretion on cycle 1 day 9 and cycle 1 day 16. Mechanical infusion pumps are recommended, but gravity-dependent infusions are permitted if the 30-minute infusion duration can be reliably maintained. 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). In case of resolution of hepatic abnormalities, dose escalation may be considered.

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. See Table 13 and Table 14 to review the arm 1 and arm 2 dosing schedules, respectively.

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), 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 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.

Table 3. Dose Modification Guidelines for Thrombocytopenia and Neutropenia

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

ANC = absolute neutrophil count.

6.2.1.5 Carfilzomib: Guidelines of Nonhematologic Toxicity

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

Table 4. Dose Modification Guidelines for Nonhematologic Toxicities

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

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Footnotes defined on the next page of the table

Table 4. Dose Modification Guidelines for Nonhematologic Toxicities

Symptom/Sign/Investigation	Recommended Action
Congestive heart failure	Any subject with congestive heart failure, whether or not drug related, must have the dose held until resolution or return to baseline. Appropriate medical management should be initiated. If no resolution after 4 weeks, carfilzomib will be permanently discontinued.
< Grade 3	Once congestive heart failure resolves or returns to baseline, resume at full dose.
Grade≥ 3	Once congestive heart failure resolves or returns to baseline, treatment may continue at 1 dose level reduction.
Infection (grade 3 or 4)	Hold carfilzomib. Once infection is controlled and the subject is without infection-related symptoms, and if ANC > 1.0 x 10^9/L, resume at full dose. If ANC < 1.0 x 10^9/L, follow hematologic toxicities dose reduction guidelines.
Hepatitis B Virus Reactivation	Hold carfilzomib until infection is adequately controlled (see Section 6.7.1).
Neuropathy (grade 2 with emergent pain, or grade 3)	Hold carfilzomib until resolved to ≤ grade 2 without pain; then resume at 1 dose decrement.
Neuropathy (grade 4)	Permanently discontinue carfilzomib.
Dyspnea (grade ≥ 2)	Hold carfilzomib until resolution to grade 1 or baseline, then resume at 1 dose decrement. Investigate cause and record findings. If caused by another adverse event listed in this table, follow recommendations for that adverse event.
Hypertension (SBP > 140 and/or DBP > 90, measured per Appendix F)	
< Grade 3	Continue at same dose if initiation of appropriate treatment controls hypertension (see Appendix F for guidance)
Grade≥ 3	Hold carfilzomib until resolution to normal or baseline. Initiate appropriate anti-hypertensive therapy prior to resuming carfilzomib at 1 dose decrement.
Pulmonary toxicity: Non-infectious interstitial lung disease, acute respiratory failure, ARDS (≥ grade 3)	Hold carfilzomib until resolution to grade 1 or baseline and restart at 1 dose decrement.
Pulmonary hypertension (grade ≥ 3)	Hold carfilzomib until resolution to grade 1 or baseline and restart at 1 dose decrement
Posterior reversible encephalopathy syndrome: Headaches, altered mental status, seizures, visual loss, and hypertension	If PRES is suspected, hold carfilzomib. Consider evaluation with neuroradiological imaging, specifically MRI, for onset of visual or neurological symptoms suggestive of PRES. If PRES is confirmed, permanently discontinue carfilzomib. If the diagnosis of PRES is excluded, carfilzomib administration may resume at same dose, if clinically appropriate.

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Footnotes defined on the next page of the table

Table 4. Dose Modification Guidelines for Nonhematologic Toxicities

Symptom/Sign/Investigation	Recommended Action
Progressive Multifocal Leukoencephalopathy	**Patients should be monitored for any new or worsening neurologic, cognitive, or behavioral signs or symptoms that may be suggestive of PML as part of the differential diagnosis of CNS disorders.** **If PML is suspected, withhold administration of carfilzomib; patients should be promptly referred to a specialist and appropriate diagnostic testing should be initiated. Discontinue carfilzomib if PML diagnosis is confirmed. If the diagnosis is excluded, carfilzomib can be restarted at the same dose.**
Thrombotic microangiopathy: Fever, microangiopathic hemolytic anemia, renal failure, thrombocytopenia, neurological manifestations	If the diagnosis is suspected, hold carfilzomib and manage per standard of care including plasma exchange as clinically appropriate. If TMA is confirmed, permanently discontinue carfilzomib. If the diagnosis is excluded, carfilzomib can be restarted **at the same dose**.
Venous thrombosis (≥ grade 3)	Hold carfilzomib and adjust anticoagulation regimen; resume at full dose once anticoagulation has been optimized per treating investigator's discretion.
Any other drug-related nonhematologic toxicity ≥ grade 3[b]	For carfilzomib attribution, hold dose. Resume at 1 dose decrement when toxicity has resolved to grade 1 or less or to baseline grade.

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

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

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

6.2.2 Non-Amgen Investigational Product: Daratumumab

6.2.2.1 Daratumumab: Dosage, Administration, and Schedule

Daratumumab will be administered as an IV infusion. On days when more than 1 investigational products are administered, the required administration is as follows: dexamethasone, other pre-infusion medications for daratumumab, carfilzomib, daratumumab, and post-infusion medications for daratumumab.

- On days 1 and 2 of cycle 1, daratumumab will be administered at 8 mg/kg in 500 mL normal saline each day.
    - If the subject's first 2 infusions of 8 mg/kg daratumumab are well-tolerated (defined as an absence of infusion-related reaction [IRR] > grade 1), the first infusion 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.

- If the 8 mg/kg infusions are not well-tolerated (defined as IRR > grade 1), the dilution will be in 1000 mL of normal saline until the subject completes an infusion without > grade 1 IRR. For any infusions that would require a large volume (eg, 1000 mL); the daratumumab dose may be divided in 2 days.

The administration may be within ± 2 days for each scheduled dose. See Table 13 to review the arm 1 dosing schedule.

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**s are** provided in Table 5 **and Table 6**.

The planned dose (mg/kg), dose (mg), start date/time, stop date/time, reason for change in planned dose, reason for dose change/withheld, reason for dose delay, reason for dose interruption and package lot number of 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 1 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.

The duration of infusion may be shortened starting in cycle 2 onwards to a 90-minute infusion for subjects without a history of an infusion related reaction after the third dose of daratumumab.

The 90-minute daratumumab accelerated infusions (Barr et al, 2017) can be administered at an initial rate of 20% of the total dose over 30 minutes, followed by the remaining 80% of the total dose over 60 minutes (90-minute total infusion time).

- **Rapid infusion will be given in a total volume of 500 mL**
- **This allows for a rate of 200 mL/hour for the first 30 minutes and a rate of 400 mL/hour for the final 60 minutes.**
- **If a subject experiences any grade infusion related reaction, the subject will not be eligible to receive additional rapid infusions until he/she has received standard infusion daratumumab without any grade hypersensitivity reaction.**

Table 6. Accelerated/Shortened Infusion Rate

Accelerated/Shortened Infusion	Dilution Volume	Initial Infusion Rate (first 30 minutes)	Subsequent Infusion Rate (last 60 minutes)	Maximum Infusion Rate
	500 mL	200 mL/hour	400 mL/hour	400 mL/hour

Rapid infusion will be given in a total volume of 500 mL. This allows for a rate of 200 mL/hour or the first 30 minutes and a rate of 400 mL/hour for the final 60 minutes. If a subject experiences any grade infusion related reaction, he/she is not eligible to receive additional rapid infusions until they have received standard infusion daratumumab without any grade hypersensitivity reaction.
Source: Barr et al, 2017.

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.

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 $\pm$ long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol $\pm$ 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.

During a cycle, a daratumumab dose must be held if any of the following criteria below are met, to allow for recovery from toxicity. The criteria for a dose delay are:

- grade 4 hematologic toxicity, except for grade 4 lymphopenia
- grade 3 thrombocytopenia with bleeding
- febrile neutropenia
- neutropenia with infection, of any grade
- grade 3 or higher non-hematologic toxicities with the following exceptions:
  - grade 3 nausea that responds to antiemetic treatment within 7 days
  - grade 3 vomiting that responds to antiemetic treatment within 7 days
  - grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - grade 3 fatigue that was present at baseline or that lasts for < 7 days after the last administration of daratumumab
  - grade 3 asthenia that was present at baseline or that lasts for < 7 days after the last administration of daratumumab

Administration of daratumumab may be restarted upon recovery from toxicity to grade 2 or baseline, with the exception that grade 2 laryngeal edema or grade 2 bronchospasm must be fully recovered.

If daratumumab administration does not commence within the prespecified window (Table 7) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up.

Table 7. Daratumumab Administration Schedule

Cycles	Frequency	Dose Held	Dosing Re-start
1 and 2	Weekly (q1wk)	> 3 days	next planned weekly dosing date
3 to 6	Biweekly (q2wks)	> 7 days	next planned biweekly dosing date
7+	Every 4 weeks (q4wks)	> 14 days	next planned every 4 weeks dosing date

Doses of daratumumab may be delayed up to 4 weeks (cycles 1 to 6) or up to 8 weeks (cycle 7 and beyond). If day 1 of a cycle is delayed, day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. However, if a within-cycle dose is delayed, then the dates of the subsequent within-cycle doses should not be adjusted. Any adverse event deemed to be related to daratumumab that requires a dose hold of more than 4 weeks (cycles 1 to 6) or more than 8 weeks (cycle 7 and beyond) will result in permanent discontinuation of daratumumab. If a dose delay 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 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 13 and Table 14 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).

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 13 and Table 14).

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

Three dose reduction levels are defined for dexamethasone based on the age of subjects, as shown in Table 8. Dose reductions are permanent, dose must not be increased following a dose reduction.

Table 8. 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 **3 dose reductions in subjects who are ≤ 75 years in the event of additional dexamethasone-related toxicities. Dexamethasone will be permanently discontinued after 2 dose reductions in subjects who are > 75 years 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 9.

Table 9. 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.

