CLINICAL STUDY PROTOCOL

Protocol Title:	Phase 1b Study of Carfilzomib Administered Once Weekly in Combination With Lenalidomide and Dexamethasone in Subjects With Multiple Myeloma
Protocol Number:	CFZ013
Name of Investigational Product:	Kyprolis® (Carfilzomib for Injection [carfilzomib])
IND Number:	IND 71,057
EudraCT Number:	
Sponsor:	Onyx Therapeutics, Inc. One Amgen Center Drive Thousand Oaks, CA 91320
Study Medical Monitor:	[redacted], MD, PhD One Amgen Center Drive MS 38-2-A Thousand Oaks, CA 91320 [redacted]
Principal Investigator:	[redacted], MD, PhD John Theurer Cancer Center at Hackensack University Medical Center 92 Second Street Hackensack, NJ 07601 [redacted]
Date of Protocol:	26 August 2014
Amendment 1:	02 March 2016
Amendment 2:	14 October 2016
Amendment 3:	**13 December 2016**
Confidentiality Statement:	This material is the property of Onyx Therapeutics, Inc., a wholly owned subsidiary of Onyx Pharmaceuticals, Inc., an Amgen Inc. subsidiary. The material is highly confidential and is to be used only in connection with matters authorized by a senior representative of Onyx Therapeutics, Inc., and no part of it is to be disclosed to a third party without the express prior written permission of Onyx Therapeutics, Inc.
Compliance Statement:	This study will be conducted in accordance with Protocol CFZ013, the relevant Onyx Therapeutics, Inc., an Amgen Inc. subsidiary, policies and procedures, the International Conference on Harmonisation (ICH), Guideline for Good Clinical Practice (GCP), and the applicable country and regional (local) regulatory requirements.

PROTOCOL ACCEPTANCE PAGE

Issue/Date: CFZ013 Amendment **3**/**13 December** 2016

I have read this protocol for Study CFZ013 entitled:

Phase 1b Study of Carfilzomib Administered Once Weekly in Combination With Lenalidomide and Dexamethasone in Subjects With Multiple Myeloma

As investigator, I understand and agree to conduct this study as outlined herein.

Investigator Name (print)

Investigator Signature

Date

Signature on this page assures the sponsor that, to the best of the investigator's knowledge, the affiliated Institutional Review Board (IRB)/Independent Ethics Committee (IEC) operates in accordance with the governing regulations, and that the investigator understands, and agrees to abide by, all governing regulatory obligations and the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) and country and regional (local) requirements while conducting this clinical investigation. Once signed, the original of this form should be detached from the protocol and returned to Onyx Therapeutics, Inc. or its designee (please retain a copy for your files).

1 SYNOPSIS

Name of sponsor/company:	Onyx Therapeutics, Inc.
Name of product:	Carfilzomib for Injection
Title of study and protocol number and phase:	CFZ013: Phase 1b study of carfilzomib administered once weekly in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma
Study objective(s):	Primary Objective • To evaluate the safety and tolerability of a once-weekly carfilzomib, lenalidomide, and dexamethasone (KRd) regimen in relapsed and refractory multiple myeloma (RRMM) and newly diagnosed multiple myeloma (NDMM) subjects Secondary Objectives • To evaluate the pharmacokinetics (PK) of carfilzomib when administered once weekly in a KRd regimen in RRMM and NDMM subjects • To evaluate the clinical activity (efficacy) of a once-weekly KRd regimen in RRMM and NDMM subjects Exploratory Objectives • To explore the genomic and transcriptional biomarkers that might predict response and resistance to a once-weekly KRd regimen • To characterize the pharmacodynamics (PDn) of proteasome inhibition with a once-weekly KRd regimen in RRMM and NDMM subjects • To assess minimal residual disease (MRD) status with a once-weekly KRd regimen in RRMM and NDMM subjects • To assess subject convenience and satisfaction with a once-weekly KRd regimen using subject questionnaire in RRMM and NDMM subjects

Study design:	This is an open-label, multicenter, Phase 1b, dose-finding study of carfilzomib administered once weekly in combination with lenalidomide and dexamethasone (KRd). Once-weekly carfilzomib in a KRd regimen will be evaluated in RRMM and NDMM subjects. There will be 2 parts in the study: Dose Evaluation and Dose Expansion. Prior to protocol amendment 2: Two dose levels of once-weekly carfilzomib in a KRd regimen (Cohort 1 and Cohort 2) will be evaluated during the Dose-evaluation Component in RRMM subjects; a third optional KRd regimen (with a reduced dose level of lenalidomide) may also be evaluated (Cohort 3). Approximately 8 dose-limiting toxicity (DLT) evaluable RRMM subjects will be enrolled into each opened Dose-evaluation cohort. The second part is the Dose-expansion Component during which approximately 60 subjects (30 RRMM and 30 NDMM subjects) will receive the KRd regimen selected in the Dose-evaluation Component. Per protocol amendment 2: NDMM subjects will be enrolled into an additional Dose-evaluation Cohort 4. Approximately 8 DLT-evaluable subjects will be treated with carfilzomib given once weekly with 2-step-up dosing in a KRd regimen. The Cohort Safety Review Committee (CSRC) may then elect to open enrollment to a Dose-expansion Component for an additional 30 NDMM subjects. Subjects may continue to receive study treatment for up to 18 cycles. Newly diagnosed multiple myeloma subjects may interrupt therapy after cycle 4 for autologous stem cell transplant (ASCT). All subjects will be evaluated for safety at an End of Treatment (EOT) visit, 28 ± 7 days after the last study treatment, and with an EOT echocardiogram (ECHO), done within 28 ± 7 days after the last study treatment. Following the EOT, subjects who have not had disease progression or allogeneic stem cell transplant will enter Active Follow-up.
Number of investigational sites:	Approximately 30 sites
Planned number of subjects:	Approximately 114 subjects in total. Prior to protocol amendment 2, 56 RRMM and 20 NDMM subjects were enrolled in the study. Twenty-two RRMM subjects were enrolled into the RRMM Dose-evaluation Component; 34 RRMM subjects were enrolled into the RRMM Dose-expansion Component of the study. Enrollment of RRMM subjects is completed. Per protocol amendment 2, approximately 38 NDMM subjects will be enrolled in the study: approximately 8 subjects will be enrolled into the NDMM Dose-evaluation Component, and approximately 30 subjects will be enrolled in the second NDMM Dose-expansion Component of the study. NDMM subjects enrolled prior to protocol amendment 2 who are DLT-evaluable at Cohort 4 dosing will be considered Cohort 4 subjects.
Sample size justification:	Sample sizes are determined to provide preliminary information on safety, clinical activity, PDn, and PK. With respect to safety, 38 subjects with relapsed disease in the dose cohort selected to move into the expansion component and 38 NDMM subjects will allow an approximately 86% probability to detect an occurrence of an adverse event (AE) with 5% incidence rate.
Study population:	Subjects with relapsed multiple myeloma who have received 1 to 3 prior lines of therapy and subjects with newly diagnosed, transplant-eligible or transplant-ineligible multiple myeloma.

Treatment regimen(s):	Dose-evaluation Component Carfilzomib combination therapy will be given for up to 18 cycles. The combination regimens evaluated in the Dose-evaluation Component include: *Cohort 1 (RRMM):* KRd = carfilzomib 20/56 mg/m^2/ lenalidomide 25 mg/ dexamethasone 40 mg Carfilzomib dosing: 20 mg/m^2 Day 1 of Cycle 1; 56 mg/m^2 Days 8 and 15 of Cycle 1; Days 1, 8, and 15 of Cycle 2 and beyond *Cohort 2 (RRMM):* KRd = carfilzomib 20/70 mg/m^2/ lenalidomide 25 mg/ dexamethasone 40 mg Carfilzomib dosing: 20 mg/m^2 Day 1 of Cycle 1; 70 mg/m^2 Days 8 and 15 of Cycle 1; Days 1, 8, and 15 of Cycle 2 and beyond *Optional Cohort 3 (RRMM):* KRd = carfilzomib 20/70 mg/m^2/ lenalidomide 10 mg/ dexamethasone 40 mg Carfilzomib dosing: 20 mg/m^2 Day 1 of Cycle 1; 70 mg/m^2 Days 8 and 15 of Cycle 1; Days 1, 8, and 15 of Cycle 2 and beyond *Cohort 4 (NDMM):* 2-step-up KRd = carfilzomib 20/56/56/70 mg/m^2/ lenalidomide 25 mg/ dexamethasone 40 mg. Carfilzomib dosing: 20 mg/m^2 Day 1 of Cycle 1; 56 mg/m^2 on Days 8 and 15 of Cycle 1; 70 mg/m^2 on Days 1, 8, and 15 of Cycle 2 and beyond KRd will be given in 28-day cycles: • Carfilzomib will be administered once weekly intravenously (IV) on Days 1, 8, and 15 • Lenalidomide will be administered once daily by mouth on Days 1–21. • Dexamethasone will be administered once daily by mouth or IV on Days 1, 8, and 15. Dexamethasone will also be given on Day 22 of Cycles 1–8. Dose-expansion Component If a regimen evaluated during the Dose-evaluation Component is safe and tolerable, approximately 30 additional subjects may be enrolled for treatment in **a** Dose-expansion **arm**.
Inclusion criteria:	1. Age ≥ 18 years 2. Able to provide written informed consent in accordance with federal, local, and institutional guidelines 3. Newly diagnosed or relapsed multiple myeloma a. For subjects with relapsed multiple myeloma: i. 1 to 3 prior lines of therapy for multiple myeloma (induction therapy followed by stem cell transplant and consolidation/maintenance therapy will be considered as one line of therapy), and ii. Documented response of at least partial response (PR) to 1 line of prior therapy. Investigator assessment is acceptable as PR documentation. b. For subjects with newly diagnosed, transplant-eligible or transplant-ineligible multiple myeloma: i. Symptomatic multiple myeloma (per International Myeloma Working Group [IMWG] diagnostic criteria) and ii. No prior treatment for multiple myeloma

Inclusion criteria (cont'd):	4. Measurable disease with at least 1 of the following assessed within 21 days prior to Cycle 1 Day 1: a. Serum M-protein ≥ 0.5 g/dL, b. Urine M-protein ≥ 200 mg/24 hour, c. In subjects without detectable serum or urine M-protein, serum free light chain (SFLC) > 100 mg/L (involved light chain) and an abnormal serum kappa lambda ratio d. For immunoglobulin (Ig) A subjects whose disease can only be reliably measured by serum quantitative immunoglobulin (qIgA), a qIgA level of ≥ 750 mg/dL (0.75 g/dL) 5. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 2 6. Left ventricular ejection fraction (LVEF) ≥ 40% 8. Absolute neutrophil count (ANC) ≥ 1000/mm^3 within 21 days prior to Cycle 1 Day 1 with (1) no nonpegylated growth factor support for ≥ 7 days and (2) no pegylated growth factor support for ≥ 14 days 9. Hemoglobin ≥ 8.0 g/dL within 21 days prior to Cycle 1 Day 1. Use of erythropoietic stimulating factors and red blood cell (RBC) transfusions per institutional guidelines is allowed 10. Platelet count ≥ 50,000/mm^3 (≥ 30,000/mm^3 if myeloma involvement in the bone marrow is > 50%) within 21 days prior to Cycle 1 Day 1 with no platelet transfusions for ≥ 7 days 11. Calculated or measured creatinine clearance (CrCl) of ≥ 50 mL/min within 21 days prior to Cycle 1 Day 1. Calculation must be based on standard formula such as the Cockcroft and Gault. 12. Females of childbearing potential (FCBP) must have a negative serum pregnancy test within the 10 to 14 days prior to study drug administration and a negative urine or serum pregnancy test within the 24 hours prior to the first study drug administration 13. FCBP and male subjects who are sexually active with a FCBP must agree to use 2 highly effective methods of contraception during the study. FCBP subjects are required to continue use of 2 highly effective methods of contraception for 30 days following discontinuation of study drugs. Vasectomized male subjects who have received medical confirmation of surgical success are not required to use additional methods of contraception. Otherwise, male subjects with a FCBP partner must agree to use 2 highly effective methods of contraception during study and for 90 days following discontinuation of study drugs **14.** Male subjects must agree to not donate sperm while taking study drugs and 90 days after the last dose of study drugs **15. Normal hepatic function within 21 days prior to Cycle 1 Day 1:** **a. Bilirubin ≤ the upper limit of normal (ULN)** **b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ the ULN**
Exclusion criteria:	1. Waldenström macroglobulinemia 2. For newly diagnosed multiple myeloma: multiple myeloma of IgM subtype 3. For relapsed disease: a. If treated with a lenalidomide and dexamethasone-containing combination, progression during the first 3 months after initiating treatment b. Any progression during treatment if the lenalidomide and dexamethasone-containing regimen was the most recent line of therapy c. Any prior treatment with carfilzomib

Exclusion criteria (cont'd):	4. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) 5. Plasma cell leukemia (> 2.0×10^9/L circulating plasma cells by standard differential) 6. Myelodysplastic syndrome 7. Second malignancy within the past 5 years except: a. Adequately treated basal cell or squamous cell skin cancer, or b. Carcinoma in situ of the cervix, or c. Prostate cancer < Gleason score 6 with undetectable prostate-specific antigen (PSA) over 12 months, or d. Ductal breast carcinoma in situ with full surgical resection (ie, negative margins), or e. Treated medullary or papillary thyroid cancer, or f. Similar condition with an expectation of > 95% five-year disease-free survival 8. Amyloidosis 9. Cytotoxic chemotherapy within 28 days prior to Cycle 1 Day 1 10. Immunotherapy within 21 days prior to Cycle 1 Day 1 11. Glucocorticoid therapy within 14 days prior to Cycle 1 Day 1 that exceeds a cumulative dose of 160 mg of dexamethasone 12. Radiation therapy: a. Focal therapy within 7 days prior to Cycle 1 Day 1 b. Extended field therapy within 21 days prior to Cycle 1 Day 1 13. Prior treatment with carfilzomib or oprozomib 14. Known history of allergy to Captisol (a cyclodextrin derivative used to solubilize carfilzomib) 15. Contraindication to lenalidomide or dexamethasone 16. Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to antiviral drugs or intolerance to hydration due to preexisting pulmonary or cardiac impairment 17. Active congestive heart failure (New York Heart Association [NYHA] Class III to IV), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, acute diffuse infiltrative pulmonary disease, pericardial disease, or myocardial infarction within 6 months prior to Cycle 1 Day 1 18. Active infection within 14 days prior to Cycle 1 Day 1 requiring systemic antibiotics 19. Pleural effusions requiring thoracentesis within 14 days prior to Cycle 1 Day 1 20. Ascites requiring paracentesis within 14 days prior to Cycle 1 Day 1 21. Ongoing graft-versus-host disease 22. Uncontrolled hypertension or uncontrolled diabetes 23. Significant neuropathy (≥ Grade 3) within 14 days prior to Cycle 1 Day 1 24. Known cirrhosis 25. Known human immunodeficiency virus (HIV) seropositivity, hepatitis C infection, or hepatitis B infection (subjects with hepatitis B surface antigen [SAg] or core antibody receiving and responding to antiviral therapy directed at hepatitis B are allowed) 26. Participation in another interventional study within 28 days prior to Cycle 1 Day 1 27. Major surgery (except kyphoplasty) within 28 days prior to Cycle 1 Day 1 28. Female subjects who are pregnant or lactating 29. Any other clinically significant medical disease or social condition that, in the investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent.

Treatment and assessments:	Treatment cycles are 28 days in duration and consist of KRd combination treatment as described above.

Criteria for evaluation:	
Safety variables:	Safety and tolerability will be assessed by incidence and severity of AEs and changes from baseline of all relevant parameters, including laboratory values, vital signs, electrocardiogram (ECG), and ECHO. Severity of AEs will be assessed according to the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE; version 4.03). All subjects will be monitored for AEs for 30 days after the last administration of study treatment.
Efficacy variables:	Disease assessments according to the IMWG-Uniform Response Criteria (URC) will be conducted at Screening (within 21 days before dosing on Cycle 1 Day 1) and then at Cycle 2 Day 1 and on Day 1 ± 3 days of every cycle thereafter for up to 18 cycles. Minimal residual disease (MRD) status will be assessed by using flow cytometry (FC) of cell surface markers and Next Generation Sequencing (NGS) of DNA and/or RNA from the Ig locus. The MRD analysis by FC will be performed on bone marrow aspirated at 2 time points: Cycle 8 Day 1, and upon achieving a CR or sCR. The MRD analysis by NGS will be performed using blood and bone marrow aspirates collected at 3 time points: baseline, Cycle 8 Day 1, and upon achieving a CR or sCR.
PK:	For both the Dose-evaluation and the Dose-expansion Components, blood samples will be collected from all subjects **on Day 8 of Cycle 1** for determination of plasma concentrations of carfilzomib. On the day of blood collection, blood will be collected at predose, 15 minutes after the start of the infusion, immediately prior to (within 2 minutes before) the end of the infusion, and 15 and 60 minutes after the end of the infusion.
PDn:	Whole blood will be collected from all subjects in the Dose-evaluation Component**, and the first 8 subjects enrolled in Dose-expansion Arm 3,** on Days 1, 8, 9, and 11 of Cycle 1. On Days 1 and 8 of Cycle 1 whole blood will be collected pre-carfilzomib dose and post-carfilzomib dose. On Days 9 and 11 of Cycle 1, when carfilzomib is not administered, one PDn sample will be collected at approximately the same time as when the pre-infusion sample was taken on Day 8.
Genomics:	Analysis of genetics, gene expression, and cell surface biomarkers that may predict for response and resistance to treatment with proteasome inhibitors will be performed. Exploratory studies will be conducted on all subjects who consent to optional genomic biomarker analysis. These analyses will be performed on bone marrow aspirate (the remaining portion of the bone marrow aspirate sample left after the amount required for fluorescent in situ hybridization (FISH) analysis has been collected at baseline), as well as a sample of blood and saliva also collected at the time of baseline. At progression, an optional additional bone marrow sample for biomarker analysis may be collected from all subjects who consent. Whole genome sequencing (WGS), whole exome sequencing (WES), whole transcriptome sequencing (RNA-Seq), and/or other methods of nucleic acid and protein quantification will be conducted on isolated tumor (CD138+) cells from these bone marrow aspirate samples. In addition, WGS or WES will be performed on a normal tissue sample (eg, CD3+ T cells isolated from peripheral blood or saliva) to distinguish germ line mutations from somatic mutations in tumor cell samples.
Other:	Subject convenience and satisfaction with the carfilzomib dosing schedule will be assessed by questionnaire at Cycle 3 Day 1 and Cycle 18 Day 1.
Statistical methods and analyses:	All safety and efficacy analyses will be based upon the Safety Population, defined as subjects receiving treatment with at least 1 dose of carfilzomib. In addition, response data (overall response rate [ORR], complete response rate [CRR], progression-free survival

Statistical methods and analyses (cont'd):

[PFS], duration of response [DOR]) may also be analyzed based on the Response-evaluable Population, defined as subjects who are included in the Safety Population, have a baseline disease assessment and at least 1 postbaseline disease assessment, or dropped out due to AE prior to the first postbaseline disease assessment.

Primary Endpoints:

- Safety and tolerability of carfilzomib administered once weekly in combination with lenalidomide and dexamethasone, as defined by the type, incidence, and severity of AEs, and changes from baseline in key laboratory analyses, including immunoglobulin levels, vital signs, and the extent and duration of exposure to study drugs.

  All treatment-emergent AEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) preferred term, NCI CTCAE grade, and investigator assessment of causality. In addition, all serious adverse events (SAEs), including deaths, will be listed separately. Extent of exposure to the study treatment will be summarized using descriptive statistics. Laboratory parameters will be summarized using descriptive statistics and by postdose shifts relative to baseline. Vital signs will also be summarized descriptively for each scheduled protocol time point.

Secondary Endpoints:

- Pharmacokinetics (PK) of carfilzomib
- Overall Response Rate (ORR), defined as the proportion of subjects who achieve a best overall response of stringent complete response (sCR), CR, very good partial response (VGPR), or PR in accordance with IMWG-URC
- Complete Response Rate (CRR), defined as the proportion of subjects who achieve a best overall response of either sCR or CR in accordance with IMWG-URC
- Progression-free Survival (PFS), defined as the time from the first day of study treatment to the earlier of disease progression or death due to any cause
- Duration of Response (DOR), defined as the time from the first evidence of confirmed PR or better to disease progression or death due to any cause among subjects who respond

Point estimates for ORR and CRR along with their exact 2-sided 95% confidence intervals will be calculated. The distribution of time-to-event endpoints (PFS and DOR) will be summarized descriptively using the Kaplan-Meier method.

Safety and efficacy analyses will be performed by dose levels and by populations (newly diagnosed and relapsed).

Pharmacokinetics:

The PK parameter estimates for carfilzomib will be summarized, including total plasma exposure (expressed as area under the curve; AUC), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), total plasma clearance, and plasma terminal half-life (as appropriate for data collected). Estimates for these parameters will be tabulated and summarized (ie, mean, standard deviation). The PK parameters will be summarized descriptively.

Exploratory Endpoints:

- Pharmacodynamics (PDn) of proteasome inhibition by carfilzomib measured in whole blood
- MRD[-] rate, defined as the proportion of subjects who have negative MRD at Cycle 8 Day 1. Point estimates for MRD[-] rate along with exact 2-sided 95% confidence intervals will be calculated for both MRD assessment methods
- Subject convenience and satisfaction with the carfilzomib dosing schedule.
- WGS, WES, whole transcriptome sequencing, and other nucleic acid and protein quantification data and immunoglobulin levels in tumor cells

WGS, WES, RNA-Seq, and/or other nucleic acid and protein quantification data will be analyzed to characterize whether drug response is related to alterations in genes regulated by or involved in activation of nuclear factor kappa light chain enhancer of activated B cells (NF-Kappa B) transcription factors as well as in genes involved in immunoglobulin production and protein homeostasis. Immunoglobulin levels in tumor cells will be quantified by enzyme-linked immunosorbent assay (ELISA) and/ or other protein quantification methods. The genomic data as a whole will also be used to derive new hypotheses about mechanisms of drug response, resistance, and safety.

TABLE OF CONTENTS

Page

List of Tables

List of Figures

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ARDS	acute respiratory distress syndrome
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
AUC	area under the curve
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CBR	clinical benefit rate
C_{max}	maximum plasma concentration
CMP	carfilzomib, melphalan, and prednisone
CR	complete response
CR/nCR	complete response/near complete response
CRA	Clinical Research Associate
CrCl	creatinine clearance
CRF	case report form
CRR	complete response rate
CSRC	Cohort Safety Review Committee
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
D5W	5% Dextrose Injection
DBP	diastolic blood pressure
Dex	Dexamethasone
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELISA	Enzyme-Linked Immunosorbent Assay
EOT	end of treatment
FDA	Food and Drug Administration

Abbreviation	Definition
FISH	fluorescent in situ hybridization
FCBP	Females of childbearing potential
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplantation
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IMWG-URC	International Myeloma Working Group-Uniform Response Criteria
IND	Investigational New Drug
IP	investigational product
IPIM	investigational product instruction manual
IRB	Institutional Review Board
IST	investigator-sponsored trial
IUD	intrauterine device
IV	intravenous (ly)
K	Kyprolis®(carfilzomib)
KRd	Kyprolis (carfilzomib)/Revlimid® (lenalidomide)/dexamethasone
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
NDMM	newly diagnosed multiple myeloma
nCR	near complete response
NCI	National Cancer Institute (US)
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NF kappa B	nuclear factor kappa light chain enhancer of activated B cells
NGS	Next Generation Sequencing

Abbreviation	Definition
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PD	progressive disease
PDn	pharmacodynamic(s)
PET	positron emission tomography
PK	pharmacokinetic(s)
PFS	progression-free survival
PN	peripheral neuropathy
PO	oral(ly)
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PS	performance status
PSA	prostate-specific antigen
qIgA	quantitative immunoglobulin A
QTc	corrected QT (interval)
R	Revlimid (lenalidomide)
RBC	red blood cell
RNA-Seq	whole transcriptome sequencing
RRMM	relapsed and refractory multiple myeloma
SAE	serious adverse event
SAg	surface antigen
SBP	systolic blood pressure
SC	subcutaneous(ly)
sCR	stringent complete response
SFLC	serum free light chain
SmPC	Summary of Product Characteristics
SPEP	serum protein electrophoresis
SWI	Sterile Water for Injection
$t_{1/2}$	terminal half-life
TLS	tumor lysis syndrome
t_{max}	time to maximum plasma concentration
ULN	upper limit of normal
UPEP	urine protein electrophoresis
URC	Uniform Response Criteria
USP	United States Pharmacopeia

Abbreviation	Definition
VGPR	very good partial response
VRd	Velcade (bortezomib)/Revlimid (lenalidomide)/dexamethasone
WBC	white blood cell
WES	whole exome sequencing
WGS	whole genome sequencing

3 BACKGROUND INFORMATION

3.1 INTRODUCTION

Kyprolis (Carfilzomib for Injection [carfilzomib]) is a proteasome inhibitor that received accelerated approval from the United States (US) Food and Drug Administration (FDA) in July 2012 for the treatment of patients with multiple myeloma who have received at least 2 prior therapies, including bortezomib and an IMiD and have demonstrated disease progression on or within 60 days of completion of the last therapy. The approval was based on the results of the Study PX-171-003 – Part 2 (A1) in 266 subjects with relapsed and/or refractory multiple myeloma. Subsequent full approval in the US and European Union was based on two phase 3 trials: PX-171-009 (ASPIRE) and 2011-003 (ENDEAVOR). Following these approvals, Kyprolis in combination with either lenalidomide and dexamethasone or dexamethasone alone is indicated for treatment of relapsed and refractory multiple myeloma (RRMM).

The study detailed in the current protocol will evaluate several dose levels of carfilzomib in combination with lenalidomide and dexamethasone.

RRMM and newly diagnosed multiple myeloma (NDMM) subjects will be treated with carfilzomib given once weekly in combination with lenalidomide (Revlimid) and dexamethasone as part of a carfilzomib (K), lenalidomide (R) and dexamethasone (d) regimen (KRd). Carfilzomib will be given as a 30-minute infusion once weekly for the first 3 weeks of a 4-week (28-day) cycle as part of a KRd regimen.

This study will evaluate the safety and tolerability of once-weekly carfilzomib regimens in subjects with relapsed multiple myeloma or newly diagnosed multiple myeloma.

3.2 MULTIPLE MYELOMA

Multiple myeloma, a clonal neoplastic proliferation of plasma cells, is the second most common hematologic malignancy and is responsible for approximately 72,000 annual deaths worldwide (Ferlay 2010). There are an estimated 11,000 deaths per year in the US and more than 19,000 deaths per year in Europe (American Cancer Society 2014; Boyle 2005). Multiple myeloma is characterized by anemia, bone destruction, monoclonal gammopathy,

renal failure, hypercalcemia, and increased susceptibility to infections. The disease is systemic and chemotherapy is indicated for management of symptomatic myeloma.

Current treatment options for people with newly diagnosed multiple myeloma commonly include combination chemotherapy with regimens consisting of melphalan (Alkeran), bortezomib (Velcade), thalidomide (Thalomid), and lenalidomide (Revlimid) with or without corticosteroids such as dexamethasone or prednisone. For people whose tolerance is not limited by age or co-morbidities, the preferred treatment is standard chemotherapy or VRd followed by high dose, myeloablative chemotherapy and autologous stem cell transplantation (ASCT).

Despite improvements in progression-free survival (PFS) and overall survival (OS) over the past 15 years, essentially all patients eventually relapse even with the best available approved treatments.

3.3 NOVEL THERAPIES FOR MULTIPLE MYELOMA

3.3.1 PROTEASOME BACKGROUND

Proteasome inhibition has emerged as an important therapeutic strategy in multiple myeloma (Moreau 2012). The proteasome is a multicatalytic proteinase complex that is responsible for degradation of a wide variety of protein substrates within normal and malignant 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.

3.3.2 CARFILZOMIB BACKGROUND (NONCLINICAL)

Carfilzomib is a tetrapeptide epoxyketone-based inhibitor of the chymotrypsin-like activity of the 20S proteasome. It is structurally and mechanistically different from the dipeptide boronic acid proteasome inhibitor bortezomib and showed less off-target activity when measured against a broad panel of proteases including metallo-, aspartyl-, and serine proteases compared to bortezomib; the latter showed off-target inhibitory activity in the nanomolar range against several serine proteases (Arastu-Kapur 2009). This selectivity may

be responsible for the reductions in myelosuppression and neuropathy observed in nonclinical studies comparing carfilzomib with bortezomib.

Based upon in vitro and in vivo studies, it is anticipated that a more intense and sustained proteasome inhibition can be achieved with carfilzomib relative to bortezomib, resulting in enhanced antitumor activity. Continuous 72-hour exposure to carfilzomib was associated with potent cytotoxic and pro-apoptotic activity across a broad panel of tumor-derived cell lines in culture (Demo 2007). 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. Carfilzomib was also cytotoxic in bortezomib-resistant tumor cell lines (Suzuki 2011; Kuhn 2007).

Nonclinical studies in rats and monkeys have been performed administering carfilzomib IV for 5 consecutive days followed by 9 days of rest for 2 cycles. Proteasome inhibition of more than 80% was achieved, suggesting that high-level inhibition of the proteasome with the epoxyketone class is possible, affording new opportunities to escalate dose to optimize antitumor effects (Yang 2011). This finding was in contrast to nonclinical testing with the boronate class of inhibitors that prohibited uninterrupted daily dosing due to substantial morbidity and mortality. Carfilzomib has also been administered to rats and monkeys for 6 and 9 months, respectively (once daily × 2: once daily dosing for 2 consecutive days 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 (current Carfilzomib Investigator's Brochure [IB]). In contrast, rats and monkeys treated with bortezomib in chronic toxicity studies were shown to have reduced motor activity, convulsions, tremors, and hind-limb paralysis accompanied by histological degeneration in peripheral nerves, as well as significant neutropenia (Velcade [bortezomib] full prescribing information [Millennium Pharmaceuticals 2012]; Velcade Summary of Product Characteristics [SmPC] 2012 [High Wycombe, Bucks, UK 2012]).

3.3.3 CARFILZOMIB BACKGROUND (CLINICAL)

Carfilzomib entered clinical studies in September 2005.

As of 10 July 2016, an estimated 4833 subjects and 4114 subject-years have been exposed to carfilzomib in clinical trials conducted by Onyx Therapeutics, Inc. since the beginning of the development program.

Carfilzomib has been administered on 2 consecutive days weekly for 3 weeks in a 28-day cycle in most studies conducted to date.

Study PX-171-006 was the first to explore the option of combination therapy using carfilzomib and lenolidamide (the IMiD most widely employed for the treatment of multiple myeloma; Wang 2013). This investigation was the model for another Phase 2 study of the carfilzomib, lenalidomide, dexamethasone (KRd) combination conducted by the Multiple Myeloma Research Consortium, and it used a maximum planned dose of 36 mg/m^2 twice weekly in patients with newly diagnosed multiple myeloma (Jakubowiak 2012). The Phase 3 ASPIRE study compared the efficacy of KRd versus lenalidomide and dexamethasone alone in a much larger trial that enrolled 792 RRMM subjects. ASPIRE showed an improved overall response rate and PFS with KRd therapy and provides a strong incentive to optimize the KRd regimen (Stewart 2015).

The Phase 1/Phase 2 CHAMPION 1 trial of subjects with relapsed or progressing multiple myeloma who had received 1 to 3 prior regimens evaluated the safety and efficacy of carfilzomib administered once weekly at doses higher than the 56 mg/m^2 maximum tolerated dose (MTD) previously established for the twice-weekly administration routine (Berenson 2016). All subjects received carfilzomib (20 mg/m^2) on Cycle 1 Day 1 but received the cohort-assigned test dose on Cycle 1 Days 8 and 15. Testing started at 45 mg/m^2 in the first cohort and was escalated to 56, 70, and 88 mg/m^2 in successive cohorts until the MTD was determined. Subjects received dexamethasone 40 mg (IV or orally) on Days 1, 8, 15, and 22 of Cycles 1 through 8 and on Days 1, 8, and 15 from Cycle 9 onward.

No dose-limiting toxicities (DLTs) were observed during dose escalation in the cohorts at 45, 56, or 70 mg/m^2. At a carfilzomib dose of 88 mg/m^2, 2 DLTs were observed during Cycle 1: Grade 3 dyspnea (Days 9–11) and Grade 3 vomiting (Day 15). Therefore, the MTD of once-weekly carfilzomib in combination with dexamethasone was determined to be

70 mg/m^2; a total of 104 subjects were treated at 70 mg/m^2 carfilzomib dose level on the phase 1/2 CHAMPION-1 study.

Five treatment-emergent serious adverse events (SAEs) were reported. One subject had 2 treatment-emergent SAEs (Grade 3 increased blood creatinine and Grade 4 hyponatremia), 1 subject had Grade 3 pneumonia, 1 subject had Grade 3 dyspnea, and 1 subject had Grade 3 chronic obstructive pulmonary disease. The Grade 3 dyspnea event occurred in a subject receiving 88 mg/m^2 carfilzomib and was considered to be related to carfilzomib treatment. All other SAEs were determined to be unrelated to carfilzomib or dexamethasone treatment. The treatment regimen showed promising efficacy with an overall response rate (ORR) of 81% and a clinical benefit rate (CBR) of 93% (Berenson 2016), raising the question of whether weekly carfilzomib administered in combination with other antimyeloma agents might provide even greater patient benefit.

3.3.4 COMBINATIONS OF IMMUNOMODULATORY AGENTS AND PROTEASOME INHIBITORS

Nonclinical studies showing that the IMiD lenalidomide sensitizes multiple myeloma cells to the proteasome inhibitor bortezomib suggested that combination therapy may enhance clinical activity (Mitsiades 2002). The treatment paradigm involving proteasome inhibitor, immunomodulatory agent, and dexamethasone now forms the core of other treatment approaches aimed at improving either efficacy or tolerability (Kumar 2010). The results of selected trials of proteasome inhibitors, lenalidomide and dexamethasone in subjects with multiple myeloma are summarized in Table 1.

Table 1 Combination Studies of Proteasome Inhibitors and Immunomodulatory Agents

	Regimen	Response
Richardson (2009) Phase 1/ n = 38 Relapsed/Refractory	• VRd; 21-day cycle • Bortezomib 1.0 mg/m^2, Days 1, 4, 8, 11 • Lenalidomide 5, 10 or 15 mg, Days 1–14 • Dexamethasone 20 or 40 mg, Days 1, 2, 4, 5, 8, 9, 11, 12	• ≥ MR: 61% • CR/nCR: 8%
Richardson (2014) Phase 2/ n = 64 Relapsed/Refractory	• VRd; 21-day cycle • Bortezomib 1.0 mg/m^2, Days 1, 4, 8, 11 • Lenalidomide 15 mg, Days 1–14 • Dexamethasone 20 or 40 mg (Cycles 1–4) or 10 or 20 mg (Cycles 5– 8), Days 1, 2, 4, 5, 8, 9, 11, 12	• ≥ MR: 78% • ≥ PR: 64% • CR/nCR: 25%
Dimopoulos (2010) Phase 2/ n = 49 Relapsed/Refractory	• VRd; 21-day cycle • Bortezomib 1.0 mg/m^2, Days 1, 4, 8, 11 • Lenalidomide 15 mg, Days 1–14 • Dexamethasone 40 mg, Days 1–4	• ≥ PR: 63% • VGPR: 14% • CR: 6%
Richardson (2010) Phase 1, 2/ n = 66 Newly Diagnosed	• VRd; 21-day cycle • Bortezomib 1.0 or 1.3 mg/m^2, Days 1, 4, 8, 11 • Lenalidomide 15–25 mg, Days 1–14 • Dexamethasone 20 or 40 mg, Days 1, 2, 4, 5, 8, 9, 11, 12	• CR/nCR: 40% • VGPR: 27% • PR: 33%
Niesvizky (2013) Phase 1b/ n = 40 Relapsed/Refractory	• KRd; 28-day cycle • Carfilzomib, Days 1, 2, 8, 9, 15, 16 doses- 15, 20, 27 mg/m^2 • Lenalidomide 10 to 25 mg, Days 1–21 • Dexamethasone 40 mg, Days 1, 8, 15, 22	• sCR: 2.5% • VGPR: 32.5% • PR: 27.5%
Jakubowiak (2012) Phase 1, 2/ n = 53 Newly Diagnosed	• KRd; 28-day cycle • Carfilzomib 36 mg/m^2, Days 1, 2, 8, 9, 15, 16 • Lenalidomide 25 mg, Days 1–21 • Dexamethasone 20 or 40 mg, Days 1–4	• sCR: 42% • ≥ nCR: 62% • ≥ VGPR: 81% • ≥ PR: 98%
Korde (2013) Phase 2/ n = 45 Newly Diagnosed	• KRd; 28-day cycle • Carfilzomib 36 mg/m^2, Days 1, 2, 8, 9, 15, 16 • Lenalidomide 25 mg, Days 1–21 • Dexamethasone 10 mg (IV) or 20 mg (PO), Days 1, 2, 8, 9, 15, 16, 22, 23	• ORR: 98% • CR/nCR: 51% • ≥ VGPR: 88% • PR: 9%

CR = complete response; IV = intravenous (ly); KRd = Kyprolis/Revlimid/dexamethasone; MR = minimal response; nCR = near complete response; ORR = overall response rate; PO = oral(ly); PR = partial response; sCR = stringent complete response; VGPR = very good partial response; VRd = Velcade/Revlimid/dexamethasone.

These studies demonstrated the efficacy of regimens that combine lenalidomide with proteasome inhibitors (bortezomib or carfilzomib). The regimens are effective and well tolerated both in patients newly with diagnosed multiple myeloma as well as those who have relapsed.