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Table 9. Treatment Guidelines for Dexamethasone-related Toxicity

Symptom	Findings	Recommended Action
General Disorders	Limb edema > grade 3 (> 30% limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self-care activities of daily living)	• Hold dexamethasone until symptoms return to baseline. • Diuretics as needed, and restart dexamethasone at 1 dose decrement; if edema persists despite above measures, decrease dose by another dose decrement. • Discontinue dexamethasone permanently if symptoms persist despite second reduction.
Psychiatric Disorders	Confusion or mood alteration ≥ grade 2 (interfering with function ± interfering with activities of daily living)	• Hold dexamethasone until symptoms return to baseline. • Restart dexamethasone at 1 dose decrement. • If symptoms persist despite above measures, reduce by another dose decrement.
Musculoskeletal	Muscle weakness ≥ grade 2 (symptomatic and interfering with function ± interfering with activities of daily living)	• Decrease dexamethasone by 1 dose decrement. • If weakness persists, decrease dose by another dose decrement. • Discontinue dexamethasone permanently if symptoms persist.
Metabolism and Nutrition Disorders	Hyperglycemia ≥ grade 3 (fasting glucose > 250 mg/dL)	• Treat with insulin or other hypoglycemic agents as needed until glucose is ≤ grade 2 (< 250 mg/dL) then resume dexamethasone. • If uncontrolled despite above measures, decrease dose by 1 dose decrement until ≤ grade 2 (< 250 mg/dL).
All Other	Other toxicity ≥ grade 3 felt related to dexamethasone	• Hold dexamethasone dose. Resume at 1 dose decrement when toxicity has resolved to ≤ grade 2. • If toxicity recurs, hold dexamethasone dose until toxicity has resolved to ≤ grade 2 and resume dexamethasone dose by another dose decrement. • If toxicity recurs despite 2 dose decrements, discontinue dexamethasone permanently.

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6.4 Conditions Not Requiring Dose Reduction

Carfilzomib, daratumumab, and dexamethasone do not need to be held in the following cases:

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

6.4.1 Medical Devices

No investigational medical devices will be used in the conduct of this study.

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

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

6.5 Other Protocol-required Therapies

All other protocol-required therapies listed below are commercially available and will not be provided or reimbursed by Amgen (except if required by local regulation). The Investigator will be responsible for obtaining supplies of these protocol-required therapies.

6.5.1 Antiviral Prophylaxis

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

6.5.2 Thromboprophylaxis

An anticoagulant (eg, enteric-coated aspirin at standard prophylactic dose or other anticoagulant or antiplatelet medication such as clopidogrel bisulfate, low molecular weight heparin, or warfarin), is a suggested concomitant medication in subjects based on an individual benefit/risk assessment (Li et al, 2016).

6.5.3 Tumor Lysis Syndrome Prophylaxis

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

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

6.5.4 Proton-pump Inhibitor

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

6.5.5 Bone Health Therapy

Concomitant bone health therapy is strongly recommended for all subjects with evidence of lytic destruction of bone or with osteopenia (Terpos et al, 2013; Gralow et al; 2013). Commercially available therapies are preferred when available, and should be used according to the manufacturer's recommendations, as described in the prescribing information, for subjects with osteolytic or osteopenic myelomatous bone disease.

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

6.5.6 Prophylaxis for Pneumocystis Jirovenci

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

6.5.7 Prophylaxis for Hepatitis B Virus

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

6.5.8 Other Permitted Therapies

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

- antivirals
- hyperglycemia medical management
- prevention of constipation (eg, adequate hydration, high-fiber diet, and stool softeners, if needed)
- prophylactic antiemetics, with the exception of corticosteroids
- colony stimulating factors, erythropoietin, and transfusion of platelets and RBCs
- loperamide is recommended for the treatment of diarrhea, starting at the time of the first watery stool. The loperamide dose and regimen is according to institutional guidelines. Prophylactic loperamide is not recommended.
- adequate hydration is recommended for prevention of myeloma-related kidney disease
- intravenous immunoglobulins may be given at the discretion of the investigator according to local guidelines, eg, where low serum IgG concentrations may result in recurrent upper respiratory tract infections

6.6 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Table 4 (carfilzomib), Section 6.2.2.2 (daratumumab), and Table 9 (dexamethasone) for stopping and rechallenging requirements when subjects have abnormal hepatic laboratory values (ie, alkaline phosphatase, AST, ALT, total bilirubin) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis.

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).

6.7 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.9. Concomitant therapies are to be collected from informed consent, through 30 days following the last dose of all study drug(s).

For concomitant therapies being taken for the disease under study (eg, pre/post-infusion medications), collect therapy name, indication, dose, unit, frequency, route, start dates, and enter in the subject's eCRF.

For all other concomitant therapies (eg, those listed in Section 6.4.1), collect therapy name, indication, dose, unit, frequency, route, start and stop dates, and enter in the subject's eCRF.

It is recommended to follow the Eighth Joint National Committee 2014 evidence-based guideline for the management of high blood pressure in adults (James et al, 2014 and Appendix H). For elderly subjects, it is recommended to implement the 2013 ESH and ESC guidelines (Mancia et al, 2013 and Appendix I).

Any patient presenting at screening with a blood pressure outside parameter is suggested to have consultation with the institution's hypertension service for treatment recommendation.

6.7.1 Management of Hepatitis B Virus Reactivation

Local hepatitis B testing (HBsAg, anti-HBs, and anti-HBc) will be performed at the next scheduled visit for all subjects that do not already have a **known** medical history of hepatitis B infection or who have not had testing conducted within the previous 12 weeks.

Subjects with **evidence of** positive **HBV** serology or who have a **known** history of HBV infection should have consultation with a specialist in HBV and **be monitored for clinical signs** of HBV **reactivation with** HBV DNA **testing** every 12 weeks (± 2 weeks) or more frequently as clinically indicated **during and for 30 days following the last dose of all study drug(s)** (follow-up visit 1). **Thereafter, s**ubjects in arm 1 (KdD) will continue to be monitored and **have HBV DNA testing** for **a maximum of** 6 months following last dose of daratumumab. Subjects that have received Hepatitis B vaccination with only anti-HBs positivity and no clinical signs of hepatitis do not require HBV DNA testing and monitoring.

Any subject who becomes HBV DNA positive or develops reactivation of HBV will have study treatment interrupted and **a hepatitis specialist should be consulted to undergo full assessment and make decisions regarding HBV reactivation treatment and/or confirmation whether HBV reactivation is adequately controlled to resume study drugs**. **In consultation with the investigator, the hepatitis specialist may consider and advise r**esumption of study treatment in subjects whose

HBV reactivation is controlled and where the benefits of study treatment outweigh the risks. After cessation of study therapy for any reason, any ongoing monitoring, testing, and anti-viral treatment should be under the guidance of a specialist in HBV.

6.8 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any drug(s), device(s) or combination product(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

- carfilzomib
- daratumumab

Any product complaint(s) associated with an investigational product(s) or non-investigational product(s) or device(s) supplied by Amgen are to be reported.

6.9 Excluded Treatments and/or Procedures During Study Period

Concurrent therapy with a marketed or investigational anticancer therapeutic or radiation to large marrow reserves for either a palliative or therapeutic intent is excluded. Long-term corticosteroids for nonmalignant conditions (eg, asthma, inflammatory bowel disease) equivalent to a dexamethasone dose $>$ 4.0 mg/day or prednisone $>$ 20 mg/day are not permitted. Corticosteroids given short-term (up to 2 weeks) for non-malignant conditions are permitted provided that the cumulative dose is less than 40 mg per week dexamethasone equivalent. Medical monitor should be contacted in the event that short-term corticosteroid use is required greater than 2 weeks or at cumulative dose of more than 40 mg dexamethasone equivalent.

Vaccination with live attenuated vaccines is not permitted at any time while the subject is receiving study treatment. Plasmapheresis is not permitted at any time while the subject is receiving study treatment. For subjects requiring plasmapheresis while on study treatment, every attempt should be made to document disease status by IMWG criteria first. Study treatment must be discontinued**,** and the subject will enter LTFU.

6.10 Contraceptive Requirements

Female of Childbearing Potential

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

Female in the following categories are not considered of child bearing potential:

1. Premenopausal female with 1 of the following:
   a. Documented hysterectomy
   b. Documented bilateral salpingectomy
   c. Documented bilateral oophorectomy

   Note: Site personnel documentation from the following sources is acceptable: 1) review of subject medical records, 2) subject medical examination, or 3) subject medical history interview.
2. Premenarchal female
3. Postmenopausal female
   a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b. Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

6.10.1 Female Subjects

Females of childbearing potential should be advised to avoid becoming pregnant while being treated with carfilzomib. Given that carfilzomib was clastogenic in the in vitro chromosomal aberration test in peripheral blood lymphocytes, as a precaution, FCBP and/or their male partners should use highly effective contraception methods or abstain from sexual activity during treatment and for 30 days after treatment with carfilzomib and for 3 months after cessation of daratumumab treatment.

Female subjects of childbearing potential must agree to use 1 highly effective method of contraception (as described in Table 10). It cannot be excluded that the efficacy of oral contraceptives may be reduced during carfilzomib treatment. In addition, due to an increased risk of venous thromboembolic events associated with carfilzomib, females should avoid the use of hormonal contraceptives that are associated with a risk of thrombosis during treatment with carfilzomib. Female subjects of childbearing potential

who are using oral contraceptives or a hormonal method of contraception that is associated with a risk of thrombosis should switch to an alternative non-hormonal method of highly effective contraception.

Table 10. Highly Effective Contraceptive Methods for Female Subjects

Failure rate of < 1% per year when used consistently and correctly
• Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (oral, intravaginal [vaginal ring], or transdermal) • Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable) • Intrauterine device (IUD) • Intrauterine hormonal-releasing system (IUS) • Bilateral tubal ligation/occlusion • Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success) • Sexual abstinence: Defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence must be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.

If a female subject is suspected of being pregnant, the protocol-required therapies must be stopped immediately and may not be resumed until absence of pregnancy has been medically confirmed.

Lactation

It is not known if carfilzomib is transferred into breast milk. If the subject is breastfeeding and wishes to be in this study, they will be required to discontinue nursing during study treatment and for an additional 30 days after stopping carfilzomib.

There is no information regarding the presence of daratumumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG is known to be present in human milk.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for daratumumab and any potential adverse effects on the breast-fed child from daratumumab or from the underlying maternal condition.

6.10.2 Male Subjects

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

Male subjects with a partner of childbearing potential must agree to not father a child during treatment of carfilzomib and/or daratumumab and for an additional 90 days after the last dose of carfilzomib and/or daratumumab.