3.4 DOSE RATIONALE

The dose rationale for this study derives from considerations of carfilzomib, lenalidomide, and dexamethasone dose combinations that are currently in use, as shown in Table 1. Dose combinations for this study are shown in Table 2. Prior to protocol amendment 2, dose-evaluation cohorts were planned only for RRMM subjects (Cohorts 1, 2, and 3). Schemas for enrollment prior to protocol amendment 2 are shown in Appendix E (Figure 2 and Figure 3). **With** protocol amendment 2, **a** Dose-evaluation cohort **is** added for NDMM subjects.

Cohorts 1, 2, and 3

The initial dosing for the proposed weekly KRd combinations (Cohorts 1, 2, and 3) in this study reflects a triangulation of the individual components of the studies listed in Table 1. The Dose-evaluation Component of the study begins with carfilzomib 56 mg/m^2, lenalidomide 25 mg, and dexamethasone 40 mg in RRMM subjects (Cohort 1, Table 2). As shown in Table 1, carfilzomib, in combination with dexamethasone, has been administered at weekly doses as high as 70 mg/m^2/day given once weekly and 56 mg/m^2 given on 2 consecutive days (total weekly exposure of 112 mg/m^2). Carfilzomib given as part of a KRd regimen has been administered safely at doses as high as 36 mg/m^2 given on 2 consecutive days each week (total weekly exposure of 72 mg/m^2). Of note, no DLTs were identified at this dose in the Phase 1 study; dose escalation was stopped at 36 mg/m^2 twice-weekly because it was the maximum dose planned in the protocol. The safety information from these trials supports a starting dose for Cohort 1 of carfilzomib 56 mg/m^2, lenalidomide 25 mg, and dexamethasone 40 mg.

Cohort 4

A 2-step-up KRd regimen will be evaluated in NDMM subjects: carfilzomib will be given at 20 mg/m^2 on Day 1 of Cycle 1, 56 mg/m^2 on Days 8 and 15 of Cycle 1, then 70 mg/m^2 on Days 1, 8, and 15 beginning with Cycle 2 (Cohort 4; Table 2). This regimen was selected by the Cohort Safety Review Committee (CSRC) for Dose-evaluation in NDMM subjects, after the occurrence of 2 SAEs in NDMM subjects during Cycle 1 of treatment at Cohort 2 dose-level **(Arm 1)**.

Table 2 Carfilzomib Combination Regimens

	Regimen			Maximum Weekly Exposure		
	Drug	**Dosing**	**Schedule**	**K mg/m^2**	**R mg**	**d mg**
Cohort 1 KRd	Carfilzomib	20 mg/m^2	Day 1 of Cycle 1	56	175	40
		56 mg/m^2	Days 8, 15 of Cycle 1 Days 1, 8, 15 of Cycles 2-18			
	Lenalidomide	25 mg	Days 1–21			
	Dexamethasone	40 mg	Days 1, 8, 15, 22 of Cycles 1-8			
			Days 1, 8, 15 of Cycles 9-18			
Cohort 2 KRd	Carfilzomib	20 mg/m^2	Day 1 of Cycle 1	70	175	40
		70 mg/m^2	Days 8, 15 of Cycle 1 Days 1, 8, 15 of Cycles 2-18			
	Lenalidomide	25 mg	Days 1–21			
	Dexamethasone	40 mg	Days 1, 8, 15, 22 of Cycles 1-8			
			Days 1, 8, 15 of Cycles 9-18			
Cohort 3 (optional) KRd	Carfilzomib	20 mg/m^2	Day 1 of Cycle 1	70	70	40
		70 mg/m^2	Days 8, 15 of Cycle 1 Days 1, 8, 15 of Cycles 2-18			
	Lenalidomide	10 mg	Days 1–21			
	Dexamethasone	40 mg	Days 1, 8, 15, 22 of Cycles 1-8			
			Days 1, 8, 15 of Cycles 9-18			
Cohort 4 2-step-up KRd	Carfilzomib	20 mg/m^2	Days 1 of Cycle 1	70	175	40
		56 mg/m^2	Days 8, 15 of Cycle 1			
		70 mg/m^2	Days 1, 8, 15 of Cycles 2-18			
	Lenalidomide	25 mg	Days 1–21			
	Dexamethasone	40 mg	Days 1, 8, 15, 22 of Cycles 1-8			
			Days 1, 8, 15 of Cycles 9-18			

d = dexamethasone, K = carfilzomib; KRd = Kyprolis (carfilzomib)/Revlimid (lenalidomide)/dexamethasone; R = lenalidomide.

3.5 STUDY RATIONALE

Exploration of therapeutic variations aimed at improving tolerance, patient convenience, efficacy, and treatment adherence are important considerations for treatment outcomes. A study comparing routes of bortezomib administration showed no loss of efficacy with the more convenient subcutaneous (SC) route relative to that seen with the established IV route of administration (Moreau 2011). Likewise, twice-weekly bortezomib IV administration was

used in the early trials of this agent (Richardson 2009). A later study comparing once-weekly with twice-weekly bortezomib administration demonstrated improved safety, in particular a reduction in the rate of peripheral neuropathy, with no apparent effect on efficacy (Bringhen 2010).

The combination of carfilzomib (twice-weekly), lenalidomide, and dexamethasone is a highly efficacious regimen in RRMM and NDMM subjects (Stewart 2015; Jakubowiak 2012; Korde 2013). Of specific note, 23 of 26 subjects who reached nCR/CR achieved negative minimal residual disease (MRD[-]) status in one study (Jakubowiak 2012), while in another trial 27 of 27 subjects who reached nCR/CR achieved MRD[-] status (Korde 2013), further emphasizing the efficacy of this combination. A favorable safety profile and promising preliminary efficacy for once-weekly carfilzomib in RRMM subjects was observed in the CHAMPION 1 study (Berenson 2016).

This study will explore the safety and tolerability of once-weekly carfilzomib administered with lenalidomide and dexamethasone as part of a KRd regimen for RRMM and NDMM subjects. Once-weekly carfilzomib is expected to improve tolerance, convenience, and treatment adherence. The results will help inform decisions on future efficacy studies involving once-weekly carfilzomib administration.

4 STUDY OBJECTIVES

4.1 PRIMARY OBJECTIVES

- The primary objective of the study is to evaluate the safety and tolerability of a once-weekly KRd regimen in RRMM and NDMM subjects.

4.2 SECONDARY OBJECTIVES

Secondary objectives are the following:

- To evaluate the pharmacokinetics (PK) of carfilzomib when administered once-weekly in a KRd regimen in RRMM and NDMM subjects
- To evaluate the clinical activity (efficacy) of a once-weekly KRd regimen in RRMM and NDMM subjects

4.3 EXPLORATORY OBJECTIVES

Exploratory objectives include:

- To explore the genomic and transcriptional biomarkers that might predict response and resistance to a once-weekly KRd regimen
- To characterize the pharmacodynamics (PDn) of proteasome inhibition with a once-weekly KRd regimen in RRMM and NDMM subjects
- To assess MRD status with a once-weekly KRd regimen in RRMM and NDMM subjects
- To assess subject convenience and satisfaction with a once-weekly KRd regimen using subject questionnaire in RRMM and NDMM subjects

5 STUDY DESIGN

This is an open-label, multicenter, Phase 1b, dose-finding study of carfilzomib administered once-weekly in combination with lenalidomide and dexamethasone (KRd) in 28-day cycles to subjects with multiple myeloma.

Subjects may continue to receive study treatment for up to 18 cycles or until 1 or more of the following events occurs:

- Disease progression
- Allogeneic stem cell transplant
- Withdrawal from the study for any reason
- Study termination by the sponsor
- Death

Disease assessments will be conducted at Screening (within 21 days before dosing on Cycle 1 Day 1) and then on Day 1, ± 3 days, of every cycle beginning with Cycle 2. Response will be evaluated using the International Myeloma Working Group (IMWG) - Uniform Response Criteria (URC; Rajkumar, 2011; Appendix C).

NDMM subjects may interrupt study treatment to proceed to hematopoietic stem cell collection, or stem cell collection and ASCT. The investigator will communicate transplant plans with the clinical study team. Upon completion of collection, subjects may resume study treatment (for up to the total of 18 cycles). Study treatment interruption for autologous hematopoietic stem cell collection may not exceed 42 days. Subjects with interruptions longer than 42 days may resume therapy on trial only with the written permission of the

sponsor study medical monitor. Subjects may interrupt study treatment and proceed to ASCT at any time after Cycle 4. Subjects who undergo ASCT may resume study treatment at any time up to posttransplant day 100, as elected by the investigator.

There will be 2 parts in the study.

The first part is the Dose-evaluation Component during which carfilzomib combination regimens will be evaluated (Table 2 and Figure 1). Approximately 8 dose-limiting toxicity evaluable subjects will be enrolled into each opened Dose-evaluation cohort. Before opening Dose-expansion **arms**, it must be determined that there are not more than 2 dose-limiting toxicities in 8 DLT-evaluable subjects at the dose selected for Dose-expansion. Dose-expansion **arms** may open once all safety data for at least 1 cycle at maximal dose carfilzomib is reviewed by the CSRC.

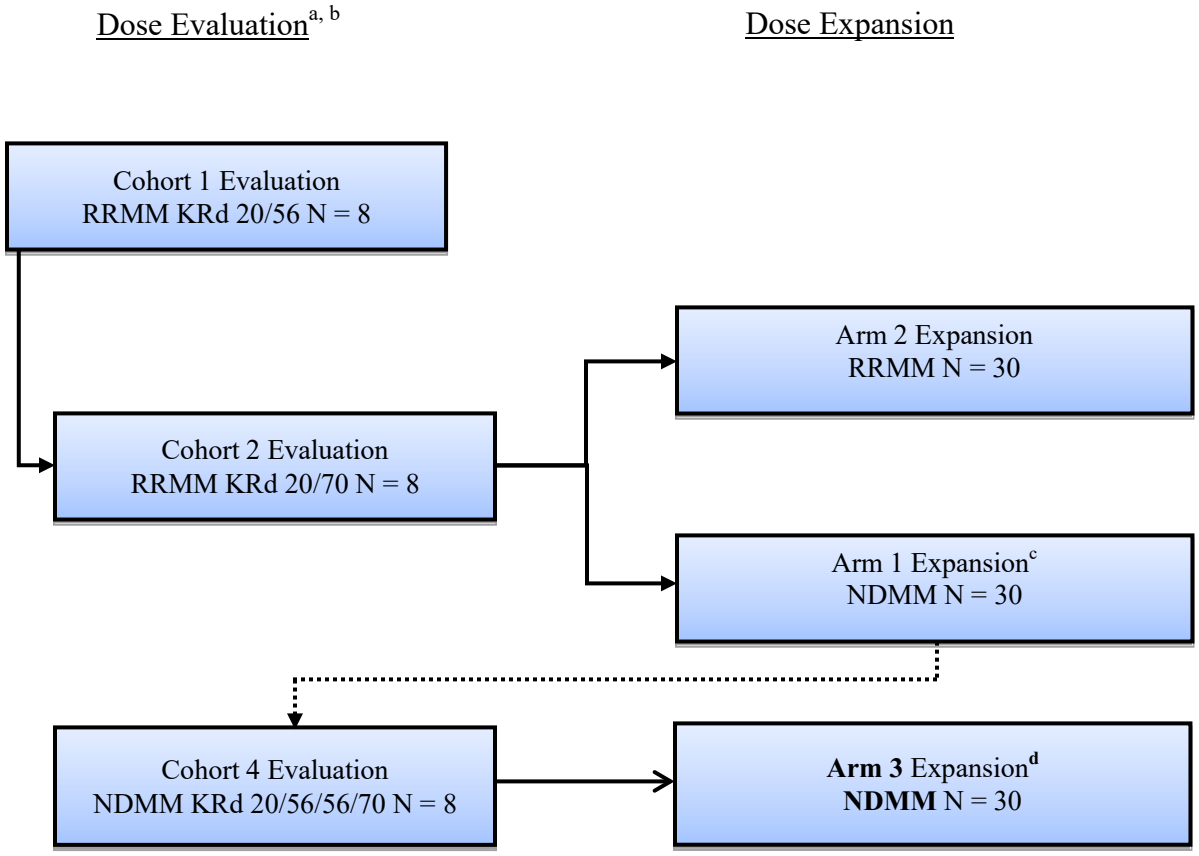
The second part is the Dose-expansion Component.

Prior to protocol amendment 2, dose evaluation was performed on RRMM subjects treated at Cohort 1 and Cohort 2 dosing (Table 2). Cohort 2 dosing was selected for expansion with a plan for approximately 30 RRMM subjects and 30 NDMM subjects to be treated in the Dose-expansion Component (**Arms 1 and 2;** Appendix E; Figure 2 and Figure 3).

In the first 8 NDMM subjects treated in Dose-expansion **Arm 1** at Cohort 2 dosing, 2 SAEs were observed during Cycle 1 (Table 2). Thus, **with** protocol amendment 2, Dose-evaluation Cohort 4 is added for NDMM subjects (Table 2 and Figure 1). A Dose-expansion **arm** for NDMM subjects may open once all safety data for at least 1 cycle at maximal planned carfilzomib dose is reviewed by the CSRC as described in Section 5.4.

All subjects will be evaluated for safety at an End of Treatment (EOT) visit, 28 ± 7 days after the last study treatment, and with an EOT echocardiogram (ECHO), done within 28 ± 7 days of the last study treatment. The EOT visit will include a pregnancy test for females of childbearing potential (FCBP). Following the EOT, subjects who have not had disease progression or allogeneic stem cell transplant will enter Active Follow-up. For details regarding Active Follow-up, please refer to Section 5.6.

Figure 1 Study Schema



N = number; NDMM = newly diagnosed multiple myeloma; RRMM = relapsed refractory multiply myeloma; KRd = Kyprolis (carfilzomib)/Revlimid® (lenalidomide)/dexamethasone'

[a] Optional Cohort 3 was not opened.

[b] Full dosing information is presented in Table 2.

[c] Twenty out of 30 planned NDMM subjects were enrolled in Dose expansion, at cohort 2 dosing, prior to protocol amendment 2.

[d] **Subjects in dose-expansion Arm 3 will be treated with KRd at 20/56 (full dosing regimen as shown for Cohort 1 in Table 2).**

5.1 STUDY POPULATION

Subjects with relapsed multiple myeloma who have received 1 to 3 prior lines of therapy for multiple myeloma will be included in the Dose-evaluation Component and the Dose-expansion Component of the study.

Prior to protocol amendment 2, subjects with newly diagnosed, previously untreated multiple myeloma were included only in the Dose-expansion Component (Appendix E; Figure 2, Arm 1). After protocol amendment 2, NDMM subjects will be enrolled into a NDMM Dose-evaluation cohort, which may be expanded after safety evaluation by the CSRC (**Arm 3,** Figure 1).

Complete eligibility criteria are described in Section 6.

5.2 DEFINITION OF DOSE-LIMITING TOXICITY

Dose-limiting toxicity (DLT) of the KRd regimens will be evaluated during Cycle 1 (Cohorts 1, 2, and 3), or Cycles 1 and 2 (Cohort 4), of the Dose-evaluation Component. Subjects in the Dose-evaluation Component of the study who do not complete the dose evaluation period for reasons unrelated to toxicity will be considered unevaluable for DLT and may be replaced. DLT are the toxicities defined below and attributable to carfilzomib, lenalidomide, or dexamethasone.

5.2.1 NONHEMATOLOGIC DLT

- ≥ Grade 3 nonhematological toxicity (excluding nausea, vomiting, diarrhea, alopecia, fatigue lasting < 14 days, increased serum creatinine or electrolyte abnormalities that are not clinically significant and require no treatment)
- ≥ Grade 3 acute kidney injury (creatinine > 3 × baseline or > 4.0 mg/dL) lasting > 72 hours
- ≥ Grade 3 nausea, vomiting, or diarrhea uncontrolled by maximal antiemetic/antidiarrheal therapy

5.2.2 HEMATOLOGIC DLT

- Grade 4 neutropenia (absolute neutrophil count [ANC] < 500/mm^3) lasting for > 7 days
- Febrile neutropenia (ANC < 1000/mm^3 with a fever ≥ 38.3ºC) of any duration
- Grade 4 thrombocytopenia (platelet count < 25,000/mm^3) that persists for > 14 days with or without platelet transfusion, despite holding treatment
- Grade 3 or 4 thrombocytopenia (platelet count < 50,000/mm^3) associated with > Grade 1 bleeding

5.3 COHORT SAFETY REVIEW COMMITTEE

A CSRC comprised of the lead investigator, selected additional investigators, the sponsor study medical monitor, and sponsor's drug safety representative will review all available safety data and make recommendations regarding ongoing enrollment and opening of subsequent cohorts during the Dose-evaluation Components. The CSRC will also select the KRd regimens to be evaluated in the Dose-expansion Components.

5.4 PART 1: DOSE-EVALUATION COMPONENT

Approximately 8 dose-evaluable subjects will be enrolled into each Dose-evaluation cohort (Table 2, Figure 1). Enrollment will be gated such that the first 4 subjects in Cohort 1 will complete Cycle 1 and undergo a safety evaluation prior to further enrollment.

- If ≥ 2 of the first 4 subjects of Cohort 1 experience a DLT, enrollment to that cohort will stop and the study will terminate
- If ≤ 1 of the first 4 subjects experience a DLT, the cohort will recommence enrollment of an additional 4 subjects for up to 8 dose-evaluable subjects total
    - Cohort 2 (n = approximately 8) will open to enrollment

When both Cohorts 1 and 2 are open for concurrent enrollment, subjects will be assigned to a cohort on an alternating basis. Safety will be evaluated in both cohorts on an ongoing basis.

- If ≥ 2 of the first 4 subjects experience DLTs or ≥ 3 subjects experience DLTs at any time in Cohort 2, enrollment to that cohort will be stopped, and the optional third cohort (Cohort 3) may be opened to enrollment of an additional 8 subjects (approximately).
- The CSRC will review all evaluable safety data (Section 5.3). If < 3 subjects experience a DLT in an opened cohort, that dose may be selected for dose expansion.
- For NDMM subjects evaluated in Cohort 4, the CSRC will review all safety data from the first 2 cycles and may elect to expand NDMM enrollment

To be DLT evaluable, subjects must have received all planned doses of carfilzomib, at least 80% of planned doses of lenalidomide, and at least 75% of planned doses of dexamethasone or received at least 1 dose of carfilzomib and experienced a DLT prior to completion of study treatment for Cycle 1 (Cohorts 1-3) or Cycle 2 (Cohort 4). Subjects who withdraw from treatment after receiving a dose of carfilzomib but before completing the first 28-day cycle (Cohorts 1-3) or the first two 28-day cycles (Cohort 4) for reasons unrelated to toxicity will be considered unevaluable for DLTs. Subjects who are not DLT-evaluable may be replaced.

The schema for the Dose-evaluation Component of the study for RRMM subjects is presented in Figure 2 (Appendix E).