Contraceptive options for male subjects include:

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with protocol-required therapies). The reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject, or
- Use of a condom during treatment of carfilzomib and/or daratumumab and for an additional 90 days after the last dose of carfilzomib and/or daratumumab.

The female partner is to use an acceptable method of effective contraception such as: hormonal, intrauterine device (IUD), intrauterine hormonal-releasing system (IUS), female barrier method (diaphragm, cervical cap, contraceptive sponge [a female condom is not an option because there is a risk of tearing when both partners use a condom]). Male subjects must not donate sperm during treatment of carfilzomib and/or daratumumab and for an additional 90 days after the last dose of carfilzomib and/or daratumumab.

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

6.10.3 Unacceptable Methods of Birth Control for Male and Female Subjects

Birth control methods that are considered unacceptable in clinical trials include: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method.

Male and female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to fetus if they become pregnant or father a child during treatment of carfilzomib and/or daratumumab and for 90 days after the last dose of carfilzomib and/or daratumumab.

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

7. STUDY PROCEDURES

7.1 Schedule of Assessments

For Schedule of Assessments, please refer to Table 11 and Table 12. For the dosing schedule of investigational products and other protocol-required therapies in arm 1 and arm 2, please refer to Table 13 and Table 14, respectively.

Note that assessment cycles and dosing cycles both work to a 28-day cycle, but are independent (Table 12). [redacted], disease assessments should be obtained every 28 days from cycle 1 day 1, regardless of cycle duration including dose delays. [redacted].

Table 11. Schedule of Assessments

Assessment	Screening	Assessment Cycle Days							Follow-up[a]	LTFU	Notes
		1	2	8	9	15	16	22	Visit 1		
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		
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		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.

Table 11. Schedule of Assessments

Assessment	Screening	Assessment Cycle Days							Follow-up[a]	LTFU	Notes
		1	2	8	9	15	16	22	Visit 1		
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).
Survival										X	Every 12 weeks (± 2 weeks) after last follow-up visit.
Subsequent Antimyeloma Therapies									X	X	Data on subsequent antimyeloma therapy will be collected regardless of whether the subject has progressed (see Section 7.3.14).
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 7.3.15.
Hematology: cycles 2+		X							X		
Chemistry: Screen/cycle 1	X	X		X		X		X			
Chemistry: cycles 2+		X							X		

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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.

Table 11. Schedule of Assessments

Assessment	Screening	Assessment Cycle Days							Follow-up[a]	LTFU	Notes
		1	2	8	9	15	16	22	Visit 1		
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									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
[redacted]											
Anti-daratumumab antibodies: Cycles: 1, 7, 12		(X)									Arm 1 only. Scheduled samples are taken from PK sample.

(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 11. Schedule of Assessments

Assessment	Screening	Assessment Cycle Days 1	2	8	9	15	16	22	Follow-up[a] Visit 1	LTFU	Notes
Laboratory Assessments (continued)											
HBV testing		At the next scheduled site visit and every 12 weeks ± 2 weeks or more frequently as clinically indicated through follow-up visit 1.								**(X) Situational testing and monitoring will continue for subjects in arm 1 for a maximum of 6 months following the last dose of daratumumab.**	Local hepatitis B testing (HBsAg, anti-HBs, and anti-HBc) will be performed at the next scheduled visit for all subjects that do not already have a **known** medical history of hepatitis B infection or who have not had testing conducted within the previous 12 weeks. **See Sections 6.7.1 and 7.3.15 for additional information.**

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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.

Table 11. Schedule of Assessments

Assessment	Screening	Assessment Cycle Days							Follow-up[a]	LTFU	Notes
		1	2	8	9	15	16	22	Visit 1		
Optional Assessments (consent must be obtained)											
[redacted]											
Pharmacogenetic analysis (saliva sample): cycle 1		X									Sample obtained prior to dosing on C1D1.
Pharmacogenetic analysis (bone marrow aspirate): cycle 1 and follow-up visit 1		X							(X)		One bone marrow aspirate sample (obtained prior to dosing on C1D1) can be used for FISH, MRD, and pharmacogenetic analyses. Follow-up sample collected only from subjects who achieve a CR or better while on study.
Biomarker assessment (plasma): Screen/cycle 1	X					(X)					Screening samples to be obtained prior to dosing on C1D1.
Biomarker assessment (plasma): cycles 3, 6, 13, and follow-up visit 1		(X)							X		Samples to be obtained on C1D15, C3D1, C6D1, C13D1, and follow-up. Also collected from consenting subjects who achieve a CR.
Biomarker assessment (serum): Screen/cycle 1	X					(X)					Screening samples to be obtained prior to dosing on C1D1.
Biomarker assessment (serum): cycles 3, 6, and follow-up visit 1		(X)							X		Samples to be obtained on C1D15, C3D1, C6D1, and follow-up.

(X) = Parentheses indicate that the particular test is situational at that time point, as specified in the respective notes.
AE = adverse event; ADA = anti-drug antibody; BSA = body surface area; CR = complete response; CxDx = cycle X day X; D = daratumumab; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; FCBP = female patients of childbearing potential; FISH = fluorescence in-situ hybridization; HBV = hepatitis B virus; IAT = indirect antiglobulin test; K = carfilzomib; LTFU = long-term follow-up; LVEF = left ventricular ejection fraction; MRD = minimal residual disease; PD = progressive disease; [redacted] PFT = pulmonary function test; PK = pharmacokinetics; QTc = corrected QT (interval); SAE = serious adverse event.
[a] Follow-up occurs: 30 days (+ 3) after the last administration of all study drug(s).

Table 12. Schedule of Disease Assessments

Assessment	Screening	Every 28 Calendar Days[a] (Starting From C1D1)	If Clinically Indicated	To Confirm PD	Notes
Disease Assessments					
Bone marrow sample for FISH and MRD[-]:	X	(X)			See Section 7.3.21.2 for additional timing details regarding FISH and MRD[-] assessments. **Samples for MRD analysis are not required** [redacted]
Bone lesion assessment	X		X	X	Within 30 days prior to randomization; will be repeated if worsening clinical symptoms suggest PD, or as clinically indicated.
Plasmacytoma evaluation	(X)	(X)	X	X	Will be done at screening only if clinically suspected. Screening evaluation may be done within 30 days prior to randomization, if performed as a part of standard of care. Assessment will be performed locally every 28 days (for physical exam) or every 12 weeks (for radiological exam).
SPEP/UPEP/immunofixation	X	X			Screening values may be used if within 14 days prior to C1D1. Post C1D1, UPEP and urine immunofixation will be measured every disease assessment.
SFLC	X	X			

(X) = Parentheses indicate that the particular test is situational at that time point, as specified in the respective notes.
CxDx = Cycle X day X; **DCO = data cutoff;** FISH = fluorescence in-situ hybridization; MRD = minimal residual disease; **OS = overall survival;** PD = progressive disease; PR = partial response; SFLC = serum free light chain; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.
[a] [redacted], **d**isease assessment should be performed every 28 ± 7 days until PD regardless of cycle duration including dose delays. Subjects who discontinue treatment prior to PD, but remain on study are required to complete the following assessments every 28 ± 7 days until PD. [redacted].

Table 13. 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 14. 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 11 and Table 12). 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, 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 11 and Table 12). 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

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**oratory** 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 11 and Table 12). 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)
- ECG
- Vital signs
- ECHO
- PFTs
- Laboratory assessments: hematology, serum chemistries, pregnancy test (FCBP), HBV serologies and HBV DNA testing (see Section 6.7.1)
- Disease assessments (every 28 ± 7 days): SPEP/UPEP/IFE, SFLC
- MRD assessments (see Section 7.3.21.2 for time points): bone marrow aspirate

- Disease assessments (to confirm PD or as clinically indicated): plasmacytoma evaluation, bone lesion assessment
- Additional assessments: carfilzomib PK
- Additional assessments (arm 1 only): daratumumab PK, anti-daratumumab antibodies
- Optional assessments (additional consent must be obtained): carfilzomib PDn
- Optional assessments (additional consent must be obtained): pharmacogenetics samples (saliva sample and/or bone marrow aspirate)
- Optional assessments (additional consent must be obtained): biomarker samples (plasma and serum)

7.2.4 Follow-up Visits

The following procedures will be completed during the follow-up visit (30 days [+ 3] after last dose of all study drug(s) as listed in the Schedule of Assessments (Table 11). Details of these procedures can be found in Section 7.3.

- Adverse event/serious adverse event reporting
- Concomitant medications
- Physical examination as per standard of care
- ECOG PS
- Vital signs
- Laboratory assessments: hematology, chemistry**,** and **HBV DNA testing**
- **Subjects with a known history of HBV infection or who test positive for HBV serologies may require additional testing (see Sections 6.7.1 and 7.3.15)**
- Subsequent antimyeloma therapy
- Optional assessments (consent must be obtained): pharmacogenetics sample (bone marrow aspirate) and biomarker assessment (plasma and serum)

[redacted], subjects who discontinue treatment prior to PD, but remain on study are required to complete the following assessments every 28 ± 7 days until PD as listed in Table 12 (these visits may overlap with follow-up visits that are scheduled based on last dose of all study drug[s]):

- Disease assessments: SPEP/UPEP/IFE, SFLC (analyzed by central laboratory)

[redacted]

7.2.5 Long-term Follow-up

Survival information and information on subsequent antimyeloma therapies will be collected during LTFU as listed in the Schedule of Assessments (Table 11) via a phone

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

Arm 1 (KdD) **subjects with evidence of positive HBV serology or** with a known **medical** history of HBV infection **will be monitored for clinical signs and** local HBV DNA **testing for a maximum of** 6 months following the last dose of daratumumab (see Section 7.3.15).

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) x 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 11).

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.

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 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, [redacted] 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.

7.3.14 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, [redacted] or the study is closed, whichever is earliest.

7.3.15 Laboratory Assessments

Laboratory tests including hematology and serum chemistries during scheduled visits will be performed at a central laboratory [redacted], **and at the local laboratory thereafter. In the absence of central laboratory values, all**

local laboratory values must be recorded in the eCRF. 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**oratory** 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.

Subjects who do not have a prior medical history of hepatitis B or who have not had testing conducted within the previous 12 weeks, will be tested locally for HBsAg, anti-HBs, and anti-HBc at their next visit. In addition, subjects with a clinical history of hepatitis B infection or who test positive for 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 (± 2 weeks) or more frequently if clinically indicated through follow-up visit 1. Subjects in arm1 (KdD) will continue to be monitored and tested for 6 months following the last dose of daratumumab.

Table 15 below outlines the specific analytes that will be assessed during the study.

Table 15. Laboratory Analyte Listing

Central/Local Laboratory: Chemistry[a]	**Central/Local Laboratory: Hematology**[a]	**Central Laboratory: Disease Assessments**[b]	**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 [redacted] 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)[c] HBV DNA testing[d]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; **DCO = data cutoff**; 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; **OS = overall survival;** 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] **Laboratory tests (including hematology and serum chemistries) will be performed at a central laboratory [redacted], laboratory tests will be performed at a local laboratory.**

[b] **Disease assessments will be performed at the central laboratory [redacted]**

[c] Hepatitis B serology testing is only required for subjects who do not have a **known** medical history of HBV or who have not had testing conducted within the previous 12 weeks.

[d] Serial testing for HBV DNA is only required for subjects who have a **known** medical history of HBV or who test positive for HBV serologies.

7.3.16 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. More frequent pregnancy tests may be conducted if required per local regulations.

7.3.17 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

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.

7.3.18 Pharmacokinetic Samples

[redacted]

7.3.20 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 according to Table 11. 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.

7.3.21 Tumor Response and Multiple Myeloma Disease Assessment

[redacted], **d**isease assessments will be based on central laboratory data obtained every 28 ± 7 days until confirmed PD (Section 7.3.21.5) 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 [redacted]. **Locally obtained disease assessment values will not be recorded in the eCRF.**

Disease response and progression assessments include: SPEP, UPEP, SFLC, serum and urine immunofixation (SIFE, UIFE, respectively) (Section 7.3.21.1), bone marrow sample evaluation (Section 7.3.21.2), serum calcium, bone lesion evaluation (Section 7.3.21.3), and plasmacytoma evaluation (Section 7.3.21.4).

7.3.21.1 SPEP, UPEP, SFLC, SIFE, and UIFE

[redacted], **s**erum 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-4 hour urine samples will be obtained for UPEP and UIFE. Results for SPEP, UPEP, or SFLC must be available at screening and before randomization. Serum

protein electrophoresis (SPEP), UPEP, and SFLC will be repeated on cycle 1 day 1 (unless screening values are within 14 days of cycle 1 day 1). Post cycle 1 day 1, UPEP and UIFE will be measured every disease assessment as well as SPEP. [redacted].

Subjects will be evaluated for disease response and progression according to the IMWG response criteria in Appendix M. Disease status categories include CR, VGPR, PR, SD, and PD. [redacted], investigator evaluation of disease response is to be based solely on the central laboratory results, not on local laboratory results for laboratory-based parameters.

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

- All response categories require 2 consecutive assessments made at any time before initiation of any new therapy
- All categories also require no known evidence of progression including new bone lesions if radiographic studies were performed
- Confirmation of CR or sCR requires bone marrow assessment (aspirate or biopsy)
- Extramedullary plasmacytoma evaluation (if present at screening)

For subjects with light chain multiple myeloma, both serum and urine IFE test and SFLC assay will be performed every disease assessment.

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

A baseline bone marrow sample (aspirate slides and/or biopsy) will be collected prior to first dose and will be used to confirm the diagnosis and quantify the percent (%) of myeloma cell involvement. Biopsy or aspirate slides obtained as standard of care may be used as baseline if taken within 45 days prior to randomization and are sent to the central laboratory for processing. The priority of bone marrow aspirate testing at screening (prior to dosing at cycle 1 day 1) is 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 aspirate will be obtained as clinically indicated to confirm a response of CR. 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 24 months (± 4 weeks) for all subjects that have reached a CR (at any time prior to the 24 month timepoint) and have not had 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 time prior to the 24 month timepoint 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. **Samples for MRD analysis are not required** [redacted].

7.3.21.3 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) 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.

7.3.21.4 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.

7.3.21.5 Progressive Disease Assessment

[redacted]**, p**rogressive 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**oratory** evaluations. Local laboratory evaluation will not be accepted. The assessments outlined in Appendix M are required for PD. **Subjects** 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). [redacted].

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 aspirates will be collected prior to first dose from each screened, consenting subject and at 12 months (± 2 weeks). The bone marrow aspirates will be processed and stored according to a protocol that is provided to the central lab**oratory**. The samples will be analyzed centrally by the NGS-based MRD assay. See Section 7.3.21.2 for details on priority of samples for bone marrow aspirate testing.

Whole blood will be collected from participating subjects at screening, cycle 1 day 15, cycle 3 day 1, cycle 6 day 1**, and at follow-up** to explore the relationship between

serum- and plasma-based biomarkers and subject response to treatment. Plasma collected at study start, cycle 13 day 1, **at follow-up,** and upon achievement of CR, will be used for isolation and analysis of circulating tumor DNA (ctDNA). ctDNA will be analyzed by DNA-sequencing for the determination of biomarkers, including but not limited to, disease progression, treatment resistance, and patient-specific DNA mutations associated with MRD. Serum collected at study start will be analyzed by enzyme-linked immunosorbent assay (ELISA) for the determination of biomarkers including, but not limited to, soluble CD38 (sCD38) protein.

7.5 Pharmacogenetic Studies

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of multiple myeloma and/or to identify subjects who may have positive or negative response to protocol-required therapies. Saliva samples (collected predose on cycle 1 day 1, specifically for this optional test) and bone marrow aspirates (collected predose on cycle 1 day 1 and the first follow-up visit, as part of required protocol assessments) are collected for this part of the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted.

Bone marrow aspirate collected will be subjected to $CD138^{+}$ enrichment to isolate malignant plasma cells and these malignant cells will then be used for both RNA- and DNA-sequencing to identify genomic alterations that may be associated with prognosis or prediction of drug response (see Section 7.3.21.2 for details on priority of samples for bone marrow aspirate testing). Saliva will be used to isolate genomic DNA (gDNA) for use in DNA sequencing, to assist in the identification of tumor-specific mutations in the bone marrow.

7.6 Sample Storage and Destruction

Any blood, biomarker, PK, or PDn samples collected according to the Schedule of Assessments (Table 11) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

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

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

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

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

appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.
See Section 11.3 for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product, device or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 11) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, as applicable. Subjects who have discontinued investigational product and/or protocol required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data. The investigator must document the level of follow-up that is agreed to by the subject.

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

8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

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

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.1.

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal From Treatment

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

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, pregnancy)
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)
- disease progression

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

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. **All adverse events of HBV reactivation for arm 1 subjects with evidence of positive HBV serology or known medical history of HBV infection are required to be reported through end of study.**

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 **end of study** 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 **awareness** 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 **(as defined in Section 9.2.1.2)** or after end of study. However, these serious adverse events **should** be reported to Amgen **(regardless of causality). Per local requirements, i**n 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 **awareness** of the event.

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

9.2.1.4 Method of Detecting Adverse Events and Serious Adverse Events

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

9.2.1.5 Regulatory Reporting Requirements for Serious Adverse Events

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

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

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

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

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

9.2.1.6 Safety Monitoring Plan

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

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 **awareness** of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification **Form** (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 **awareness** of event. Report a lactation case on the Lactation Notification **Form** (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)

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 $\geq$ 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.

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. [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. [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.

[redacted] It is based

on safety and survival follow-up as described in Section 3.5.2. It is not directly linked to sample size calculation based on the primary endpoint of PFS outlined in this section.

The sample size calculation was performed using East® software (Version 6.3 or above).

10.3 Planned Analyses

10.3.1 Data Monitoring Committee (DMC)

An independent DMC will be convened for this study and will act in an advisory capacity to the sponsor with respect to safeguarding the interests of study subjects, assessing [redacted] safety and efficacy data, monitoring the overall conduct of the study, and providing with recommendations relating to continuing, modifying, or stopping the study based on these findings (International Council for Harmonisation Good Clinical Practice [ICH GCP 5.5.2]). Details of the DMC will be described in the DMC Charter. The initial assessment from this committee will be planned after 30 subjects (approximately 20 for the experimental arm and 10 for the control arm) have been enrolled and have finished the first cycle of treatment to ensure safety of all arms. A provision will be made allowing an early follow-up DMC meeting to be decided at the time of the initial assessment. The DMC will meet approximately every 6 months **until the Primary Analysis is completed**.

10.3.2 Independent Review Committee (IRC)

The membership criteria and operational details of the IRC will be described in the IRC Charter. The primary responsibility of the IRC is the independent assessment of individual patient efficacy outcomes in accordance with the IMWG-URC. The IRC will centrally review the disease related tests and assessments (Section 7) to evaluate disease progressions and responses without the knowledge of randomization assignments. The IRC assessment will be used for the primary analysis of endpoints.

10.3.3 Primary Analysis

The timing for the primary analyses of PFS for arm 1 vs arm 2 will be event driven and will happen when approximately 188 PFS events are reached cumulatively in these 2 arms.

[redacted]

[redacted]

10.4 Planned Methods of Analysis

10.4.1 General Considerations

The efficacy analyses of PFS and key secondary endpoints will be conducted on the full analysis set. Treatment effects in efficacy endpoints will be evaluated and compared KdD vs Kd.

In principle, summary statistics including mean, standard deviation, median, first and third quartiles, will be provided for continuous variables. Frequency and percentage will be summarized by treatment arm for binary and categorical variables. Proportions and the corresponding 95% CI will be based on normal approximations and the treatment comparison will be based on Cochran-Mantel-Haenszel test. Exact tests will be considered for subgroup analyses when the cell size is considered small. Time to-event endpoints will be estimated using the Kaplan-Meier (K-M) method. Stratified log-rank test statistics and associated p-values will also be calculated. Hazard ratios will be estimated using stratified Cox proportional hazards models.

For PFS, response and disease progression will be determined by an IRC in a blinded manner. In addition, response and disease progression outcomes will be determined locally by investigators in an unblinded manner and centrally by the sponsor using a validated computer algorithm (Onyx Response Computer Algorithm, ORCA) in a blinded manner. The primary analysis of PFS will be based on IRC assessed outcomes; the timing will be event driven and will happen when approximately 188 PFS events are reached. The PFS outcomes assessed by the investigators as well as by ORCA will serve as supportive analyses of PFS.