Cohort 4

A 2-step-up KRd regimen will be evaluated in NDMM subjects: carfilzomib will be given at 20 mg/m^2 on Day 1 of Cycle 1, 56 mg/m^2 on Days 8 and 15 of Cycle 1, then at 70 mg/m^2 on Days 1, 8, and 15 beginning with Cycle 2 (Cohort 4; Table 2). This regimen was selected by the CSRC for dose-evaluation in NDMM subjects, after the occurrence of 2 SAEs in NDMM subjects during Cycle 1 of treatment at Cohort 2 dose level during the **Arm 1** NDMM Dose-expansion **(Figure 1)**.

5.5 PART 2: DOSE-EXPANSION COMPONENT

Per protocol amendment 2:

Enrollment of NDMM into Dose-expansion Arm 1 will stop (Appendix E; Figure 3).

NDMM subjects will be enrolled into Dose-evaluation Cohort 4 (Figure 1; Table 2). Arm 1 subjects enrolled prior to protocol amendment 2 who are DLT evaluable at Cohort 4 dosing will be included in Dose-evaluation Cohort 4 (Figure 1; Table 2).

The CSRC will evaluate all safety data for all NDMM subjects**. F**ollowing the **DLT** rules above**, t**he CSRC may elect to open an NDMM Dose-expansion **arm**, and may enroll an additional 30 NDMM subjects (Section 5.4).

5.6 ACTIVE FOLLOW-UP

Subjects who have terminated or completed study treatment (for reasons other than progressive disease, allogeneic stem cell transplant, death, or withdrawal of consent) will enter Active Follow-up for 1 year. For subjects in Active Follow-up, tumor response and disease assessment measurements will be performed every 8 weeks (every 56 ± 4 days). The investigators will make every reasonable effort to keep each patient in active follow-up for 1 year, or until the subject has progressive disease (PD), begins treatment with any antimyeloma medication, has withdrawn consent for further participation, is lost to follow up, has died, or the study is closed, whichever is earliest.

5.7 ESTIMATED STUDY DURATION AND STUDY CLOSURE

The total study duration is expected to be a minimum of 60 months. Approximately 6 months will be required to enroll subjects in the RRMM Dose-evaluation Component of the study. Approximately 9 months will be required to enroll subjects in the RRMM Dose-expansion Component of the study. Subjects will be followed for up to 17 months in order to complete primary safety and efficacy evaluations with up to an additional 12 months of Active Follow-up.

It will take up to approximately **12** months to enroll NDMM subjects into Dose-evaluation Cohort 4, review the safety data, and enroll NDMM subjects into the NDMM Dose-expansion **Arm 3**. Subjects will be followed for up to 17 months on treatment (with an allowed interruption of up to 4.5 months for ASCT), and for 12 months for Active Follow up.

Based on these assumptions, it is estimated that the final analysis will occur approximately 60 months after the first subject is enrolled.

The end of study will occur when the last subject leaves Active Follow-up.

5.8 MINIMIZING BIAS

5.8.1 RANDOMIZATION

This is not a randomized study.

Subjects in the RRMM Dose-evaluation Component will be assigned to the open cohort at time of enrollment; when/if Cohort 1 and Cohort 2 are both open to enrollment, enrollment will alternate between Cohort 1 and Cohort 2 until Cohort 1 is filled.

5.8.2 BLINDING

This is an open-label study; there is no blinding.

6 SUBJECT SELECTION

Approximately 114 subjects will be enrolled in this study. Subjects will be evaluated for study entry within the 21 days prior to Cycle 1 Day 1.

Fifty-six RRMM subjects enrolled prior to protocol amendment 2. Twenty NDMM subjects were enrolled prior to protocol amendment 2. Protocol amendment 2 allows for enrollment of up to 38 additional NDMM subjects.

6.1 INCLUSION CRITERIA

1. Age ≥ 18 years
2. Able to provide written informed consent in accordance with federal, local, and institutional guidelines
3. Newly diagnosed or relapsed multiple myeloma
   a. <u>For subjects with relapsed multiple myeloma:</u>
      i. 1 to 3 prior lines of therapy for multiple myeloma (induction therapy followed by stem cell transplant and consolidation/maintenance therapy will be considered as one line of therapy), and
      ii. Documented response of at least partial response (PR) to 1 line of prior therapy. Investigator assessment is acceptable as PR documentation.
   b. <u>For subjects with newly diagnosed, transplant-eligible or transplant-ineligible multiple myeloma:</u>
      i. Symptomatic multiple myeloma (per IMWG diagnostic criteria) and
      ii. No prior treatment for multiple myeloma
4. Measurable disease with at least 1 of the following assessed within 21 days prior to Cycle 1 Day 1:
   a. Serum M-protein ≥ 0.5 g/dL,
   b. Urine M-protein ≥ 200 mg/24 hour,
   c. In subjects without detectable serum or urine M-protein, serum free light chain (SFLC) > 100 mg/L (involved light chain) and an abnormal serum kappa lambda ratio
   d. For immunoglobulin (Ig) A subjects whose disease can only be reliably measured by serum quantitative immunoglobulin (qIgA), a qIgA level of ≥ 750 mg/dL (0.75 g/dL)
5. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 2
6. Left ventricular ejection fraction (LVEF) ≥ 40%
8. Absolute neutrophil count (ANC) ≥ 1000/mm^3 within 21 days prior to Cycle 1 Day 1 with (1) no nonpegylated growth factor support for ≥ 7 days and (2) no pegylated growth factor support for ≥ 14 days

9. Hemoglobin ≥ 8.0 g/dL within 21 days prior to Cycle 1 Day 1. Use of erythropoietic stimulating factors and red blood cell (RBC) transfusions per institutional guidelines is allowed
10. Platelet count ≥ 50,000/mm^3 (≥ 30,000/mm^3 if myeloma involvement in the bone marrow is > 50%) within 21 days prior to Cycle 1 Day 1 with no platelet transfusions for ≥ 7 days
11. Calculated or measured creatinine clearance (CrCl) of ≥ 50 mL/min within 21 days prior to Cycle 1 Day 1. Calculation must be based on standard formula such as the Cockcroft and Gault.
12. Females of childbearing potential (FCBP) must have a negative serum pregnancy test within the 10 to 14 days prior to study drug administration and a negative urine or serum pregnancy test within the 24 hours prior to the first study drug administration
13. FCBP and male subjects who are sexually active with a FCBP must agree to use 2 highly effective methods of contraception during the study. FCBP subjects are required to continue use of 2 highly effective methods of contraception for 30 days following discontinuation of study drugs. Vasectomized male subjects who have received medical confirmation of surgical success are not required to use additional methods of contraception. Otherwise, male subjects with a FCBP partner must agree to use 2 highly effective methods of contraception during study and for 90 days following discontinuation of study drugs
14. Male subjects must agree to not donate sperm while taking study drugs and 90 days after the last dose of study drugs
15. **Normal hepatic function within 21 days prior to Cycle 1 Day 1:**
    a. **Bilirubin ≤ the upper limit of normal (ULN)**
    b. **Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ the ULN**

6.2 EXCLUSION CRITERIA

1. Waldenström macroglobulinemia
2. For newly diagnosed multiple myeloma: multiple myeloma of IgM subtype
3. For relapsed disease:
    a. If treated with a lenalidomide and dexamethasone-containing combination, progression during the first 3 months after initiating treatment.
    b. Any progression during treatment if the lenalidomide and dexamethasone-containing regimen was the most recent line of therapy.
    c. Any prior treatment with carfilzomib.

4. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
5. Plasma cell leukemia (> 2.0×10^9/L circulating plasma cells by standard differential)
6. Myelodysplastic syndrome
7. Second malignancy within the past 5 years except:
    a. Adequately treated basal cell or squamous cell skin cancer, or
    b. Carcinoma in situ of the cervix, or
    c. Prostate cancer < Gleason score 6 with undetectable prostate-specific antigen (PSA) over 12 months, or
    d. Ductal breast carcinoma in situ with full surgical resection (ie, negative margins), or
    e. Treated medullary or papillary thyroid cancer, or
    f. Similar condition with an expectation of > 95% five-year disease-free survival
8. Amyloidosis
9. Cytotoxic chemotherapy within 28 days prior to Cycle 1 Day 1
10. Immunotherapy within 21 days prior to Cycle 1 Day 1
11. Glucocorticoid therapy within 14 days prior to Cycle 1 Day 1 that exceeds a cumulative dose of 160 mg of dexamethasone
12. Radiation therapy:
    a. Focal therapy within 7 days prior to Cycle 1 Day 1
    b. Extended field therapy within 21 days prior to Cycle 1 Day 1
13. Prior treatment with carfilzomib or oprozomib
14. Known history of allergy to Captisol (a cyclodextrin derivative used to solubilize carfilzomib)
15. Contraindication to lenalidomide or dexamethasone
16. Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to antiviral drugs, or intolerance to hydration due to preexisting pulmonary or cardiac impairment
17. Active congestive heart failure (New York Heart Association [NYHA] Class III to IV), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, acute diffuse infiltrative pulmonary disease, pericardial disease, or myocardial infarction within 6 months prior to Cycle 1 Day 1
18. Active infection within 14 days prior to Cycle 1 Day 1 requiring systemic antibiotics

19. Pleural effusions requiring thoracentesis within 14 days prior to Cycle 1 Day 1
20. Ascites requiring paracentesis within 14 days prior to Cycle 1 Day 1
21. Ongoing graft-versus-host disease
22. Uncontrolled hypertension or uncontrolled diabetes
23. Significant neuropathy (≥ Grade 3) within 14 days prior to Cycle 1 Day 1
24. Known cirrhosis
25. Known human immunodeficiency virus (HIV) infection, hepatitis C infection, or hepatitis B infection (subjects with hepatitis B surface antigen [SAg] or core antibody receiving and responding to antiviral therapy directed at hepatitis B are allowed)
26. Participation in another interventional study within 28 days prior to Cycle 1 Day 1
27. Major surgery (except kyphoplasty) within 28 days prior to Cycle 1 Day 1
28. Female subjects who are pregnant or lactating
29. Any other clinically significant medical disease or social condition that, in the investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent

7 SUBJECT SCREENING

A signed and dated informed consent form (ICF) will be obtained before any study-specific tests may be performed. Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the study-specific evaluations, provided they meet the time windows described below. It is recommended that study-specific tests unrelated to subject eligibility (including a bone marrow aspirate) be done only after screening tests confirm subject eligibility for the study. Subjects will acknowledge and agree to the possible use of this information for the study by giving informed consent.

All subjects who sign consent will be assigned a unique study number. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The screening period for a particular subject commences at the point at which the subject signs the ICF, and must be completed within 21 days before dosing on Cycle 1 Day 1.

8 STUDY TREATMENT

8.1 CARFILZOMIB

8.1.1 PHYSICAL DESCRIPTION

Carfilzomib is a synthetic small molecule peptide bearing the chemical name (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide.
The molecular formula is $C_{40}H_{57}N_5O_7$ and the molecular weight is 719.91. It specifically functions as an inhibitor of the chymotrypsin-like activity of the 20S proteasome which leads to the accumulation of protein substrates within the cell and induction of apoptosis.

Carfilzomib for Injection will be provided as a lyophilized powder which, when reconstituted, contains a 2 mg/mL isotonic solution of carfilzomib Free Base in 10 mM sodium citrate buffer (pH 3.5) containing 10% (w/v) sulfobutylether-beta-cyclodextrin (SBE beta CD, Captisol).

8.1.2 PACKAGING AND LABELING

Carfilzomib for Injection is supplied as a lyophilized parenteral product in single-use vials packaged in multivial cartons. The lyophilized product is reconstituted with Sterile Water for Injection (SWI), United States Pharmacopeia (USP), to a final carfilzomib concentration of 2.0 mg/mL prior to administration.

Institutional pharmacies will be supplied with open stock vials with appropriate labels. Additional information on carfilzomib may be found in the IB.

8.1.3 STORAGE

Study drugs should be stored in a securely locked area with access limited to appropriate study personnel. Lyophilized Carfilzomib for Injection must be stored at 2°C to 8°C (36°F−46°F) in a refrigerator. Vials must be kept in cartons in order to protect from light until ready for reconstitution.

Once a drug vial is reconstituted and inspected, the clear solution can be stored in a refrigerator (recommended) controlled temperature from 2°C to 8°C (36°F–46°F) for up to

24 hours. Once reconstituted, Carfilzomib for Injection must be used by the time points outlined in Table 3 below.

Table 3 Stability of Reconstituted Carfilzomib for Injection (60 mg/vial)

Storage Conditions of Reconstituted Carfilzomib	Stability (in Hours) per Container		
	Vial	Syringe	IV Bag (D5W)
Refrigerated (2°C to 8°C; 36°F to 46°F)	24	24	24
Room Temperature (15°C to 30°C; 59°F to 86°F)	4	4	4

D5W = 5% Dextrose Injection, USP; IV = intravenous(ly).

8.2 LENALIDOMIDE

Lenalidomide is a thalidomide analogue indicated for the treatment of subjects with multiple myeloma, in combination with dexamethasone, in subjects who have received at least 1 prior therapy. Lenalidomide is also indicated for transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities and those with mantle cell lymphoma whose disease has relapsed or progressed after 2 prior therapies, one of which included bortezomib.

Lenalidomide is a commercially available drug, available for oral administration, depending upon local health authority approvals (Celgene Corporation 2013). Sites are advised to refer to the prescribing information that is specific to the lenalidomide product used.

All precautions and restrictions included in the Prescribing Information (eg, pregnancy testing and contraception) must be observed when dispensing and administering lenalidomide as part of this protocol.

8.3 DEXAMETHASONE

Dexamethasone is a commercially available drug. The description, how supplied, and storage instructions for dexamethasone product 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 they are using.

8.4 STUDY DRUG ACCOUNTABILITY

The sponsor (or designee) and the investigator will maintain records of each shipment of investigational product (IP). Upon receipt of IP, the designated recipient at the study site will inspect the shipment, verify the number and condition of the vials, and prepare an inventory or drug accountability record. The records will document shipment dates, method of shipment, batch numbers, product presentation, quantity of vials contained in the shipment, and dispensation to individual subjects using the subject identification number.

Sites will be required to record and document subject compliance regarding lenalidomide and dexamethasone dosing.

Additional details are provided in the IPIM (Investigational Product Instruction Manual).

9 DOSAGE AND TREATMENT ADMINISTRATION

9.1 TREATMENT REGIMEN

Carfilzomib, lenalidomide, and dexamethasone will be administered in 28-day cycles up to a total of 18 cycles. All cycles will start 28 days (± 2) after the start of the prior cycle. Cycle delays of more than 2 days must be discussed with the sponsor study medical monitor. All carfilzomib infusions and dexamethasone administrations will be within the 2 days of the scheduled administration unless approved by the sponsor study medical monitor.

9.2 INTRAVENOUS HYDRATION

Intravenous hydration will be given before each carfilzomib infusion during Cycle 1. This will consist of 250 to 500 mL normal saline or other appropriate IV fluid. Thereafter, pre-carfilzomib IV hydration should only be administered if the subject's condition and/or risk factors require hydration. The reason for hydration after Cycle 1 will be collected.

9.2.1 STUDY TREATMENT ADMINISTRATION

Weekly carfilzomib/lenalidomide/dexamethasone (KRd) will be given in 28-day cycles (see Table 4):

- Carfilzomib will be administered once weekly IV on Days 1, 8, and 15
- Lenalidomide will be administered once daily by mouth on Days 1–21
- Dexamethasone will be administered once daily by mouth or by IV on Days 1, 8, and 15. Dexamethasone will also be given on Day 22 of Cycles 1–8.

Table 4 Carfilzomib/lenalidomide/dexamethasone Dosing Regimen

		28-day Cycles																								
		Week 1							Week 2							Week 3							Week 4						
	Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
K	CFZ	X[a]							X							X													
R	Len	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
d	Dex	X							X							X							X[b]						

CFZ= carfilzomib, Len = lenalidomide, Dex = dexamethasone.

[a] Cycle 1 Day 1 carfilzomib dose level will be 20 mg/m^2.

[b] Dexamethasone will be administered on Day 22 of Cycles 1-8 only.

9.2.1.1 Carfilzomib

Carfilzomib will be administered onceweekly over 30 minutes (approximate) followed by a flush (see IPIM for details) on Days 1 (± 2), 8 (± 2), and 15 (± 2) of each cycle. The dose can be calculated using the subject's actual body surface area (BSA) at baseline; however, dosing adjustments for subsequent actual BSA determinations is allowed per institutional guidelines. Subjects with a BSA > 2.2 m^2 will receive a dose based upon a 2.2 m^2 BSA. Dose adjustments must be made for weight gains/losses of ≥ 20% of baseline body weight. Mechanical infusion pumps are recommended but gravity-dependent infusions are permitted if the 30-minute infusion duration can be reliably maintained.

Cohorts 1, 2, and 3

Carfilzomib will be administered at 20 mg/m^2 on Cycle 1 Day 1 and given once weekly. Beginning on Cycle 1 Day 8 the carfilzomib dose will be according to the assigned level of 56 mg/m^2 or 70 mg/m^2.

Cohort 4:

Carfilzomib will be administered once-weekly at the following dosing schedule: 20 mg/m^2 on Day 1 of Cycle 1, 56 mg/m^2 on Day 8 and Day 15 of Cycle 1, and 70 mg/m^2 on Day 1 of Cycle 2 and beyond.

Carfilzomib infusion must occur at a facility capable of managing hypersensitivity reactions. Subjects will remain at the investigational site under observation for at least 1 hour following each infusion of carfilzomib in Cycle 1.

9.2.1.2 Lenalidomide

Lenalidomide will be taken once-daily by mouth with or without food. Lenalidomide capsules should be swallowed whole with water. The capsules should not be opened, broken, or chewed. Subjects will be instructed to take the lenalidomide dose at approximately the same time every day. If a planned administration of lenalidomide is missed, it should be taken as soon as possible within the same calendar day with a return to schedule the following day. If a calendar day of dosing is missed, subjects should not make up doses, but should resume the dosing regimen on schedule with the next course. Missed doses must be reported.

For FCBP, nonpregnant state must be documented prior to the first dose of lenalidomide, every week for the first cycle, prior to the start of each subsequent cycle**, and at EOT**.

Subjects must be advised to not donate blood during treatment with lenalidomide and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female subject whose fetus must not be exposed to lenalidomide.

9.2.1.3 Dexamethasone

Dexamethasone will be taken by mouth or by IV infusion once-daily on Days 1 (± 2), 8 (± 2), and 15 (± 2) for all cycles and on Day 22 (± 2) of Cycles 1 through 8. Dexamethasone will be administered at least 30 minutes (but no more than 4 hours) prior to carfilzomib. Subjects receiving dexamethasone IV on Days 1, 8, and 15 may receive dexamethasone orally on Day 22.