The primary comparison of PFS will be tested using a log rank test stratified by the randomization stratification factors per IxRS at 1-sided significance level of 0.025. Testing of the key secondary endpoints will be hierarchal in the order of ORR, MRD[-]CR, and OS such that the overall Type I error rate is strongly controlled under 0.025 (1-sided). Progression free survival, ORR, and MRD[-]CR will be tested at the PFS primary analysis, and OS will be tested at [redacted] and [redacted] analyses according to sequential testing order.

The specific testing procedure for the primary and the key secondary endpoints is as follows:

- PFS (arm 1 vs arm 2) is tested at alpha level of 0.025 at the primary analysis
- If PFS is significant at the primary analysis, then ORR and MRD[-]CR are tested sequentially at alpha level of 0.025
- If PFS, ORR, and MRD[-]CR are all statistically significant, then OS will be tested multiple times with an overall alpha of 0.025. [redacted]

Further details of secondary endpoint testing will be described in the SAP.

10.4.2 Primary Efficacy Endpoint

The primary comparison for PFS between arm 1 and arm 2 will use the log-rank test stratified by the randomization stratification factors per IxRS. The HR (95% CI) will be estimated using a stratified Cox proportional hazards regression model as relative treatment effect. The distribution of PFS including median will be summarized descriptively using the K-M method for each treatment group.

The primary endpoint will be analyzed within each of the subgroups listed in Section 10.1.3. Specifically, to determine whether the treatment effect is consistent across subgroups including, but not limited to, various geographical regions (eg, North America, Europe, Asia, and other), the estimate of the hazard ratios (with 95% CI) by Cox proportional hazards regression model for PFS between the treatment groups will be provided. Additionally, a treatment-by-subgroup interaction test will be provided as appropriate.

10.4.3 Secondary Efficacy Endpoint(s)

If PFS is significant, the key secondary endpoints will be tested by sequential testing in the order of ORR, MRD[-]CR by NGS, and OS.

The analysis for ORR and MRD[-]CR will be done if the primary analysis of PFS reaches statistical significance.

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. [redacted]

[redacted]

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.

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.

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 the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

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

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

12.2 Study Documentation and Archive

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

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

Electronic CRF entries may be considered source data if the eCRF is the site of the original recording (ie, there is no other written or electronic record of data).

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

Elements to include:

- Subject files containing completed CRFs, ICFs, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

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

12.3 Study Monitoring and Data Collection

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

The Clinical Monitor is responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Monitor is to have access to subject medical records and other study-related records needed to verify the entries on the eCRFs.

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

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

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the CRFs must be maintained and readily available.

- Updates to eCRFs will be automatically documented through the software's "audit trail."
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this EDC study or the investigator applies an electronic signature in the EDC system if the study is set up to accept an electronic signature. This signature indicates that investigator inspected or reviewed the data on the eCRF, the data queries, and agrees with the content.

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 11), the investigator can search publically available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

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

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

12.6 Publication Policy

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

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3, and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 Compensation

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

If permitted under applicable regional laws or regulatory guidelines, study subjects may be reimbursed for reasonable travel costs and other expenses directly related to participation in this clinical trial.

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix B. Sample Electronic Serious Adverse Event Contingency Report Form

A Study # 20160275 Carfilzomib	**Electronic Serious Adverse Event Contingency Report Form** For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day Month Year

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

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 06 Congenital anomaly / birth defect; 08 Other medically important serious event

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

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

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A Study # 20160275 Carfilzomib	**Electronic Serious Adverse Event Contingency Report Form** For Restricted Use

								☐ Unavailable / Unknown

	Site Number	Subject ID Number	

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

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

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

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

Date (Day Month Year)	Test / Unit											
	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

A 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 C. Pregnancy and Lactation Notification Forms

AMGEN® Pregnancy Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20160275

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

AMGEN® Lactation Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20160275

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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Appendix D. ECOG Performance Status

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

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

Appendix E. Guidelines for Documenting Prior Treatment

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

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

Appendix F. 2013 ESH/ESC Office Blood Pressure Measurement

Table 5 Office blood pressure measurement

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

BP = blood pressure.

Appendix G. NHLBI Table of Asthma Severity

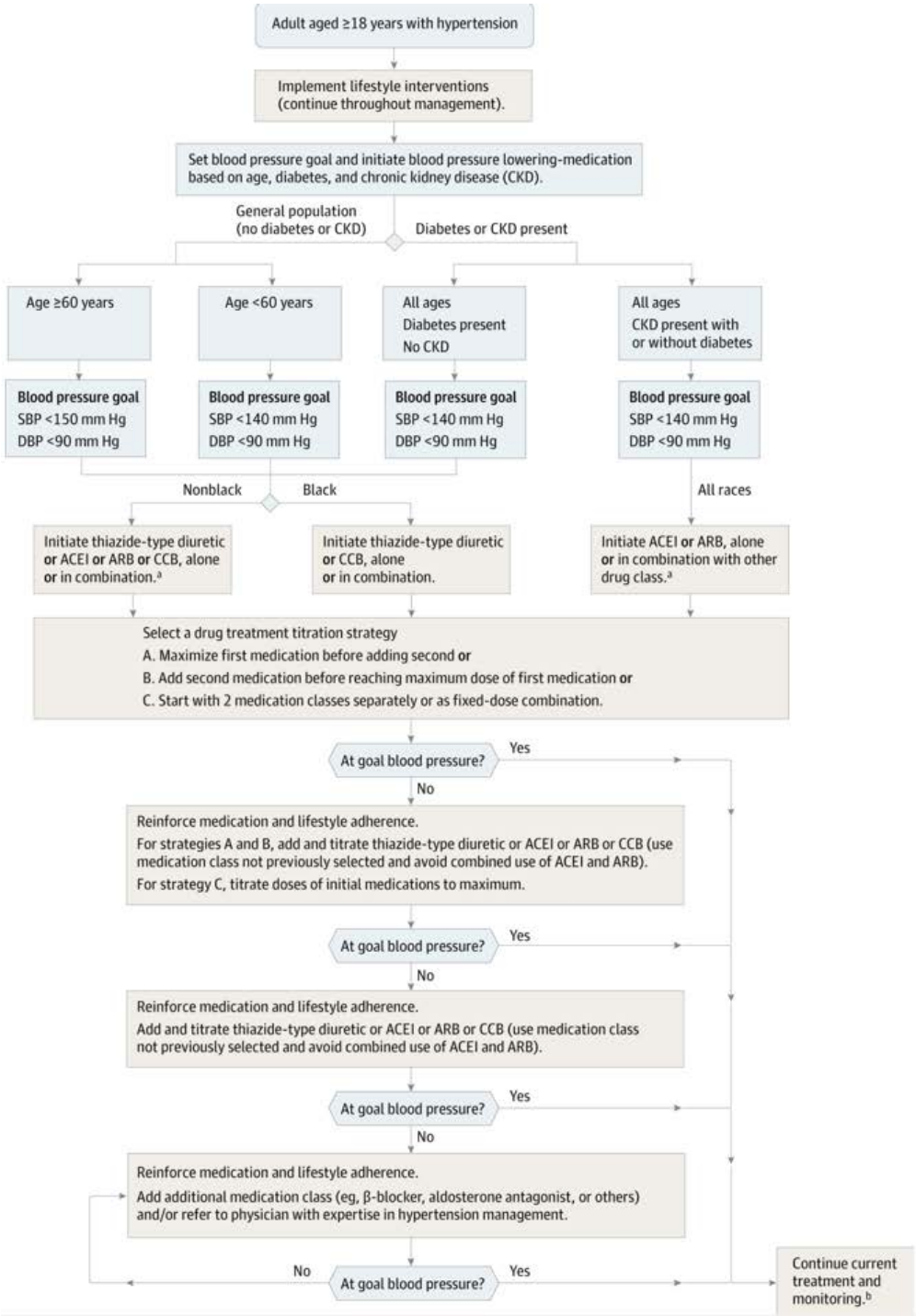
Components of Severity		Intermittent			Persistent								
					Mild			Moderate			Severe		
		Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years	Ages 0–4 years	Ages 5–11 years	Ages ≥12 years
Impairment	Symptoms	≤2 days/week			>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 bronchospam; 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.

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.

Appendix I. 2013 EHC/ESC Antihypertensive Guidelines for Elderly Blood Pressure Goal Recommendations

Recommendations	Class
A SBP goal of <140mmHg:	
a) Is recommended in patietns at low-moderate CV risk	I
b) Is recommended in patients with diabetes	I
c) Should be considered in patients with previous stroke or TIA	IIa
d) Should be considered in patients with coronary heart disease	IIa
e) Shoud be considered in patients with diabetic or non-diabetic chronic kidney disease	IIa
In elderly hypertensive <80 years old with SBP ≥160mmHg there is solid evidence to recommend reducing SBP to between 150-140 mmHg	I
In fit elderly <80 years old and SBP values <140 mmHg may be considered, whereas in the fragile elderly SBP goals should be adapted to individual tolerability	IIb
In >80 years old and initial SBP ≥ 160 mmHg, it is recommended to reduce SBP between 150 and 140 mmHg provided they are in good physical and mental conditions	I
Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes octogenarian	IIa
A DBP of <90 is always recommended, except in patients with diabetes in whom values <85mmHg are recommended. It should nevertheless be considered that DBP values between 80 and 85 mmHg are safe and well tolerated	I
All hypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonist may be preferred in isolated systolic hypertension	I

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): ____
Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