9.2.2 CARFILZOMIB AND LENALIDOMIDE DOSE MODIFICATION GUIDELINES

Dose reduction levels of carfilzomib and lenalidomide for toxicity management of individual subjects are provided in Table 5 and Table 6, respectively:

Table 5 Dose Decrements for Carfilzomib

Nominal Dose (mg/m^2)	Reduced Carfilzomib Doses (mg/m^2)		
	Dose -1	Dose -2	Dose -3
20	Discontinue		
56	45	36	Discontinue
70	56	45	36

Table 6 Dose Decrements for Lenalidomide

Nominal Dose (mg)	Reduced Lenalidomide Doses (mg)		
	Dose -1	Dose -2	Dose -3
25	15	10	5
10	5	Discontinue	—

Treatment guidelines for specific hematologic toxicities are outlined in Section 9.2.2.1 and nonhematologic toxicities in Section 9.2.2.2. In addition to dose reductions, administration of carfilzomib and/or lenalidomide may be held temporarily in the event of a treatment-related toxicity at the investigator's discretion. When administration of carfilzomib and/or lenalidomide is held, the reason must be documented in the case report form (CRF), and the medical monitor must be notified within 2 business days of the scheduled dose (Section 9.1).

If either the lenalidomide or carfilzomib dose level is reduced during a given cycle, the reduced dose level will be continued for the next cycle. If the reduced dose level is tolerated for a complete cycle, the subject may, at the investigator's discretion, resume the dose level prior to the reduction at the start of the subsequent cycle.

Carfilzomib or lenalidomide 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 still on protocol treatment as long as carfilzomib is being administered.

9.2.2.1 Hematologic Toxicity

Guidelines for dose modification in the event of thrombocytopenia are summarized in Table 7 and those for neutropenia in Table 8.

Table 7 Treatment Guidelines for Thrombocytopenia

When Platelets:	Recommended Action		
	Lenalidomide	Carfilzomib	
Fall to < 30×10^9/L[a]	• Hold dose, follow CBC weekly • Hold prophylactic anticoagulation until platelets return to ≥ 30×10^9/L[a] • Then resume at 1 dose decrement	If platelets 10–30×10^9/L without evidence of bleeding	• Hold • With resolution restart at previous dose
		If evidence of bleeding or platelets < 10×10^9/L	• Hold • With resolution restart at 1 dose decrement
For each subsequent drop to < 30×10^9/L[a]	• Hold dose, follow CBC weekly • Hold prophylactic anticoagulation until platelets return to ≥ 30×10^9/L[a] • Then resume at additional dose decrement	If platelets 10–30×10^9/L without evidence of bleeding	• Hold • With resolution restart at previous dose
		If evidence of bleeding or platelets < 10×10^9/L	• Hold • With resolution restart at 1 dose decrement

CBC = complete blood count.

[a] For subjects entering the study with myeloma involvement in the bone marrow > 50%, a lower threshold of 20×10^9/L may be applied for lenalidomide dose reductions.

Table 8 Treatment Guidelines for Neutropenia

When ANC:	Recommended Action		
	Lenalidomide	Carfilzomib	
Falls to < 0.75×10^9/L	• Hold dose, administer myeloid growth factor • Follow CBC weekly • Resume at full dose when ANC ≥ 0.75×10^9/L	If ANC 0.5–0.75×10^9/L	• Continue at full dose
		If ANC < 0.5×10^9/L	• Hold dose • Resume at 1 dose decrement when ANC ≥ 0.5×10^9/L
For each subsequent drop to < 0.75×10^9/L	• Hold dose, administer myeloid growth factor • Follow CBC weekly • Resume at 1 dose decrement when ANC ≥ 0.75×10^9/L	If ANC 0.5–0.75×10^9/L	• Continue at full dose
		If ANC < 0.5×10^9/L	• Hold dose • Resume at 1 dose decrement when ANC ≥ 0.5×10^9/L

ANC = absolute neutrophil count; CBC = complete blood count.

9.2.2.2 Nonhematologic Toxicity

Guidelines for dose modification in the event of nonhematologic toxicities are summarized in Table 9.

Table 9 Treatment Guidelines for Nonhematologic Toxicity

Symptom	Recommended Action	
	Lenalidomide	**Carfilzomib**
Blood and Lymphatic System		
Thrombotic microangiopathy (TMA) Fever, microangiopathic hemolytic anemia, thrombocytopenia, renal failure, neurologic changes	If the diagnosis is suspected, stop lenalidomide and carfilzomib and manage per standard of care including plasma exchange as clinically appropriate. If TMA is confirmed and related to lenalidomide or carfilzomib, permanently discontinue. If the diagnosis of TMA is excluded, lenalidomide and carfilzomib dosing may be resumed at full dose if clinically appropriate.	
Cardiac		
Congestive heart failure	Full dose	Any subject with symptoms of congestive heart failure, whether or not drug related, must have the dose held until resolution or return to baseline, after which treatment may continue at a reduced dose, or the subject may be permanently discontinued. If no resolution after 4 weeks, the subject will be withdrawn from all study treatment.
Hypertensive crisis Sustained or persistent SBP ≥ 180 mm Hg or DBP ≥ 110 mm Hg	Full dose	Hold carfilzomib until resolution to baseline, then resume at 1 dose decrement
LVEF Reduction < 40% or < 55% if the drop is greater than 20% from baseline	Full dose	Hold carfilzomib until LVEF returns to ≥ 40% or, if held due to a drop to < 55%, to within 15% of baseline. Resume at 1 dose decrement.
Infections and Infestations		
Infection Grade 3 or 4	Hold both lenalidomide and carfilzomib until systemic treatment for infection is complete. If ANC > 1,000/μL, resume both drugs at full dose. If ANC < 1,000/μL, follow hematologic toxicities dosage guidelines.	
Hepatic Dysfunction and Related Investigations		
Mild liver dysfunction, defined as 2 consecutive values, at least 28 days apart, of: **(1) total bilirubin (> 33% direct) > 1x ULN to < 1.5x ULN** **OR** **(2) an elevation of AST and/or ALT with normal bilirubin**	**Full dose.**	**25% dose reduction.** **Dose may be re-escalated if liver function tests return to normal and drug-induced hepatotoxicity is excluded.**

Page 1 of 3

Footnotes defined on last page of table

Table 9 Treatment Guidelines for Nonhematologic Toxicity (cont'd)

Symptom	Recommended Action	
	Lenalidomide	**Carfilzomib**
Hepatic Dysfunction and Related Investigations (cont'd)		
Moderate liver dysfunction, defined as 2 consecutive values, at least 28 days apart, of total bilirubin (> 33% direct) > 1.5x ULN to < 3x ULN	**Hold lenalidomide until resolution to baseline, then resume at full dose.**	**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 lenalidomide until resolution to baseline, then resume at full dose.**	**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 lenalidomide until resolution to baseline, then resume at full dose.**	**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.**
Renal Dysfunction		
CrCl[a] ≥ 30 and < 50 mL/min	Reduce dose to 10 mg once daily.	Full dose
CrCl[a] ≥ 15 and < 30 mL/min (NCI-CTCAE Grade 3)	Hold dose. If CrCl recovers resume dose at 1 dose decrement. If significant CrCl reduction reappears then reduce dose to 15 mg every 48 hours. Further dose modification will be based on individual subject treatment tolerance.	Full dose
CrCl[a] < 15 mL/min (NCI-CTCAE Grade 4)	Hold dose. If CrCl recovers to baseline, resume dose at 1 dose decrement. If significant CrCl reduction reappears reduce dose to 15 mg every 48 hours. If dialysis required, reduce dose to 5 mg once daily (administer the lenalidomide after dialysis on dialysis days). Further dose modification will be based on individual subject treatment tolerance.	Hold dose. When CrCl returns to ≥ 15 mL/ minute, resume same dose. If dialysis required, contact the medical monitor.

Page 2 of 3

Footnotes defined on last page of table

Table 9 Treatment Guidelines for Nonhematologic Toxicity (cont'd)

Symptom	Recommended Action	
	Lenalidomide	**Carfilzomib**
Metabolism		
Tumor Lysis Syndrome 3 or more of the following: • increase in creatinine of ≥ 50% • increase in uric acid of ≥ 50% • increase in phosphate of ≥ 50% • increase in potassium of ≥ 30% • decrease in calcium, OR increase in LDH of ≥ 2-fold from baseline	Hold both lenalidomide and carfilzomib until all abnormalities in serum chemistries have resolved; resume at full dose.	
Nervous System Disorders		
Neuropathy Treatment-emergent painful grade 2, or grade 3	Full dose	Hold carfilzomib until resolution to ≤ grade 2 without pain, then resume at 1 dose decrement
Neuropathy Grade 4	Discontinue	Discontinue
Posterior Reversible Encephalopathy Syndrome (PRES) headaches, altered mental status, seizures, visual loss and hypertension	If PRES is suspected, hold lenalidomide and carfilzomib. Consider neuroradiographic imaging, specifically MRI, to evaluate onset of visual or neurological symptoms suggestive of PRES. If the diagnosis of PRES is excluded lenalidomide and carfilzomib dosing may resume at the same dose, if clinically appropriate. If condition recurs, permanently discontinue carfilzomib.	
Respiratory		
Dyspnea Grade 2, 3 or 4	Full dose	Hold carfilzomib until resolution to baseline, then resume at 1 dose decrement
Pulmonary hypertension: (≥Grade 3)	Full dose	Hold carfilzomib until resolution to baseline, then resume at 1 dose decrement
Pulmonary toxicity Interstitial lung disease, acute respiratory failure, ARDS (≥Grade 3)	Hold lenalidomide until resolution to baseline then resume full dose	Hold carfilzomib until resolution to baseline, then resume at 1 dose decrement
Other Symptoms Not Listed Above		
Any other drug-related nonhematologic toxicity ≥ Grade 3[b]	For lenalidomide attribution, hold dose. Resume at 1 dose decrement when toxicity has resolved to Grade 1 or less or to baseline grade.	For carfilzomib attribution, hold dose. Resume at 1 dose decrement when toxicity has resolved to Grade 1 or less or to baseline[c] grade.

Page 3 of 3

ALT = alanine aminotransferase; ANC = absolute neutrophil count; ARDS = acute respiratory distress syndrome; AST = aspartate aminotransferase; CrCl = creatinine clearance; DBP = diastolic blood pressure; KRd = carfilzomib/lenalidomide/dexamethasone; LDH = lactate dehydrogenase; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; PRES = posterior reversible encephalopathy syndrome; SBP = systolic blood pressure; TMA = Thrombotic microangiopathy; ULN = upper limit of normal.

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

[b] In the event of a possible drug-related nonhematologic toxicity, the investigator should, to the best of his/her ability, assess its relationship to lenalidomide, carfilzomib, dexamethasone, or the combination of KRd to the extent possible. If both carfilzomib and lenalidomide are considered likely to be involved, then recommended actions for both should be instituted. For nonhematologic toxicity likely due to dexamethasone, refer to Table 11 for treatment guidelines for dexamethasone-related toxicity.

[c] For grade 3 hypertension, baseline refers to an average SBP < 140 mmHg or DPB < 90 mmHg on appropriate antihypertensive therapy.

9.2.2.3 Conditions Not Requiring Dose Reduction

The following conditions are exceptions to the above guidelines. Carfilzomib, lenalidomide, and dexamethasone do not need to be held in the following cases:

- Grade 3 nausea, vomiting, or diarrhea (unless persisting more than 3 days with adequate treatment of antiemetics or antidiarrheal agents)
- Grade 3 dexamethasone-related hyperglycemia
- Grade 3 fatigue (unless persisting for > 14 days)
- Alopecia

9.2.3 DEXAMETHASONE DOSE MODIFICATION GUIDELINES

Two dose reduction levels are defined for dexamethasone, as illustrated in Table 10 below:

Table 10 Dose Decrements for Dexamethasone

Nominal Dose (mg)	Reduced Dexamethasone Doses (mg)	
	Dose -1	Dose -2
40	20	12

Dexamethasone will be permanently discontinued after 2 dose reductions in the event of additional dexamethasone-related toxicities. At the investigator's discretion, dexamethasone may be tapered prior to complete discontinuation according to institutional practice. The subject may continue on treatment with the other protocol-specified drug(s). Guidelines for dexamethasone dose modifications are summarized in Table 11.

Table 11 Treatment Guidelines for Dexamethasone-related Toxicity

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

Page 1 of 2

Table 11 Treatment Guidelines for Dexamethasone-related Toxicity (cont'd)

Dexamethasone-related Toxicities, All Days and Cycles		
Symptom	**Findings**	**Recommended Action**
Metabolism and Nutrition Disorders	Hyperglycemia ≥ Grade 3 (fasting glucose > 250 mg /dL)	• Hold dexamethasone until glucose is ≤ Grade 2 (< 250 mg/dL) and treat with insulin or other hypoglycemic agents as needed. • 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.

Page 2 of 2

9.3 CONCOMITANT MEDICATIONS

A concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. All concomitant medications from signing of the informed consent until 30 days after the subject's last dose of study drug must be recorded on the electronic case report form (eCRF). Blood or blood products are not considered concomitant medications and must be recorded on the appropriate eCRF.

9.3.1 REQUIRED CONCOMITANT MEDICATIONS

Required prophylactic medications should be initiated at least 24 hours prior to the first administration of carfilzomib. Contraception must be in place at least 4 weeks prior to the first administration of carfilzomib and/or lenalidomide.

9.3.1.1 Antiviral Prophylaxis

Valacyclovir (or equivalent antiviral) is a required concomitant medication. Valacyclovir 500 mg orally, daily (or equivalent antiviral) should continue for the duration of treatment. Additional prophylaxis is at the investigator's discretion.

9.3.1.2 Anticoagulant Prophylaxis

Aspirin (or other anticoagulant or antiplatelet medication such as clopidogrel bisulfate, low-molecular-weight heparin, or warfarin), is a required concomitant medication while taking lenalidomide. In subjects with a prior history of deep vein thrombosis, low-molecular-weight heparin or therapeutic doses of warfarin (for a target international normalized ratio of 2–3) are required. Enteric-coated aspirin once-daily by mouth at the standard prophylactic dose should be administered for the duration of treatment with lenalidomide. Subjects with known high thrombotic risk, eg, prior deep vein thrombosis, should receive full anticoagulation at the investigator's discretion. Other antiplatelet or anticoagulation medications may be used in cases of intolerance to aspirin upon consultation with the sponsor study medical monitor.

9.3.1.3 Tumor Lysis Syndrome Prophylaxis

Allopurinol (or other approved uric acid-lowering agent) in subjects at high risk for tumor lysis syndrome (TLS) due to high tumor burden may be prescribed at the investigator's discretion. Allopurinol dose should be prescribed according to the package insert.

Subjects should be well hydrated (Section 9.2) to reduce the risk of TLS and decline in renal function; refer to the current Carfilzomib IB for safety guidance regarding TLS.

9.3.1.4 Contraception

Females of childbearing potential (FCBP) must:

- Avoid pregnancy for at least 4 weeks before beginning lenalidomide
- Have 2 negative pregnancy tests prior to starting treatment, the first, a serum pregnancy test within 10 to 14 days and the second, a urine or serum pregnancy test within 24 hours before dosing on Cycle 1 Day 1
- Pregnancy tests weekly for the first month of treatment
- Pregnancy tests monthly during treatment after the first month or semimonthly for women of childbearing potential with irregular menstruation
- Agree to abstain from heterosexual sexual intercourse or to use 2 methods of highly effective contraception beginning 4 weeks prior to initiating treatment with lenalidomide, during therapy, during dose interruptions and for 1 month following last dose of drug (more frequent pregnancy tests may be conducted if required per local regulations)

An FCBP is defined as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy, or 2) has not been naturally postmenopausal for at least 24 consecutive months (ie, no menses at any time in the preceding 24 consecutive months). Amenorrhea following cancer therapy does not rule out childbearing potential.

Male subjects whose partners are FCBP must use 1 highly effective method of birth control plus 1 additional effective method of birth control (contraception) at the SAME TIME during treatment and for 3 months following the last dose of drug, unless they have undergone a medically-confirmed successful vasectomy. Male subjects must not donate sperm while taking study drugs and for 90 days after the last dose of study drugs.

Highly effective methods of contraception include:

- Intrauterine device (IUD)
- Hormonal therapy (birth control pills, injections, implants)
- Tubal ligation
- Vasectomy, with medical confirmation of success

Additional effective methods include:

- Latex condom
- Diaphragm
- Cervical Cap

9.3.2 OPTIONAL AND ALLOWED CONCOMITANT MEDICATIONS

Mycostatin or oral fluconazole to prevent oral thrush is optional and may be given at the investigator's discretion.

Subjects may receive antiemetics and antidiarrheal agents as necessary. Myeloid growth factors may be used if neutropenia occurs but should not be given prophylactically. Subjects may receive RBC transfusions, erythropoietic stimulating agents, or platelet transfusions if clinically indicated in accordance with institutional guidelines.

Palliative radiation for pain management is permitted with the written approval of the study medical monitor.

Bisphosphonates are permitted as indicated and in accordance with institutional guidelines.

9.3.3 EXCLUDED CONCOMITANT MEDICATIONS

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 (≥ 14 days) corticosteroids for nonmalignant conditions (eg, asthma, inflammatory bowel disease) equivalent to a dexamethasone dose > 4.0 mg/day or prednisone > 20 mg/day are not permitted (other than as indicated in this protocol). Higher steroid doses given short term for exacerbations of nonmalignant conditions (eg, asthma flare) are permitted with the approval

of the sponsor study medical monitor. Investigational agents are not to be used during the study.

Subjects requiring the use of excluded concomitant medications or procedures will be withdrawn from study treatment.

10 STUDY PROCEDURES

All protocol-required tests and observations, along with their chronology, are outlined in the Schedule of Assessments (Appendix A). On-study tests and observations are summarized below.

10.1 STUDY-SPECIFIC PROCEDURES

10.1.1 BASELINE PROCEDURES

To be completed prior to initiation of therapy:

- Skeletal survey (all subjects) (Section 10.1.4.3)
- Beta-2 microglobulin (Section 10.1.4.1)
- Plasmacytoma evaluation (if clinically indicated) (Section 10.1.4.3)
- Bone marrow aspirate and biopsy (all subjects, Section 10.1.4.2)

10.1.2 VITAL SIGNS

Vital signs will include pulse, blood pressure, respiratory rate, and temperature and will be assessed at Screening, prior to and after administration of carfilzomib on treatment days, and at EOT. Resting blood pressure readings will be taken before administration of carfilzomib on Days 1, 8, and 15 of each cycle. Pre-carfilzomib blood pressure may be assessed either before or after dexamethasone administration, and for a given patient should be done consistently before dexamethasone, or consistently after dexamethasone. The time of pre-carfilzomib dosing blood pressure assessment will be recorded. The time of Day 1, 8, and 15 dexamethasone administration will also be recorded (per report by patient if self-administered). During Cycles 1 through 6, 12, and 18, pre-carfilzomib blood pressure readings will be taken in triplicate. In addition to the predosing blood pressure assessments, postdosing resting blood pressure readings will be taken in triplicate on Days 1, 8, and 15 of

Cycles 1 through 6, 12, and 18. Postdosing blood pressure will be assessed from 10 to 60 minutes after completion of carfilzomib administration.

The subject should be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If unable to be in a supine position, the subject should be in the most recumbent position possible. The position selected for a subject should be the same that is uses throughout the study and documented on the vital sign CRF. The arm should be supported at the level of the heart. Every effort should be made to use the same instrument in measuring a subject's blood pressure throughout the study. When blood pressure measurements are taken in triplicate, readings should be taken a minute or more apart.

10.1.3 PHYSICAL EXAMINATION

A physical examination will be performed during Screening, on Day 1 of Cycles 2 through 18, and at the EOT. Physical exam will include:

- ECOG PS
- Examination of cardiovascular and respiratory systems
- Weight
- BSA (at Screening and on Day 1 of Cycles 2–18 only)
- Height (at Screening only)

Abnormal physical examination findings during Screening will be captured as medical history. Abnormal physical examination findings observed after signing of the informed consent will be recorded as AEs.

10.1.4 DISEASE ASSESSMENTS

10.1.4.1 Laboratory Evaluations of Disease Status

Laboratory assessments of disease status will be performed at Screening (within 21 days before dosing on Cycle 1 Day 1); at Day 1 (± 3 days) of Cycle 2 and each cycle thereafter; at the EOT; and every 8 weeks (every 56 ± 4 days) during Active Follow-up.

Disease assessments at Screening (within 21 days before dosing on Cycle 1 Day 1) or baseline, include the following:

- Serum protein electrophoresis (SPEP) with immunofixation
- Urine protein electrophoresis (UPEP; 24-hour assessment, no substitute method is acceptable) with immunofixation
- SFLC
- Quantitative immunoglobulins
- Beta-2 microglobulin

Disease assessments at Day 1 (± 3 days) of Cycle 2 and each cycle thereafter, at the EOT, and during Active Follow-up include the following:

- Serum protein electrophoresis (SPEP) with immunofixation
- UPEP with immunofixation
- SFLC
- Quantitative immunoglobulins

SPEP with immunofixation, UPEP with immunofixation, beta-2 microglobulin, SFLC, and quantitative immunoglobulin analyses will be performed at the local laboratory.

10.1.4.2 Bone Marrow Aspirate Assessments of Disease Status

A bone marrow aspirate is required at baseline, on Cycle 8 Day 1 (± 3 days), and to confirm a CR or sCR. An optional bone marrow aspirate may also be done upon progression of disease in subjects who consent to optional genomic biomarker studies. Details of aspirate sampling and shipment are described in the central laboratory manual.

At baseline, bone marrow aspirate will be evaluated by the local pathology lab to determine percent plasma cell involvement. For subjects whose aspirate is unobtainable, a bone marrow core biopsy should be obtained for quantification of percent plasma cell involvement. Bone marrow aspirate or biopsy samples (taken as part of standard of care) within 45 days prior to Cycle 1 Day 1 may be used to quantify percent plasma cell involvement.

Baseline bone marrow aspirate samples are also sent to the central laboratories for fluorescent in situ hybridization (FISH; Section 10.2.3) and for Next Generation Sequencing

(NGS) to allow MRD analysis (Section 10.2.4); also referred to herein as "MRD"). Subjects who consent to optional genomic biomarker evaluation will have the baseline genomic biomarker analyses performed on aspirate samples remaining after central FISH testing of baseline aspirate.

Bone marrow aspirate will be collected for central MRD analysis on Cycle 8 Day 1 for all subjects regardless of response status (± 2 days; see Section 10.2.4).

Subjects with laboratory evidence of CR require confirmatory bone marrow aspirate evaluation, by the central study laboratory, for MRD (Section 10.2.4), in addition to local bone marrow assessment for evaluation of CR per IMWG-URC (Appendix C).

Consenting subjects with PD may have a bone marrow aspirate done for optional genomic biomarker studies (Section 10.2.5).

In instances where sample availability is limited, samples for disease assessments take priority over those for correlative testing as specified in the laboratory manual.

10.1.4.3 Imaging Assessments of Disease Status

All subjects will have a baseline skeletal survey. Repeat skeletal survey is recommended as clinically indicated.

Subjects with physical exam findings suggestive of plasmacytoma should undergo baseline imaging with computed tomography [CT] scan, magnetic resonance imaging [MRI], or positron emission tomography/CT [PET/CT].

Repeat plasmacytoma imaging is required only to confirm a response of PR or better, to confirm PD, or if clinically indicated. The same imaging technique should be employed for each measurement.

For study purposes, a plasmacytoma is considered measurable if the longest diameter is at least 1 cm and the product of the greatest orthogonal cross-diameters is at least 1 cm^2.

10.1.5 MYELOMA RESPONSE ASSESSMENT

Response will be determined by the investigator based on the disease assessments described above and the IMWG-URC (see definitions in Appendix C). Myeloma response laboratory studies will be drawn at the beginning of each cycle before treatment. The following confirmatory assessments are required for all response categories (stringent complete response [sCR], CR, VGPR, and PR) and progressive disease:

- All laboratory-based progressive disease and all responses require 2 consecutive assessments made at any time before initiation of any new (ie, off protocol) therapy. Confirmatory lab samples should be separated by at least 1 calendar day
- Progressive disease by nonlaboratory-based assessment (ie, plasmacytoma or skeletal lesion) does not require confirmatory report
- All response categories also require no evidence of progression including new bone lesions, if radiographic studies are performed
- Confirmation of CR or sCR requires local pathology review of a bone marrow biopsy or aspirate (a repeat confirmatory bone marrow sample is not required)
- Extramedullary plasmacytoma evaluation is required to confirm PR, CR, or sCR (if present at baseline; Rajkumar, 2011)

10.1.6 CLINICAL LABORATORY TESTS

Clinical laboratory assessments will include the following:

- Hematology: hemoglobin, hematocrit, white blood cell (WBC) with complete differential (total neutrophils, lymphocytes, monocytes, eosinophils, basophils), RBCs, platelet count
- Full serum chemistry panel: sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, calcium, magnesium, phosphate, AST, ALT, total protein, albumin, alkaline phosphatase, total bilirubin, uric acid, and lactate dehydrogenase (LDH)
- Abbreviated chemistry panel: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose
- Coagulation tests: prothrombin time, activated partial thromboplastin time, and international normalized ratio

Hematology and serum chemistry (full or abbreviated) will be performed at Screening, on Days 1, 8, and 15 of each cycle, and at EOT. On Days 8 and 15 of each cycle, from Cycle 2 onwards, an abbreviated serum chemistry panel may be performed. Coagulation will be performed at baseline and at EOT. For screening laboratory samples, historical panel may be used if within 21 days prior to dosing on Cycle 1 Day 1. Thereafter, hematology samples

may be obtained anytime within the 24 hours prior to the carfilzomib administration, and full or abbreviated chemistry panels may be performed up to 72 hours prior to carfilzomib administration.

10.1.7 ELECTROCARDIOGRAM

Twelve-lead electrocardiograms (ECGs) including corrected QT interval (QTc; representing the corrected duration of ventricular electrical activity) will be performed locally. These will be required in all subjects at Screening only. Additional ECG assessment is only required if clinically indicated

10.1.8 ECHOCARDIOGRAM

A 2-D transthoracic ECHO to assess LVEF will be performed in all subjects at Screening and at EOT. During the Dose-evaluation Component, an ECHO is also required at Cycle 2 Day 15, ± 7 days. Additional ECHO assessment is only required for subjects who develop clinically significant congestive heart failure.

If transthoracic ECHO is not available, multigated acquisition (MUGA) will be acceptable for LVEF evaluation.

10.1.9 SUBJECT CONVENIENCE AND SATISFACTION

Subject convenience and satisfaction will be assessed in all subjects by questionnaire at Cycle 3 Day 1 and Cycle 18 Day 1 (see Appendix D). The questionnaire should be administered prior to treatment with carfilzomib.

10.2 CORRELATIVE STUDIES

It is recommended that samples for correlative studies be collected only after screening laboratories confirm study eligibility for the subject.

10.2.1 PHARMACOKINETIC MEASUREMENTS

For both the Dose-evaluation and the Dose-expansion Components, blood samples will be collected from all subjects **on Day 8 of Cycle 1** for determination of plasma concentrations of carfilzomib.

Blood samples will be collected at the following time points:

- Predose (within 5 minutes before start of carfilzomib infusion)
- 15 minutes (± 5 minutes) after the start of carfilzomib infusion
- Immediately prior to (within 2 minutes before) the end of carfilzomib infusion
- 15 minutes (± 5 minutes) after the end of carfilzomib infusion
- 60 minutes (± 5 minutes) after the end of carfilzomib infusion

The actual time of PK sample collection will be recorded. Samples should be collected within a ± 5 minute time window around the nominal time points (except for the time point immediately prior to the end of carfilzomib infusion in which the PK collection needs to occur prior to end of infusion). Collecting PK samples at times other than nominal time points will not constitute a protocol deviation. These samples will be assessed at a central laboratory. Directions for collection, processing, and shipping of PK blood samples are provided in the central laboratory manual.

10.2.2 PHARMACODYNAMIC MEASUREMENTS

For pharmacodynamic measurements, whole blood will be collected from the subjects on the following schedule:

For the Dose-evaluation component Cohorts 1 and 2**, and the first 8 subjects enrolled into Dose-expansion Arm 3,** whole blood will be collected**. O**n Days 1 and 8 of Cycle 1**, whole blood will be collected pre-carfilzomib dose and post-carfilzomib dose**. On Days 9 and 11 of Cycle 1, when carfilzomib is not administered, one PDn sample will be collected at approximately the same time as when the pre-infusion sample was taken on Day 8.

Directions for collection, processing, and shipping of PDn samples are provided in the central laboratory manual.

10.2.3 FLUORESCENT IN SITU HYBRIDIZATION (FISH) TESTING

Bone marrow aspirate from all subjects will be evaluated centrally, at baseline, by FISH. Directions for collection, processing, and shipping of FISH samples are provided in the central laboratory manual.

10.2.4 MINIMAL RESIDUAL DISEASE

Analysis of MRD status will be performed by the central laboratory on all subjects by 2 methods:

Flow cytometry (FC) of cell surface markers and

NGS of DNA and/or RNA from the Ig locus.

The MRD analysis by FC will be performed on bone marrow aspirate samples collected at 2 time points: Cycle 8 Day 1 and upon achieving a CR or sCR. The MRD analysis by NGS will be performed on blood and bone marrow aspirate samples collected at 3 time points: baseline, Cycle 8 Day 1, and upon achieving a CR or sCR.

Directions for collection, processing, and shipping of MRD samples are provided in the central laboratory manual.

10.2.5 OPTIONAL GENOMIC BIOMARKERS

Analysis of genetics, gene expression, and cell surface biomarkers that may be predictive of response and resistance to treatment with proteasome inhibitors will be performed. Exploratory studies will be conducted on all subjects who consent to optional genomic biomarker analysis. These analyses will be performed on bone marrow aspirate at baseline (the remaining portion of the bone marrow aspirate sample left after the amount required for FISH analysis has been collected at baseline), as well as a sample of blood and saliva also collected at baseline. At disease progression, an additional bone marrow sample for biomarker analysis may be collected from all subjects who consent.

Whole genome sequencing (WGS), whole exome sequencing (WES), whole transcriptome sequencing (RNA-Seq), and/or other methods of nucleic acid and protein quantification will be conducted on isolated tumor (CD138+) cells from bone marrow samples taken at baseline and disease progression. In addition, WGS or WES will be performed on a normal tissue sample (eg, CD3+ T cells isolated from peripheral blood or saliva) to distinguish germ line mutations from somatic mutations in tumor cell samples.

Directions for collection, processing, and shipping of optional genomic biomarker samples are provided in the central laboratory manual.

11 STUDY DISCONTINUATION

11.1 WITHDRAWAL OF SUBJECTS FROM TREATMENT

Subjects may withdraw from study treatment at any time. Reasons for discontinuation include:

- Adverse event
- Allogeneic stem cell transplant
- Pregnancy
- Death
- Lost to follow-up
- Noncompliance
- Withdrawal by subject
- Study terminated by the sponsor
- Physician decision
- Progression of disease
- Other

The primary reason for treatment discontinuation will be documented in the eCRF. Investigators will be instructed to interview subjects to obtain the most accurate reason for study treatment discontinuation while respecting the privacy of the subject.

If the reason for treatment discontinuation is the occurrence of an AE, the subject will be followed by the investigator until such event(s) resolve, stabilize, and, according to the investigator's judgment, there is no need of further follow-up.

Treatment discontinuation due to progression should be recorded as "Disease Progression." If the Disease Progression meets any of the serious criteria, as outlined in Section 12.2.1.4, then it should also be recorded as a serious adverse event (SAE) in the AE eCRF.

Sponsor or designee must be notified within 24 hours if a subject is withdrawn from treatment.

All subjects who withdraw or are withdrawn from study treatment will be encouraged to complete all relevant safety assessments and continue in the Active Follow-up period.

11.2 WITHDRAWAL OF SUBJECTS FROM STUDY

Reasons for complete withdrawal from the study (treatment and all follow-up) before documentation of subject death include:

- Withdrawal of consent by subject for all study procedures
- Lost to follow-up
- Sponsor decision

The reason for complete withdrawal from study will be documented in the eCRF.

11.3 STUDY TERMINATION

The sponsor has the right to terminate this study or a study site from participating in a study at any time. Reasons for study termination may include:

- The incidence or severity of AEs in this or other carfilzomib studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Data recording is inaccurate or incomplete
- Investigator does not adhere to the protocol or applicable regulatory requirements in conducting the study

12 SAFETY DATA COLLECTION, RECORDING, AND REPORTING

12.1 DEFINITION OF SAFETY EVENTS

12.1.1 ADVERSE EVENTS

An AE 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 AEs observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of AEs 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 AE.

For situations when an AE or SAE 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 AE.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an AE. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an AE, refer to Section 11 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

12.1.2 SERIOUS ADVERSE EVENTS

A serious adverse event is defined as an AE 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
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An AE 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 SAE 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.

12.2 SAFETY EVENT REPORTING PROCEDURES

12.2.1 ADVERSE EVENTS

12.2.1.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

The investigator is responsible for ensuring that all AEs observed by the investigator or reported by the subject that occur after signing the informed consent form through 30 days after receiving the last dose of study drugs are reported using the Event CRF.

If initiation of new anticancer therapy occurs within 30 days following the last dose of study drugs, the date of new anticancer therapy will be recorded on the appropriate eCRF. In addition, the investigator should report any AEs that may occur after this time period which are assessed to have a reasonable possibility of being associated with study drug.

For subjects who complete the EOT visit less than 30 days following the last dose of study drug, a follow-up of ongoing AEs should be attempted by telephone and documented in the

subject's source file. AEs continuing at 30 days after the last dose of study treatment should have a comment in the source file by the investigator that the event has stabilized or is not expected to improve.

The investigator must assign the following AE attributes:

- AE 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 carfilzomib and/or other protocol-required therapies
- Action taken.

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

The investigator must assess whether the AE is possibly related to carfilzomib and/or other protocol-required therapies. 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 carfilzomib and/or other protocol-required therapies?

In the event of a possible drug-related AE, the investigator should to the best of his/her ability assess its relationship to each of the study drugs: carfilzomib, lenalidomide, and/or dexamethasone.

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

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

12.2.1.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all SAEs observed by the investigator or reported by the subject that occur after through 30 days after the last day of the study drug are recorded in the subject's medical record and are submitted to Amgen. All SAEs 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 SAE, the information is to be reported to Amgen via an electronic SAE Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix G for a sample of the SAE Worksheet /electronic SAE Contingency Report Form. For EDC studies where the first notification of a SAE is reported to Amgen via the electronic SAE Contingency Report Form, the data must be entered into the EDC system when the system is again available.

The investigator must assess whether the SAE is possibly related to carfilzomib and/or other protocol-required therapies. 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 carfilzomib and/or other protocol-required therapies? 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 SAEs until stabilization or reversibility.

New information relating to a previously reported SAE must be submitted to Amgen. All new information for SAEs 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 SAE must be consistent with that recorded on the Event CRF.

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

Amgen will report SAEs and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) in compliance with all reporting requirements according to local regulations and good clinical practice.

The investigator is to notify the appropriate IRB/IEC of SAEs occurring at the site and other AE reports received from Amgen, in accordance with local regulatory requirements and procedures.

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

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

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

12.2.1.4 Serious Adverse Events That are not to be Reported by the Sponsors to Regulatory Agencies in an Expedited Manner

Disease progression will be documented in an eCRF intended to capture PD information and will be analyzed as a study endpoint. Signs and symptoms related to disease progression (eg, pathologic fracture in a subject with progressive multiple myeloma) should be reported in the appropriate CRF as an AE or as an SAE (if the event in question meets the criteria for seriousness). Verbatim terms such as "disease progression," "progressive disease," etc. should not be reported as AEs or SAEs unless the investigator considers the progression to be atypical, accelerated, or caused by the study drug. Similarly deaths occurring as a result of disease progression should be reported on the eCRF intended to capture death information and should not be reported as SAEs.

12.3 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 in female subjects 30 days after the last study drug administration, and in a male subject's spouse or partner while enrolled in this clinical study through 90 days following the last study drug administration.

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix H) 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, the investigator should attempt to obtain information regarding the birth outcome and health of the infant. Newborns should be followed for a minimum of 12 weeks.

If the outcome of the pregnancy meets a criterion for immediate classification as a SAE (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 SAE.

If a female breastfeeds while taking protocol-required therapies report the lactation case to Amgen as specified below.

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix H).

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, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

13 STATISTICS

The final analysis will be based upon subject data collected through discontinuation of the final subject from study participation or until study discontinuation by the sponsor, whichever occurs first. All efficacy and safety analyses will be based upon the Safety Population, defined as subjects receiving at least 1 dose of study drug. All summaries will be presented by the assigned dose cohort level, by RRMM and NDMM population, as well as for the overall Safety Population. In addition, response data (ORR, complete response rate [CRR], PFS, DOR) may also be analyzed based on the Response-evaluable Population, defined as subjects who are included in the Safety Population, have a baseline disease assessment and at least 1 postbaseline disease assessment, or dropped out due to AE prior to the first postbaseline disease assessment.

13.1 STUDY ENDPOINTS

13.1.1 PRIMARY ENDPOINTS

Safety and tolerability of carfilzomib administered once weekly in combination with lenalidomide and dexamethasone, as defined by the type, incidence, and severity of AE, and changes from baseline in key laboratory analyses, including immunoglobulin levels, vital signs, and the extent and duration of exposure to study drugs.