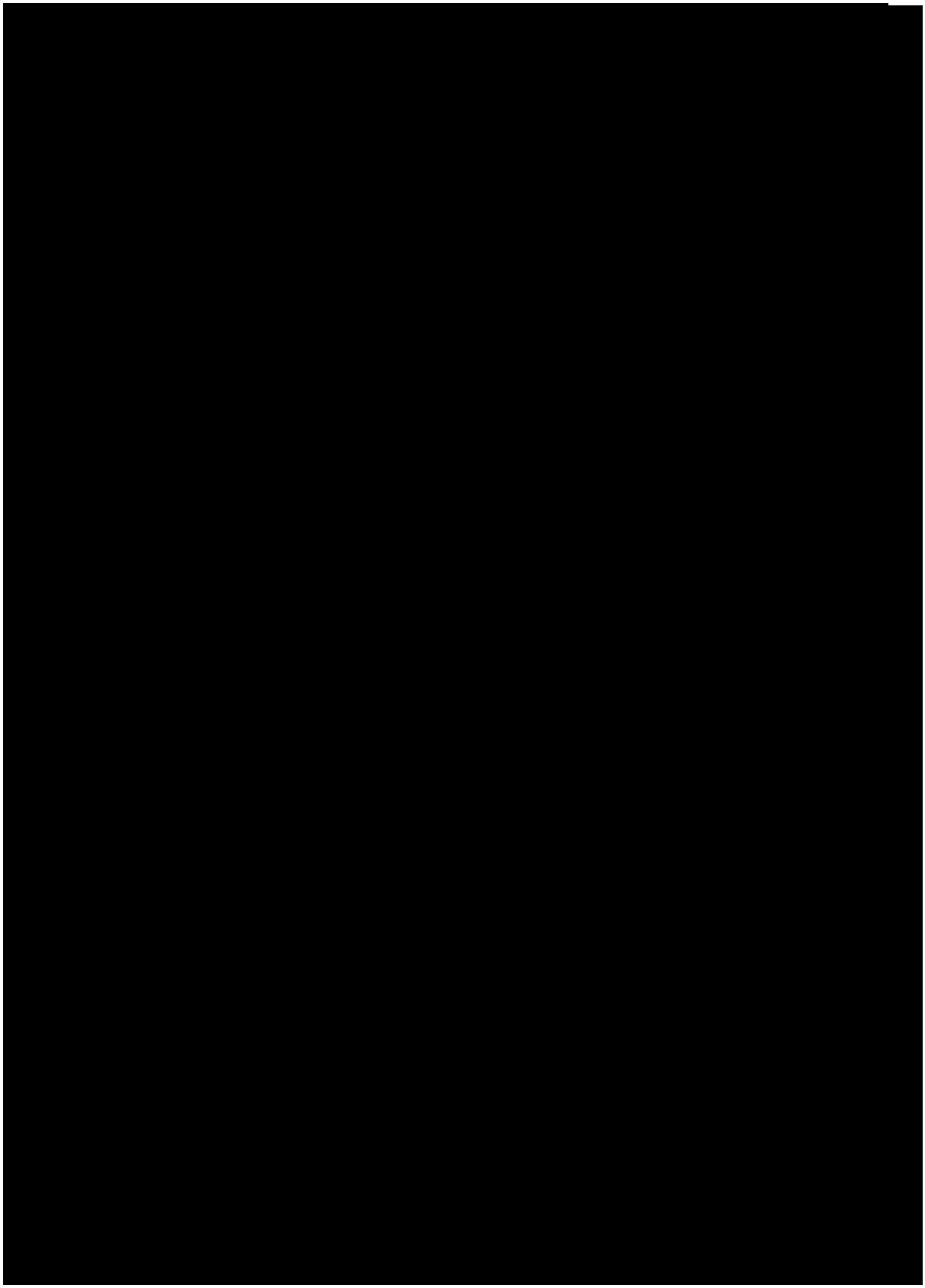
For the following questions please circle the number between 1 and 7 that best applies to you

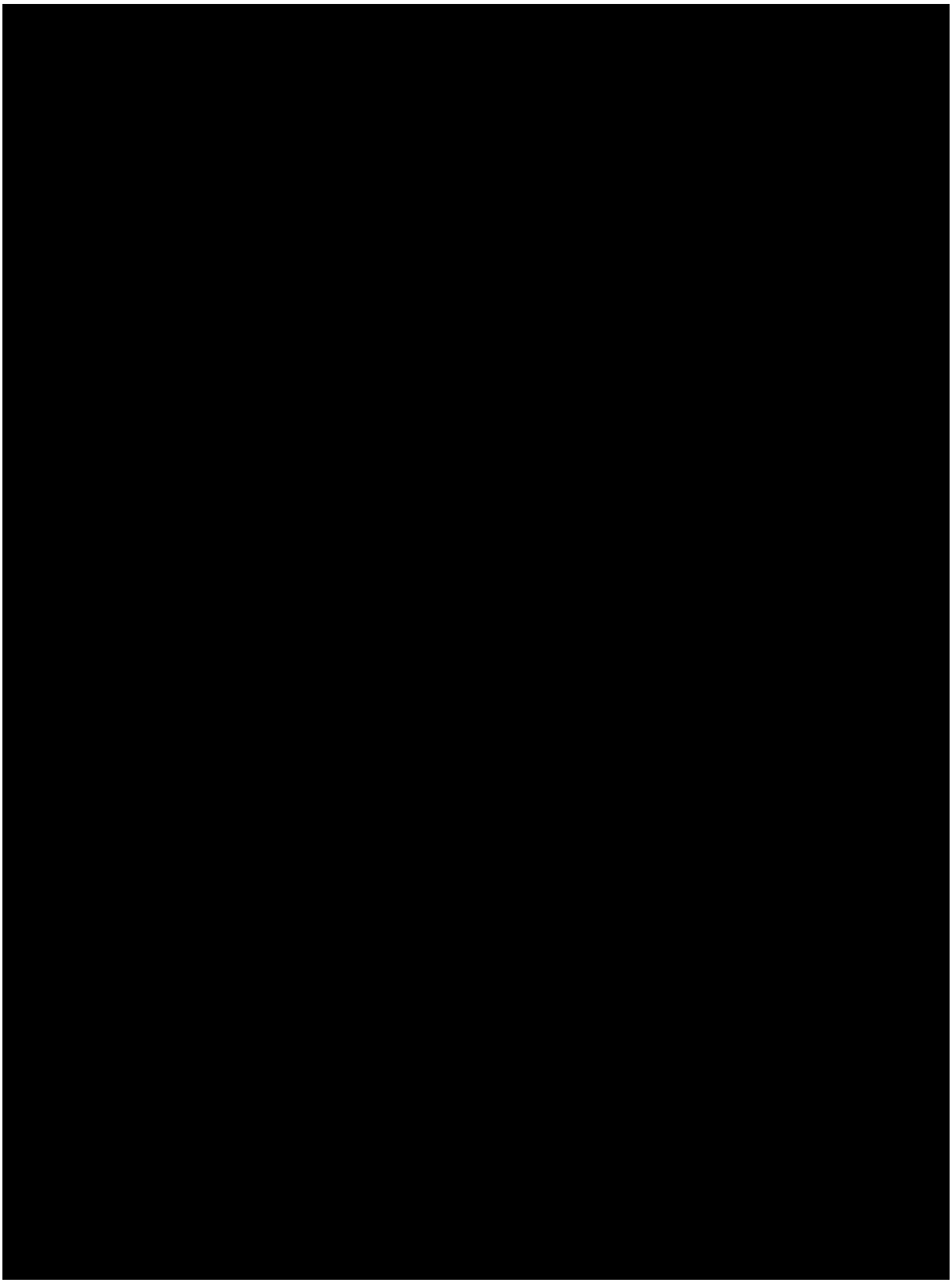
29. How would you rate your overall health during the past week?

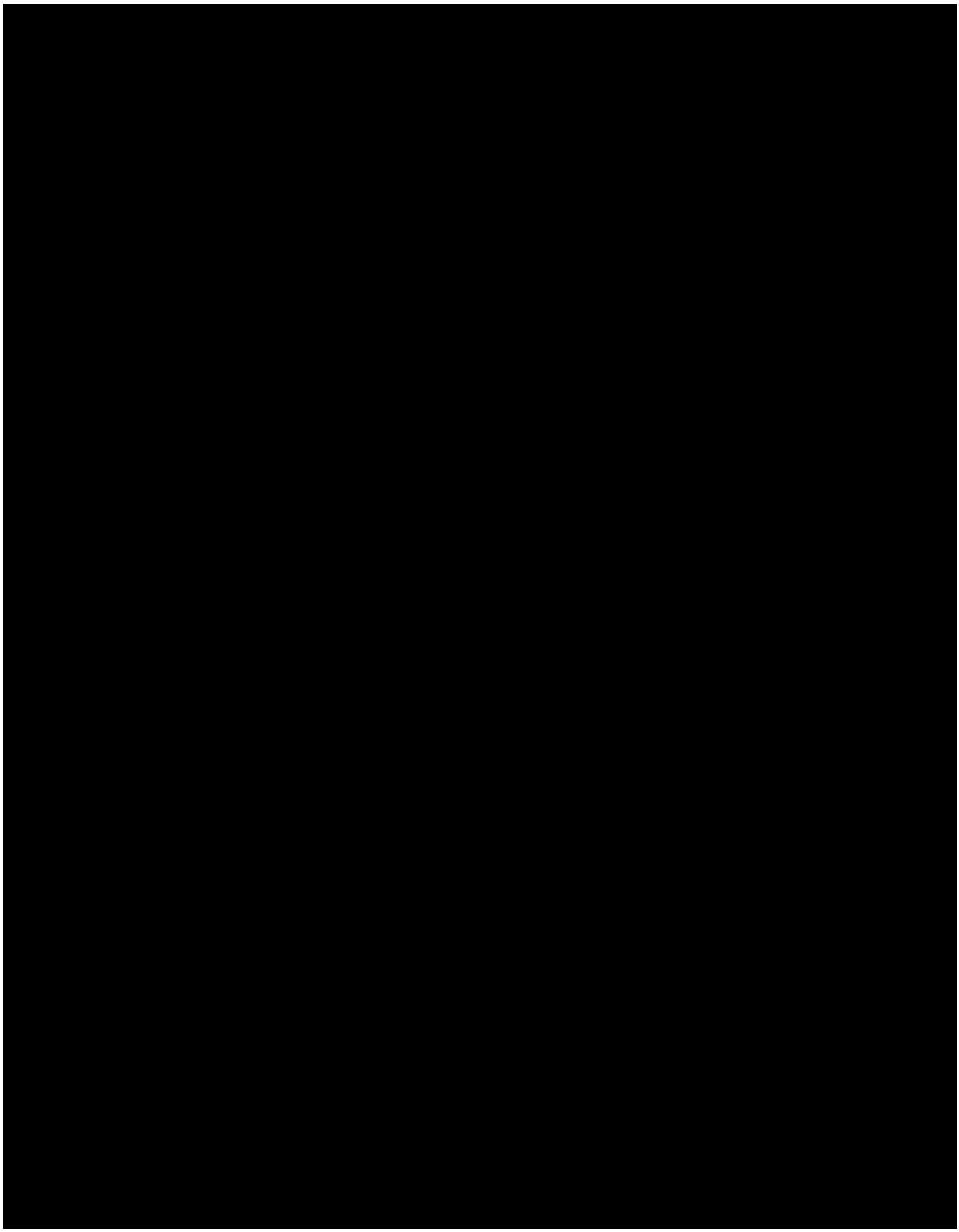
1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent







Appendix M. International Uniform Response Criteria for Multiple Myeloma

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

Response Subcategory	Multiple Myeloma Response Criteria
sCR	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow and • Normal SFLC ratio and • Absence of clonal plasma cells in bone marrow by immunohistochemistry or 2- to 4-color flow cytometry
CR	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow • In patients with measurable disease only by SFLC, normal SFLC ratio
VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-component with urine M-component < 100 mg per 24 hours • In patients with measurable disease only by SFLC, a decrease ≥ 90% in the difference between involved and uninvolved FLC levels
PR	• ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours (if both are measurable at baseline) • In patients with measurable disease only by SFLC, a decrease ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • In addition to the above criteria, if present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.
MR	• ≥ 25% but ≤ 49% reduction of serum M-protein and reduction in 24-hour urinary M-protein by 50% to 89%. In addition to the above listed criteria, if present a baseline a ≥ 50% reduction in the size (SPD) of soft tissue plasmacytoma is required
Stable Disease	• Not meeting criteria for CR, VGPR, PR, or PD

Page 1 of 2

Footnotes defined on the next page of the table.

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

Response Subcategory	Multiple Myeloma Response Criteria
PD	• Increase of 25% from lowest response value in 1 or more of the following: – Serum M-component (absolute increase must be ≥ 0.5 g/dL) and/or – Urine M-component (absolute increase must be ≥ 200 mg per 24 hours) and/or – Only in patients without measurable serum and urine M protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) – Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute percentage must be ≥ 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.75 mmol/L) attributed solely to the plasma cell proliferative disorder

Page 2 of 2

CR = complete response; FLC = free light chain; MR = minimal response; PD = progressive disease; PR = partial response; sCR = stringent complete response; SFLC = serum free light chain; SPD = maximal perpendicular diameter; VGPR = very good partial response.

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

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

If patients do not have measurable disease at baseline, they can only be assessed for at least a CR or progressive disease (PD), otherwise they will be NE.

Determination of PD while on study requires 2 consecutive assessments made at any time (no minimal interval is required, it can be done the same day; however, to confirm response or PD, 2 discrete samples are required) before classification of PD and/or the

institution of new therapy. Confirmative samples for PD after new therapy can be used. Serum M-component increases of ≥ 1 g/dL from nadir are sufficient to define progression if nadir M-component is ≥ 5 g/dL.

Plasmacytomas: A definite increase in the size is defined as a ≥ 50% increase from nadir as measured serially by the sum of the products of the maximal perpendicular diameter (SPD) of the measurable lesion or a ≥ 50% increase in the longest diameter of a previous lesion with ≥ 1 cm short axis. A plasmacytoma is considered measurable if the longest diameter is at least 1 cm and the product of the cross diameters is at least 1 cm^2. Plasmacytomas of lesser size will be considered non-measurable. The requirement for bi-directional measurements applies only to plasmacytomas. The plasmacytoma specifications for PD are based on the sponsor's interpretation of the IMWG-URC and practical considerations for study execution.

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

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

Appendix N. Corticosteroid Dose Equivalents

Equivalent Dose (mg)	Steroid
1.5	dexamethasone (long-acting)
8	methylprednisolone (intermediate-acting)
10	prednisone (intermediate-acting)
10	prednisolone (intermediate-acting)
40	hydrocortisone (short-acting)

Appendix O. Multiple Myeloma Frailty Score

Functional Scales for Calculating Frailty Score

Score	ADL Scale	IADL Scale
0 - 1	Bathing	Ability to use the phone
0 - 1	Dressing	Shopping
0 - 1	Toileting	Making meals
0 - 1	Transferring	Housekeeping
0 - 1	Continence	Laundry
0 - 1	Feeding	Transportation
0 - 1	--	Medication Independence
0 - 1	--	Financial Independence

ADL = activities of daily living; IADL = instrumental activities of daily living.
ADL and IADL are calculated by assigning either a 0 or 1 to each category on the basis of the ability to perform the task (0 indicates unable to perform and 1 indicates able to perform).
Source: Lonial and Nooka 2016; Palumbo et al, 2015.

Charlson Comorbidity Index

Score	Comorbidities
1	Myocardial infarction (history, not ECG changes only) Congestive heart failure Peripheral vascular disease (includes aortic aneurysm > 6 cm) Cardiovascular disease: CVA with mild or no residual or TIA Dementia Chronic pulmonary disease Connective tissue disease Peptic ulcer disease Mild liver disease (without portal hypertension, includes chronic hepatitis) Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia Moderate or severe renal disease Diabetes with end-organ damage (retinopathy, neuropathy, or brittle diabetes) Tumor without metastasis (exclude if > 5 year since diagnosis) Leukemia (acute or chronic) Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor AIDS (not just HIV-positive)

AIDS = acquired immunodeficiency syndrome; CVA = cardiovascular accident; ECG = electrocardiogram; HIV = human immunodeficiency virus; TIA = transient ischemic attack.
Source: Lonial and Nooka 2016; Palumbo et al, 2015.

Frailty Index Calculation

Variable	Score
Age, years	
< 75	0
75 - 80	1
> 80	2
ADL	
> 4	0
≤ 4	1
IADL	
> 5	0
≤ 5	1
CCI	
≤ 1	0
≥ 2	1
Category	
Fit	0
Intermediate Fitness	1
Frail	≥ 2

ADL = activities of daily living; CCI = Charlson Comorbidity Index; IADL = instrumental activities of daily living.
Source: Lonial and Nooka 2016; Palumbo et al, 2015.

Amendment 6

Protocol Title: A Randomized, Open-label, Phase 3 Study Comparing Carfilzomib, Dexamethasone, and Daratumumab to Carfilzomib and Dexamethasone for the Treatment of Patients With Relapsed or Refractory Multiple Myeloma

CANDOR

Study of Carfilzomib ANd Daratumumab fOr Relapsed myeloma

Amgen Protocol Number (carfilzomib) 20160275

EudraCT Number 2016-003554-33

NCT Number NCT03158688

Amendment Date: 17 March 2021

Rationale:

This protocol is being amended to include the following key changes:

- The maximum treatment duration for an individual study participant may be extended from 4 years to [redacted] to obtain additional long-term safety data per Food and Drug Administration Postmarketing Commitment.
- [redacted] as the primary endpoint for this study has been met. Disease assessments will be performed locally per standard of care.
- [redacted]. Only local laboratory testing will be utilized to monitor the safety of study participants to eliminate the logistic challenges at site including the risk of delayed lab kits as seen during the pandemic and reduce the volume of blood drawn from a study participant in excess of clinical need.
- Specified the timing and details regarding end of study to align with the safety reporting requirements for hepatitis B virus (HBV) reactivation in study participants receiving daratumumab.
- Adding new or clarifying recommended actions for carfilzomib dosage adjustments and/or treatment delays for nonhematologic toxicities, namely progressive multifocal leukoencephalopathy, renal dysfunction, tumor lysis syndrome, and thrombotic microangiopathy.

- Adding changes for daratumumab intravenous infusion rates based on available clinical data (Barr et al, 2017). Starting with cycle 2, daratumumab infusion may be shortened to a 90-minutes accelerated infusion for study participants who have received and well-tolerated the 2 prior doses of daratumumab standard infusion rates in cycle 1.
- Adding precautionary instructions that vaccination with live attenuated vaccines is not permitted at any time while the study participant is receiving study treatments due to the risk of being immunosuppressed.
- Removing bone marrow sample collection for minimal residual disease (MRD) assessments after the [redacted] (48 months after last subject enrollment [LSE]) OS DCO. After a minimum treatment duration of 3 years, it is expected that the number of subjects achieving a complete response (CR) is low. In addition, all subjects with MRD[-]CR at 12 months landmark have surpassed the MRD collection timepoint for the secondary endpoint persistence of MRD[-]CR. Therefore, omitting MRD assessments after [redacted] will not have an impact on previously reported MRD outcomes.
- To clarify that the Data Monitoring Committee (DMC) will not meet beyond the primary analysis.
- Removing Clinical Outcome Assessments based on the available data. At the primary analysis, a slightly higher health-related Quality of Life was associated with 20/56 mg/m^2 twice weekly carfilzomib, dexamethasone, and daratumumab (KdD), however it was maintained with both KdD and 20/56 mg/m^2 twice weekly carfilzomib and dexamethasone (Kd) treatments. Updated analysis at [redacted] Analysis did not show any new findings and it is expected that the difference will continue to be low.
- Removing the pregnancy test at the follow-up visit 30 (+3) days after the last dose of all study drugs for females of childbearing potential (FCBP).
- Removing reference to daratumumab interference testing aimed to mitigate the risk of underreporting treatment response of complete response. The key secondary endpoint ORR was met at the primary analysis. In addition, ~ 36 months from LSE, the overall incidence of patients achieving a best response of CR is considered low.
- Removing daratumumab pharmacokinetics (PK) and anti-Dara antibody (ADA) sample collection at Follow up Visit 2 (8 weeks after the last dose of daratumumab) including the instructions that subjects with evidence of positive anti-drug antibody levels need to be followed until they return to baseline. At present, daratumumab PK data was collected from approximately 2/3 of patients and analysis has shown that carfilzomib has no observable effect on daratumumab PK. In addition, no patient showed evidence of ADA positivity. Consistent with the overall low incidence of anti-Dara antibodies across studies (< 1%) the expected ADA rate will continue to be low and review of clinical data from antibody-positive subjects did not identify any new safety concerns or meaningful impact on efficacy.

- Removing the Follow up Visit 2 from the Schedule of Activities resulting from changes with regards to daratumumab PK and ADA sample collection. Adding medical device use, serious adverse event, and safety monitoring plan language per updates to the Amgen protocol template.
- Removing Investigational Product Instruction Manual (IPIM) language per updates to the Amgen protocol template.
- Additional administrative, typographical, and formatting changes were made throughout the protocol.

Amendment 5

Protocol Title: A Randomized, Open-label, Phase 3 Study Comparing Carfilzomib, Dexamethasone, and Daratumumab to Carfilzomib and Dexamethasone for the Treatment of Patients With Relapsed or Refractory Multiple Myeloma

Amgen Protocol Number (carfilzomib) 20160275

Amendment Date: 02 October 2019

Rationale:

The protocol is amended to:

- Expand hepatitis B testing (hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody) to include all subjects (KdD arm and Kd arm) that do not already have a prior medical history of hepatitis B or who have not had testing within the previous 12 weeks. In addition, guidance has been provided regarding HBV DNA testing and monitoring for subjects with positive hepatitis B serology or a prior history of HBV.
- Clarify that clinical outcome assessments are to be completed on Day 1 of each cycle prior to dosing.
- Remove bone marrow aspirate sample at 12 months after confirmed CR and clarified sampling criteria at 24 months. In addition, to clarify that all bone marrow samples, with the exception of the screening sample, are to only be bone marrow aspirate
- Add details regarding the disposition of the database at the time of analyses
- Clarify International Uniform Response Criteria for Multiple Myeloma

Amendment 4

Protocol Title: A Randomized, Open-label, Phase 3 Study Comparing Carfilzomib, Dexamethasone, and Daratumumab to Carfilzomib and Dexamethasone for the Treatment of Patients With Relapsed or Refractory Multiple Myeloma

Amgen Protocol Number (carfilzomib) 20160275

EudraCT number 2016-003554-33

NCT03158688

Amendment Date: 17 May 2019

Rationale:

The protocol is being amended to:

- Add [redacted] after the first subject enrolled in addition to the OS [redacted] analysis. Details were also added on the methods for the analyses and to clarify the timing for the OS [redacted] analysis.
- Update the language for the management of hepatitis B virus (HBV) reactivation, safety evaluations, and dose modification guidelines for daratumumab throughout the protocol.
- Update dexamethasone dosing for subjects who discontinue carfilzomib and for subjects with steroid intolerance.
- Update Table 4 to clarify recommended carfilzomib dose modifications for congestive heart failure.
- Extend the window for the 12-month and 24-month bone marrow aspirate collection from ± 2 weeks to "± 4 weeks" throughout the protocol. Details were also added to clarify bone marrow aspirate collection.
- Updates to the International Myeloma Working Group-Uniform Response Criteria in Appendix M.
- Add the collection of subsequent antimyeloma therapy in longterm follow-up.
- Update schedule of assessments to clarify clinical outcome assessment timing, add subsequent antimyeloma therapy collection, and to add details of HBV serology and HBV DNA testing.
- Clarify the timing of clinical outcome assessments through follow-up visit 1.
- Update Section 6.4 (Conditions Not Requiring Dose Reduction) to include hypogammaglobulinemia in conditions not requiring dose reduction.
- Update Section 6.5.5 (Bone Health Therapy) to include other bone health medications such as monoclonal antibodies as a recommended therapy for subjects with lytic destruction of bone or osteopenia.

- Update Section 6.5.7 (Other Permitted Therapies) to include intravenous immunoglobulins as a permitted therapy.
- Clarify the reporting requirements of adverse events to align with the case report form completion guidelines.
- Clarify that the pharmacist will calculate the required volume and number of vials needed for both carfilzomib and daratumumab.
- Update Table 14 to include magnesium and phosphorus under the listing for central laboratory chemistry and HBV serology and DNA testing under the listing for local laboratory other labs.
- Clarify that additional serum samples may be utilized to monitor for daratumumab interference with the IFE for subjects in arm 1.
- Remove the reference to self-evident corrections.
- Administration, typographical, and formatting changes were made throughout the protocol.

Amendment 3

Protocol Title: A Randomized, Open-label, Phase 3 Study Comparing Carfilzomib, Dexamethasone, and Daratumumab to Carfilzomib and Dexamethasone for the Treatment of Patients With Relapsed or Refractory Multiple Myeloma

Amgen Protocol Number Carfilzomib 20160275

EudraCT number 2016-003554-33

NCT03158688

Amendment Date: 19 April 2018

Rationale:

The protocol is being amended to:

- Reduce the window for the 12-month and 24-month bone marrow aspirate collection from ± 4 weeks / ± 1 month to "± 2 weeks" throughout the protocol
- Clarify the exclusion criteria that states subjects who have withdrawn consent from a previous Janssen daratumumab phase 3 study are allowed to participate in this study if they were in the control arm of the prior Janssen study and withdrew consent
- Clarify timing of pregnancy tests before first dose of study drug (rather than "randomization")
- Clarify that plasmapheresis is not permitted during the study. Details were added to describe next steps if plasmapheresis is required during the study treatment period.
- Clarify the carfilzomib prehydration requirements
- Clarify how to manage timing of cycles when dose delays occur
- Update Table 4 to clarify the recommended action for congestive heart failure
- Update Section 6.2.2.1.2 (Post-infusion Medications for Daratumumab) to align with current Janssen template language for daratumumab
- Update daratumumab management of infusion-related reactions to align with current United States prescribing information
- Clarify the criteria regarding thrombocytopenia for withholding daratumumab dose
- Update the dexamethasone dose reduction levels to add clarity for subjects > 75 years of age
- Clarify the dosage requirements/time span of corticosteroid use during the study
- Clarify the 28-day cycle for disease assessment collection
- Update references to "buccal swab" with "saliva sample"
- Update the schedule of assessments and related text to provide clarity on the screening evaluations of echocardiogram, pulmonary function tests, biomarkers, and plasmacytoma

- Clarify how the dosing of 20 mg dexamethasone can be split in arm 1
- Clarify that dexamethasone must be given as IV on cycle 1 days 1and 2 for subjects in arm 2
- Clarify that in cases of technical failure, central lab samples can be retested during screening and subject will not be considered a screen fail
- Update which laboratory assessments are performed in follow-up visits (to align with schedule of assessments)
- Clarify that subjects who do not complete clinical outcome assessments (COAs) on cycle 1 day 1, further COAs will not be collected
- Update the hematology parameter list to include “plasma cell percent” as a part of plasma cell count assessment
- Clarify that COA will be collected electronically (refer to as eCOA throughout the protocol)
- Administrative and editorial updates were made throughout the protocol

Amendment 2

Protocol Title: A Randomized, Open-label, Phase 3 Study Comparing Carfilzomib, Dexamethasone, and Daratumumab to Carfilzomib and Dexamethasone for the Treatment of Patients With Relapsed or Refractory Multiple Myeloma

CANDOR

study of Carfilzomib ANd Daratumumab fOr Relapsed myeloma

Amgen Protocol Number 20160275

EudraCT number 2016-003554-33

Amendment Date: 09 June 2017

Rationale:

This protocol is being amended to address concerns raised during European Union Voluntary Harmonisation Procedure interactions:

- Modify contraception language to address concerns regarding carfilzomib reducing efficacy of oral contraception
- Update sample size calculation with factors that contribute to study length (eg, estimated enrollment rates, drop-out rates)
- Modify primary and secondary endpoint analyses to include treatment-by subgroup analyses

Additionally, this protocol is also being amended to:

- Add additional serum collections in the Schedule of Assessments for optional biomarker samples
- Remove analysis of minimum residual disease by flow cytometry
- Add priority testing order for bone marrow samples
- Clarify the route of administration for dexamethasone (intravenous [IV] infusion only required on cycle 1 days 1 and 2, otherwise, can be IV or orally)
- Clarify timing of echocardiograms and pulmonary function tests after daratumumab infusion
- Clarify when confirmation of disease progression is needed
- Make administrative and editorial updates

Amendment 1

Protocol Title: A Randomized, Open-label, Phase 3 Study Comparing Carfilzomib, Dexamethasone, and Daratumumab to Carfilzomib and Dexamethasone for the Treatment of Patients With Relapsed or Refractory Multiple Myeloma

Amgen Protocol Number (carfilzomib) 20160275

EudraCT number 2016-003554-33

Amendment Date: 15 February 2017

Rationale:

This protocol is being amended to:

- Include safety objectives and endpoints as additional secondary objectives and endpoints
- Clarify that the evaluation of CR (for key secondary endpoint) will be based on IRC assessment
- Clarify that the original International Staging System (ISS) will be used in this study to stratify subject (as opposed to the revised ISS)
- [redacted].
- Update and clarify the International Uniform Response Criteria for Multiple Myeloma
- Update and clarify language in subject eligibility criteria based on regulatory agency and steering committee feedback
- Add additional exclusion criteria in order to maintain consistency with dose modification table and to clarify the minimal requirements for subjects that have undergone an allogeneic transplant
- Update study schema with a footnote regarding subjects with baseline chronic hepatic impairment
- Clarify the actual expected dose for subjects that have baseline chronic (mild, moderate) hepatic impairment
- Include requirements for prehydration for subjects treated with carfilzomib
- Update language regarding dosage adjustments, delays, rules for withholding or restarting, or permanent discontinuation of carfilzomib to reflect the range of management options available to investigators in case of toxicity
- Update language to allow for possible re-escalation of carfilzomib dose under certain conditions

- Update treatment guidelines for nonhematologic toxicities:
  - Add guidelines for chronic dialysis base on results from Study CFZ001
  - Clarify the parameters for holding carfilzomib during the treatment of an infection
  - Add guidance to investigate cause of dyspnea
  - Add guidance for lower grade hypertension
  - Language reworded for clarity
- Clarify timing of pulmonary function tests in relation to daratumumab infusion
- Remove total protein from laboratory analyte table as this is duplicated in the required serum protein electrophoresis needed for disease assessment
- Add DLCO assessment to allow for identification of diffusion abnormalities and in some cases to support the diagnosis of other lung diseases such as pulmonary hypertension
- Add language regarding the use of local laboratory results to be applied to screening requirements in cases where central laboratory is unable to provide these results
- Remove magnetic resonance imaging (MRI) from bone lesion assessment as X-ray, CT, or PET-CT are more appropriate in the monitoring of these lesions
- Update list of countries participating in global study
- Generally clarify language throughout the protocol for better readability
- Address typographical, grammatical, and formatting issues throughout the protocol