13.1.2 SECONDARY ENDPOINTS

The secondary endpoints of this study are:

- Pharmacokinetics (PK) of carfilzomib
- Overall Response Rate (ORR), defined as the proportion of subjects who achieve a best overall response of sCR, CR, VGPR, or PR in accordance with IMWG-URC
- Complete Response Rate (CRR), defined as the proportion of subjects who achieve a best overall response of either sCR or CR in accordance with IMWG-URC
- Progression-free survival (PFS), defined as the time from the first day of study treatment to the earlier of disease progression or death due to any cause

- Duration of Response (DOR), defined as the time from the first evidence of confirmed PR or better to disease progression or death due to any cause among subjects who respond

13.1.3 OTHER ENDPOINTS

The exploratory endpoints include:

- Pharmacodynamics (PDn) of proteasome inhibition by carfilzomib measured in whole blood
- MRD[-] rate, defined as the proportion of subjects who are negative for MRD at Cycle 8 Day 1. Point estimates for MRD[-] rate along with exact 2-sided 95% confidence intervals will be calculated for both MRD assessment methods.
- Subject convenience and satisfaction with the carfilzomib dosing schedule.
- WGS, WES, whole transcriptome sequencing, and other nucleic acid and protein quantification data and immunoglobulin levels in tumor cells

13.2 ANALYSIS OF THE CONDUCT OF THE STUDY

Enrollment, major protocol violations, study drug administration, and discontinuations from the study will be summarized by the assigned dose cohort and for all subjects. Demographic and baseline characteristics, such as age, sex, race, weight, number of prior therapies, and baseline ECOG PS (Appendix B), will be summarized using means, standard deviations, medians, and ranges for continuous variables, and proportions for categorical variables.

13.3 INDEPENDENT REVIEW COMMITTEE

All efficacy interpretation will be based on investigator assessment. An independent review committee will not be employed for this study.

13.4 DATA MONITORING COMMITTEE

A data monitoring committee will not be employed for this study.

13.5 STATISTICAL METHODS

13.5.1 EFFICACY ANALYSES

The primary analysis of efficacy will be based on the Safety Population. Additionally, response data (ORR, CRR, PFS, and DOR) may also be analyzed based on the Response-evaluable Population. Response assessment data, PFS, and DOR will be listed for

all subjects by dose cohort level. Point estimates for ORR and CRR along with their exact 2-sided 95% confidence intervals will be calculated. Summary statistics for DOR and PFS will be calculated using the Kaplan-Meier method. The follow-up time for PFS will be summarized by reverse Kaplan-Meier method (Schemper 1996).

13.5.2 SAFETY ANALYSIS

Safety will be assessed through summaries of AEs, changes from baseline in laboratory test results, including immunoglobulin levels, and vital signs, and the extent and duration of exposure to study drugs. All treatment-emergent AEs will be summarized by MedDRA preferred term, NCI-CTCAE (version 4.03) toxicity grade, and investigator assessment of causality. In addition, all SAEs and DLTs, including deaths, will be listed separately. Extent of exposure to the study treatment will be summarized using descriptive statistics. Laboratory parameters will be summarized using descriptive statistics and by postdose shifts relative to baseline. Vital signs will also be summarized descriptively for each scheduled protocol time point.

13.5.3 PHARMACOKINETIC ANALYSES

Actual collection times will be recorded and used in the analysis. Individual and mean plasma concentration versus time data will be tabulated and plotted by dose level. The PK parameter estimates for carfilzomib will be summarized, including total plasma exposure (expressed as area under the curve [AUC]), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), total plasma clearance, and plasma terminal half-life (as appropriate for data collected). Estimates for these parameters will be tabulated and summarized (ie, mean, standard deviation).

Unless otherwise specified, the PK parameter will be estimated based on noncompartmental methods. These estimates will be summarized descriptively by dose cohort and population. Exploratory analyses may be performed to evaluate the relationship between the estimated PK parameters and selected safety, biomarker, or clinical effect endpoints.

In addition to noncompartmental PK analysis, the population modeling program may be used to fit a nonlinear mixed effects model to estimate PK parameters including clearance and

volume of distribution, the inter- and intra-subject variability and the population variability in the parameter estimates. The PK concentrations obtained from subjects in the Dose-expansion portion, along with results from the Dose-evaluation Component of the study and other carfilzomib studies will be used in the development of a structural model. The best model will be evaluated by goodness of fit statistics and reduction in the objective function and posterior predictive checks. Subject characteristics such as age, gender, body weight, BSA, and race will be included in the model to identify potential covariates affecting PK of carfilzomib. Results from the population PK modeling will be reported separately.

13.5.4 EXPLORATORY ANALYSES

Exploratory analyses of MRD[-] rate, PDn, and genomic biomarkers may be conducted. Point estimates for MRD[-] rate along with exact 2-sided 95% confidence intervals will be calculated. MRD measurements will be correlated with ORR, CRR, PFS, and other clinical variables to explore the relationship of MRD to disease response and progression.

PDn will be determined from whole blood.

For genomic biomarker analyses, WGS, WES, RNA-Seq, and/or other forms of nucleic acid and protein data will be analyzed to characterize whether drug response is related to alterations in genes regulated by or involved in activation of nuclear factor kappa light chain enhancer of activated B cells (NF-Kappa B) transcription factors as well as in genes involved in immunoglobulin production and protein homeostasis. Immunoglobulin levels in tumor cells will be quantified by enzyme-linked immunosorbent assay (ELISA) and/or other protein quantification methods. The genomic data as a whole will also be used to derive new hypotheses about mechanisms of drug response, resistance, and safety.

Results from the subject convenience and satisfaction questionnaire will be summarized descriptively.

13.6 HANDLING OF MISSING DATA

Missing data for partial dates for AEs or concomitant medication may be imputed according to prespecified, conservative imputation rules. Details of missing data handling and imputation rules will be specified in the statistical analysis plan.

Subjects with no postbaseline response assessments will be classified as nonresponders in the estimation of ORR and CRR.

Progression and survival data will be collected for all subjects on study. For subjects who discontinue without having experienced progression or death, progression will be censored at the time of the last on-study disease assessment demonstrating lack of progression. Details of censoring rules will be specified in the statistical analysis plan.

13.7 DETERMINATION OF SAMPLE SIZE

Sample sizes are determined to provide preliminary information on safety, clinical activity, PDn, and PK.

For the Dose-evaluation Component of the study, it is anticipated that approximately 8 subjects will be enrolled in each dose cohort with 16 subjects total, should both cohorts be fully enrolled. Assuming beta (0.5, 0.5) prior distribution for the DLT rate, 95% credible intervals for the DLT rate and the posterior probability of DLT rate being larger than 0.33 for each toxicity scenario are provided in Table 12. For example, when 3 out of 8 subjects have DLTs, the posterior probability of the DLT rate being > 0.33 is 0.62.

Table 12 95% Credible Intervals for the Dose-limiting Toxicity Rate and Probabilities of Dose-limiting Toxicity Rate Being Larger Than 0.33

Cohort Size	# DLTs Observed	95% Credible Interval for the DLT Rate	
8	0	0	0.26
8	1	0.01	0.45
8	2	0.06	0.59
8	3	0.12	0.71
8	4	0.20	0.80
8	5	0.29	0.88
8	6	0.41	0.94
8	7	0.55	0.99
8	8	0.74	1

DLT = dose-limiting toxicity.

With combined number of subjects in both dose finding and expansion components, 38 RRMM subjects and 38 NDMM subjects will allow an approximately 86% probability to detect an occurrence of an AE with 5% incidence rate.

13.8 INTERIM ANALYSIS

No formal interim analyses with the purpose of stopping the study early for efficacy or futility will be conducted for this study. However, the following nonbinding boundaries are calculated to provide more information about the distribution of ORR for subjects with relapsed disease.

For subjects with relapsed disease, under the null hypothesis of ORR $\leq$ 55%, the alternative hypothesis of ORR $\geq$ 75%, and the beta (0.65, 0.35) prior distribution for the true ORR, the boundaries for number of subjects with overall responses based on Bayesian predictive probability (Lee 2008) are listed below in Table 13.

Table 13 Boundaries for Number of Responding Subjects (Relapsed Disease Arm)

Interim looks (# of subjects finishing 4 cycles of treatment)	Predictive probability of success < 0.05	Predictive probability of success > 0.95
8	≤ 2	≥ 8
18	≤ 8	≥ 15
28	≤ 16	≥ 21
38	≤ 25	≥ 26

Frequentist operating characteristics of the above boundaries are evaluated by simulations, which show that the overall type I error rate is controlled under 0.1 and the power is approximately 87%.

14 ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

14.1 COMPLIANCE STATEMENT

This study will be conducted in accordance with the protocol and with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, as well as all applicable country and regional legal and regulatory requirements. The investigator is responsible for ensuring that this protocol, the site's ICF, and any other information that will be presented to potential subjects are reviewed and approved by the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) prior to the enrollment of any study subjects.

14.2 INSTITUTIONAL REVIEW BOARD OR INDEPENDENT ETHICS COMMITTEE

The investigator will submit this protocol, the informed consent, investigator's brochure (IB), and any other relevant supporting information to the appropriate IRB or IEC and the local regulatory agency (where required) for review and approval prior to study initiation.

Amendments to the protocol must also be approved by the IRB/IEC and the local regulatory agency, as appropriate, prior to the implementation of changes in this study. No protocol deviations are allowed. However, the investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the study subjects without prior IRB/IEC/sponsor approval/favorable opinion. As soon as possible, the implemented

deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment, should be submitted to the IRB/IEC/sponsor. Any deviations from the protocol must be fully explained and documented by the investigator.

14.3 INFORMED CONSENT AND HUMAN SUBJECT PROTECTION

No investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the subject's legally authorized representative sufficient opportunity to consider whether or not to participate, and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in a language understandable to the subject or representative.

The sponsor or its designated representative will provide the investigator with a sample consent form. Local and/or institutional requirements may require disclosure of additional information in the ICF. Any changes to the consent form must be submitted to the sponsor or its designated representative for acceptance, prior to submission to the IRB/IEC.
The IRB/IEC will review the consent form for approval. A copy of the approved form must be submitted to the sponsor or its designated representative for its acceptance prior to initiation of the study. Before implementing any study procedure on a particular subject, informed consent shall be documented in such subject's case histories and by the use of a written consent form approved by the sponsor and the IRB/IEC and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy of the signed informed consent will be given to the subject or subject's legally authorized representative. The original signed consent must be maintained by the investigator and available for inspection by the sponsor, its designated representative, or regulatory authority at any time.

14.4 DIRECT ACCESS TO SOURCE DATA, SOURCE DOCUMENTS, AND STUDY RECORDS

The study will be carried out in keeping with applicable local laws and regulations.
This may include an inspection by sponsor representatives/designees, and/or regulatory

authority representatives at any time. The investigator/institution must agree to the inspection of study-related records by the regulatory authority/sponsor representatives/designees, and must allow direct access to source documents to the regulatory authority/sponsor representatives/ designees/IRB/IEC. The investigator must allocate time (investigator and study staff) to discuss findings and relevant issues with the regulatory authority/sponsor representatives.

14.5 DATA COLLECTION AND HANDLING

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include subject diaries, laboratory reports, and other documents. The sponsor will supply the eCRF, which will be completed in English.

Data collection will involve the use of the EDC system, to which only authorized personnel will have access.

The investigator or designee must enter all results collected during the clinical study into eCRFs. Guidelines for completion of eCRFs will be reviewed with study site personnel at the site initiation visits. Investigators are responsible for approval of the entered/corrected data. Detailed instructions may be found in the other study-specific documents.

All entries made on the eCRF, must be verifiable against source documents. In addition to periodic monitoring occurring within the system by study monitors, programmatic edit checks and data listings will be used to review the data for completeness, logic, and adherence to study protocol. As a result of this monitoring and these checks, queries may be electronically issued to the clinical study sites and electronically resolved by those sites.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to assure subject confidentiality in accordance with the legal and regulatory requirements applying to protected health information. Study records (eg, copies

of eCRFs, regulatory documents) will be retained at the study site, along with adequate source documentation. The study file and all source data should be retained for the time period required by applicable regulatory requirements and will not be destroyed until written notification is given by the sponsor or designee for destruction.

14.6 CONFIDENTIALITY

All records identifying the subject will be kept confidential and, in accordance with the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded on the case report form (CRF). If the subject name appears on any other document (eg, pathologist report) or study materials (eg, biopsy tissue slides), then that information must be redacted before a copy of the document is supplied to the sponsor. Study data stored on a computer will be stored in accordance with local data protection laws and regulations. Subjects will be informed in writing that representatives of the sponsor, IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws and regulations.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects' records to be identified in accordance with applicable laws and regulations and according to the terms and agreed upon in such subjects' signed consent forms.

14.7 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 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.

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APPENDIX A SCHEDULE OF STUDY ASSESSMENTS

Assessment		Screening[a]	Baseline[b]	Cycles 1 through 18							EOT[c]	Active Follow-up
				D1	D8	D9	D11	D15	D21	D22		
Informed Consent		X										
Inclusion/exclusion criteria		X										
Medical and treatment history		X										
Time of pre-carfilzomib resting BP and time of dexamethasone administration (Cycles 1-6, 12, and 18)				X	X			X				
Vital signs		X		X	X			X			X	
Post-carfilzomib BP (Cycles 1-6, 12, and 18)				X	X			X				
Physical examination[d] and ECOG Performance Score		X		X							X	
Hematology		X		X	X			X			X	
Full serum chemistry panel[e]		X		X							X	
Abbreviated serum chemistry panel[f]					X			X				
Coagulation			X								X	
ECG (repeat if clinically indicated)		X										
ECHO/MUGA	Dose–evaluation cohorts (Cycle 2 and as clinically indicated)	X						X			X	
	Dose–expansion **arms** (repeat if clinically indicated)	X									X	

Footnotes defined on last page of table

APPENDIX A SCHEDULE OF STUDY ASSESSMENTS (CONT'D)

Assessment		Screening[a]	Baseline[b]	Cycles 1 through 18							EOT[c]	Active Follow-up
				D1	D8	D9	D11	D15	D21	D22		
Pregnancy testing (for FCBP)	Serum (10–14 days prior to C1D1)	X									X	
	Urine or serum Cycle 1 (predose)			X	X			X		X		
	Urine or serum Cycle 2–18 (predose; no menses)			X								
	Urine or serum Cycle 2–18 (predose; irregular menses)			X				X				
SPEP/UPEP/immunofixation (except Cycle 1)		X		X							X	X
Serum free light chains (except Cycle 1)		X		X							X	X
Quantitative immunoglobulins (except Cycle 1)		X		X							X	X
Beta-2 microglobulin			X									
Skeletal survey (repeat if clinically indicated)			X									
Plasmacytoma evaluation (if clinically indicated at baseline and repeat to confirm response)			X									
Bone marrow aspirate	Percent plasma cell involvement (local lab): Baseline and upon CR		X									
	FISH testing (central lab): Baseline		X									
	MRD (central lab): Baseline; Cycle 8 Day 1; and upon achieving CR or sCR		X	X[g]								
	Genomics (optional; central lab; baseline is run on remaining sample after FISH): Baseline, EOT, and active follow-up, if PD in subjects consenting to genomics evaluation		X								X[h]	X[h]

Footnotes defined on last page of table

APPENDIX A SCHEDULE OF STUDY ASSESSMENTS (CONT'D)

Assessment		Screening[a]	Baseline[b]	Cycles 1 through 18							EOT[c]	Active Follow-up
				D1	D8	D9	D11	D15	D21	D22		
Blood for MRD/NGS (central lab): Baseline; Cycle 8 Day 1; and upon achieving CR or sCR			X	X[g]								
Genomic Biomarkers blood and saliva (optional)			X									
Plasma PK (Cycle 1 **only**)					X							
Blood for PDn Cohorts 1-2 **and first 8 subjects in Arm 3** (Cycle 1 only)				X[i]	X[i]	X[j]	X[j]					
Questionnaire: patient convenience/satisfaction (Cycles 3 and 18 only)				X								
IV hydration (Cycle 1 only)				X	X			X				
Carfilzomib administration				X	X			X				
Dexamethasone administration[k]	Cycles 1 to 8			X	X			X		X		
	Cycles 9 to 18			X	X			X				
Lenalidomide administration				→								
Adverse events		→										
Concomitant medications		→										

Footnotes defined on last page of table

Page 3 of 3

BP = blood pressure; BSA = body surface area; CR = complete response; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FCBP = females of childbearing potential; FISH = fluorescent in situ hybridization; IV = intravenous (ly); MRD = minimal residual disease; MUGA = multigated acquisition; PD = progressive disease; PDn = pharmacodynamic(s); PK = pharmacokinetic(s); sCR = stringent complete response; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis

Details of Assessments are in the protocol body.

[a] Screening samples can be collected within 21 days of Cycle 1 Day 1.

[b] It is recommended that baseline samples are collected only after subject is enrolled.

[c] EOT visit must be scheduled 28 ± 7 days after the last study treatment. EOT ECHO must be performed within 28 ± 7 days after the last study treatment.

[d] Height is only measured once at screening. BSA is not calculated on Day1 of Cycle 1 or at EOT visit.

[e] Full serum chemistry panel will also be collected on Days 8 and 15 of Cycle 1.

[f] Abbreviated serum chemistry panel will be collected Cycle 2 onwards, Days 8 and 15 (as listed in table).

[g] After baseline, collect aspirate and blood for MRD only on Day 1 Cycle 8, all subjects, and upon achieving a CR or sCR in all subjects.

[h] Optional bone marrow aspirate to be collected upon progression of disease in subjects consenting to optional genomic biomarker analysis.

[i] Predose and postdose.

[j] On Days 9 and 11, when carfilzomib is not administered, collect 1 PDn sample at approximately the same time as when the pre-infusion sample was taken on Day 8.

[k] Dexamethasone should be administered 30 minutes to 4 hours prior to initiation of carfilzomib infusion.

APPENDIX B 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

Source: Oken 1982.
Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair

APPENDIX C 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, in addition to VGPR criteria, is required
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.
Stable Disease	• Not meeting criteria for CR, VGPR, PR, or PD

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

PD	• Increase of 25% from lowest response value in any of the following: o Serum M-component (absolute increase must be ≥ 0.5 g/dL) and/or o Urine M-component (absolute increase must be ≥ 200 mg per 24 hours) and/or o 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) • 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 2.875 mmol/L) attributed solely to the plasma cell proliferative disorder

CR = complete response; sCR = stringent complete response; FLC = serum free light chain; PD = progressive disease; PR = partial response; SFLC = serum free light chain; VGPR = very good partial response.

All response categories (CR, sCR, VGPR, PR, PD) require 2 consecutive assessments made at any time before the institution of any new therapy, as well as no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow, plasmacytoma, and skeletal survey assessments are not required to be confirmed by repeat testing. SD requires a duration of ≥ 6 weeks.

For sCR: presence/absence of clonal cells is based upon the kappa lambda (κ/λ) ratio. An abnormal ratio reflecting presence of an abnormal clone is κ/λ > 4:1 or < 1:2. An abnormal kappa lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. For CR: A normal SFLC kappa lambda ratio is 0.26 to 1.65.

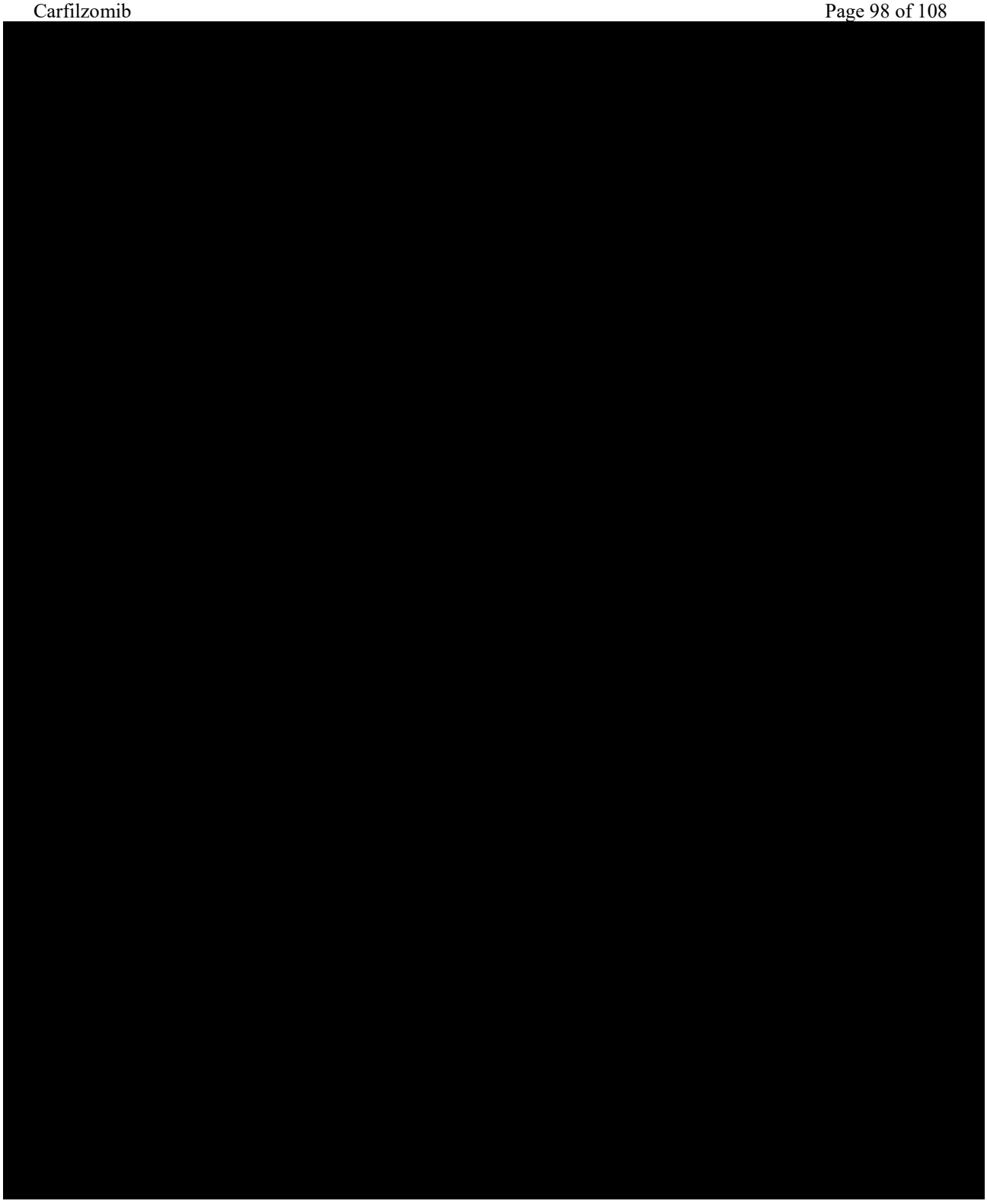
"Measurable" disease is defined by at least one of SPEP ≥ 0.5 g/dL, UPEP ≥ 200 mg per 24 hours, or in subjects without detectable serum or urine M-protein, SFLC > 100 mg/L (involved light chain) and an abnormal kappa lambda ratio.

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

Plasmacytomas: A definite increase in the size is defined as a ≥ 50% increase as measured serially by the sum of the products of the greatest orthogonal cross-diameters of the measurable lesions. A plasmacytoma is considered measurable if the longest diameter is at least 1 cm and the product of the greatest orthogonal 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.

Sources: Durie 2006; Rajkumar 2011.

APPENDIX D SUBJECT CONVENIENCE AND SATISFACTION QUESTIONNAIRE



APPENDIX E FIGURES FROM PROTOCOL AMENDMENT 1

Figure 2 Design Schematic for the Dose-evaluation Component for RRMM subjects (prior to Protocol Amendment 2)

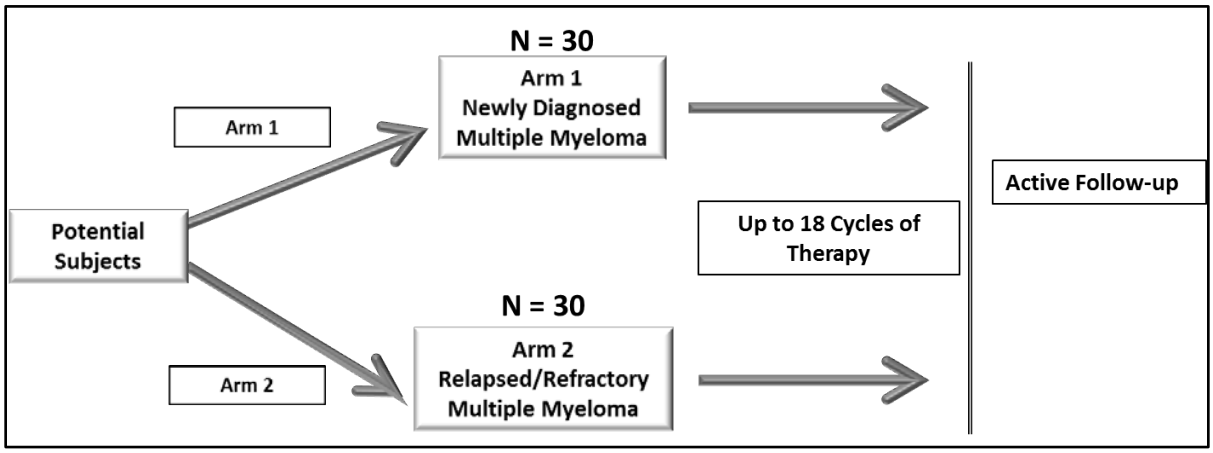
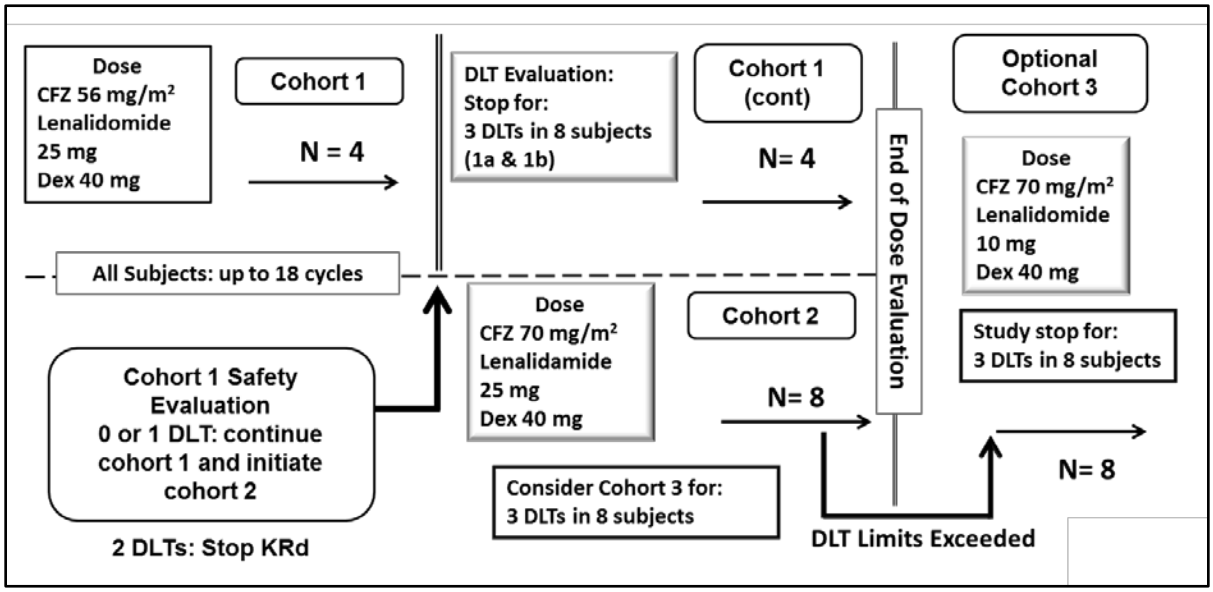


Figure 3 Design Schematic for the Dose-expansion Component (prior to Protocol Amendment 2)



APPENDIX F ADDITIONAL SAFETY ASSESSMENT INFORMATION

Whenever possible, the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 should be used to describe the event and for assessing the severity of AEs (National Cancer Institute 2010). For AEs not adequately addressed in the NCI-CTCAE version 4.03, Table 14 may be used.

Table 14 Toxicity Grading for Adverse Events Not Covered in the NCI-CTCAE (Version 4.03)

Severity	Description
GRADE 1 – Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
GRADE 2 – Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
GRADE 3 – Severe	Medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
GRADE 4 – Life-threatening	Life-threatening consequences; urgent intervention indicated
GRADE 5 – Fatal	Death

ADL = activities of daily living; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events.

APPENDIX G SAMPLE eSERIOUS EVENT CONTINGENCY FORM

AMGEN
Study # 20140241
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? <Device> No ✓ Yes ✓	<Device> No ✓ Yes ✓	<Device> No ✓ Yes ✓	<Device> No ✓ Yes ✓	Outcome of Event •Resolved •Not resolved •Fatal •Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No							
				☐Yes ☐No							
				☐Yes ☐No							

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

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

AMGEN Study # 20140241 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

AMGEN Study # 20140241 carfilzomib	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

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

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

Date (Day Month Year)	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

APPENDIX H PREGNANCY AND LACTATION NOTIFICATION WORKSHEETS

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20140241

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 DOB:** mm___/ dd___/ yyyy_____

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 LMP mm___/ dd___/ yyyy_____ ☐ Unknown

Estimated date of delivery mm___/ dd___/ yyyy_____ ☐ Unknown ☐ N/A

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:** _____

Effective Date: March 27, 2011

Page 1 of 1

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: 20140241

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 Date of Birth:** mm_____ / dd_____/ yyyy_____

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:** _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

APPENDIX I SUMMARY OF CHANGES IN STUDY CFZ013 AMENDMENT 3

This Summary of Changes outlines noteworthy changes from protocol amendment **2**.0 to protocol amendment **3**.0, and includes rationales for the changes. Administrative updates, typographical and formatting changes were made throughout the protocol. The main purposes for revising the CFZ013 (20140241) protocol are **listed below.**

Protocol amendment 3 specifies the dosing selected for newly diagnosed multiple myeloma (NDMM) Dose-expansion Arm 3. The carfilzomib, lenalidomide, and dexamethasone (KRd) dosing for Arm 3 is as follows: carfilzomib 20 mg/m^2 on Day 1 of Cycle 1, then 56 mg/m^2 on Days 8 and 15 of Cycle 1, and Days 1, 8, and 15 of Cycles 2-18. Lenalidomide will be given at 25 mg on Days 1-21, and dexamethasone at 40 mg on Days 1, 8, 15, 22 of Cycles 1-8, and on Days 1, 8, and 15 of Cycles 9-18 (see Cohort 1 dosing in Table 2).

The pharmacokinetics (PK) and pharmacodynamics (PDn) sample collection schedule was modified to reflect the dosing selected. Cycle 2 sampling that was introduced in protocol amendment 2, in anticipation of a 2-step-up dosing regimen, has been removed as it is not required for the dosing selected for Dose-expansion Arm 3.

Two revisions were made in response to the carfilzomib US Prescribing Information (USPI) labelling change approved by FDA in November 2016, which required a 25% dose reduction in patients with mild or moderate hepatic impairment:

- **Table 9 (Treatment Guidelines for Nonhematologic Toxicity) has been modified to align with requested changes. Specifically, NCI Organ Dysfunction Working Group definition of mild, moderate and severe hepatic impairment were used (Shibata et al, 2013):**
  - **mild: total bilirubin (>33% direct) > the upper limit of normal (ULN) and ≤ 1.5x ULN OR total bilirubin (>33% direct) ≤ ULN and alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > ULN;**
  - **moderate: total bilirubin .5x ULN and ≤ 3x ULN, any ALT or AST;**
  - **severe: total bilirubin > 3x ULN, any ALT or AST.**

  Subjects with treatment-emergent mild or moderate hepatic impairment, per this definition, are to have a 25% carfilzomib dose reduction. In cases of severe

hepatic impairment, carfilzomib is to be held. In moderate or severe hepatic impairment, lenalidomide is to be held.

- **Inclusion criteria have been modified in Section 6.1. Previous protocol amendments allowed enrollment of subjects with baseline mild hepatic insufficiency. With protocol amendment 3 (under which only the NDMM dose-expansion Arm 3 subjects will be enrolled), subjects will be required to have normal hepatic function. The intent of this modification is to maximize the ability to give full, protocol-specified 20/56 mg/m^2 carfilzomib dosing to the enrolled NDMM subjects.**

Other minor changes:

- **To maintain internal consistency of the document, Dose-expansion groups are uniformly referred to "Arms" with the term "Cohort" reserved for Dose-evaluation groups.**
- **Changed the duration of enrollment from 8 to 12 months.**

Description of Changes

Section: Global

Change:

Minor typographic and formatting errors were corrected throughout the protocol.

Section: Title page

Add:

Amendment 3: 13 December 2016

Section: Protocol Acceptance Page

Replace:

CFZ013 Amendment 2/14 October 2016

With:

CFZ013 Amendment **3/13 December** 2016

Section: Synopsis (Study design)

Paragraph 7

Delete:

All subjects will be evaluated for safety at an End of Treatment (EOT) visit, 28 ± 7 days after the last study treatment, and with an EOT echocardiogram (ECHO), done within ~~scheduled~~ 28 ± 7 days after the last study treatment.

Section: Synopsis (Treatment regimen[s])

Paragraph 4

Delete:

Cohort 2 (RRMM~~ and NDMM~~):

Section: Synopsis (Treatment regimen[s])

Paragraph 11

Replace:

Dose-expansion Component

If a regimen evaluated during the Dose-evaluation Component is safe and tolerable, approximately 30 additional subjects may be enrolled for treatment with that regimen in the Dose-expansion Component.

With:

Dose-expansion Component

If a regimen evaluated during the Dose-evaluation Component is safe and tolerable, approximately 30 additional subjects may be enrolled for treatment ~~with that regimen~~ in **a** Dose-expansion **arm**.

Section: Synopsis (Inclusion criteria) and Section 6.1

Inclusion criterion 7

Delete:

~~7. Adequate hepatic function within 21 days prior to Cycle 1 Day 1:~~

~~a. Bilirubin < 1.5 times the upper limit of normal (ULN)~~

~~b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 times the ULN~~

Section: Synopsis (Inclusion criteria) and Section 6.1

Add:

15. Normal hepatic function within 21 days prior to Cycle 1 Day 1:

a. Bilirubin ≤ the upper limit of normal (ULN)
b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ the ULN

Section: Synopsis (PK)

Replace:

For both the Dose-evaluation and the Dose-expansion Components, blood samples will be collected from all subjects for determination of plasma concentrations of carfilzomib. For NDMM subjects, blood will be collected on Day 1 of Cycle 2; for the remaining

subjects, blood will be collected on Day 8 of Cycle 1.

With:

For both the Dose-evaluation and the Dose-expansion Components, blood samples will be collected from all subjects **on Day 8 of Cycle 1** for determination of plasma concentrations of carfilzomib. ~~For NDMM subjects, blood will be collected on Day 1 of Cycle 2; for the remaining subjects, blood will be collected on Day 8 of Cycle 1.~~

Section: Synopsis (PDn)

Replace:

Whole blood will be collected from all subjects in the Dose evaluation Component on Days 1, 8, 9, and 11 of Cycle 1. On Days 1 and 8 of Cycle 1 whole blood will be collected pre-carfilzomib dose and post-carfilzomib dose. On Days 9 and 11 of Cycle 1, when carfilzomib is not administered, one PDn sample will be collected at approximately the same time as when the pre-infusion sample was taken on Day 8.

Per protocol amendment 2:

For the first 8 NDMM subjects enrolled under protocol amendment 2, whole blood will be collected pre-carfilzomib dose and post-carfilzomib dose on Cycle 1 Day 1 and Cycle 2 Day 1; post-carfilzomib dose on Days 8 and 15 of Cycles 1-2.

With:

Whole blood will be collected from all subjects in the Dose-evaluation Component**, and the first 8 subjects enrolled in Dose-expansion Arm 3,** on Days 1, 8, 9, and 11 of Cycle 1. On Days 1 and 8 of Cycle 1 whole blood will be collected pre-carfilzomib dose and post-carfilzomib dose. On Days 9 and 11 of Cycle 1, when carfilzomib is not administered, one PDn sample will be collected at approximately the same time as when the pre-infusion sample was taken on Day 8.

~~Per protocol amendment 2:~~

~~For the first 8 NDMM subjects enrolled under protocol amendment 2, whole blood will be collected pre-carfilzomib dose and post-carfilzomib dose on Cycle 1 Day 1 and Cycle 2 Day 1; post-carfilzomib dose on Days 8 and 15 of Cycles 1-2.~~

Section: 3.4 DOSE RATIONALE

Paragraph 1

Replace:

The dose rationale for this study derives from considerations of carfilzomib, lenalidomide, and dexamethasone dose combinations that are currently in use, as shown in Table 1. Dose combinations for this study are shown in Table 2. Prior to protocol amendment 2, dose-evaluation cohorts were planned only for RRMM subjects (Cohorts 1, 2, and 3). Schemas for enrollment prior to protocol amendment 2 are shown in Appendix E (Figure 2 and Figure 3). Per protocol amendment 2, Dose-evaluation cohorts are added for NDMM subjects.

With:

The dose rationale for this study derives from considerations of carfilzomib, lenalidomide, and dexamethasone dose combinations that are currently in use, as shown in Table 1. Dose combinations for this study are shown in Table 2. Prior to protocol amendment 2, dose-evaluation cohorts were planned only for RRMM subjects (Cohorts 1, 2, and 3). Schemas for enrollment prior to protocol amendment 2 are shown in Appendix E (Figure 2 and Figure 3). **With** protocol amendment 2, **a** Dose-evaluation cohort **is** added for NDMM subjects.

Section: 3.4 DOSE RATIONALE

Paragraph 3

Replace:

Cohort 4

A 2-step-up KRd regimen will be evaluated in NDMM subjects: carfilzomib will be given at 20 mg/m^2 on Day 1 of Cycle 1, 56 mg/m^2 on Days 8 and 15 of Cycle 1, then 70 mg/m^2 on Days 1, 8, and 15 beginning with Cycle 2 (Cohort 4; Table 2). This regimen was selected by the Cohort Safety Review Committee (CSRC) for Dose-evaluation in NDMM subjects, after the occurrence of 2 SAEs in NDMM subjects during Cycle 1 of treatment at Cohort 2 dose-level during the Dose-expansion Component.

With:

Cohort 4

A 2-step-up KRd regimen will be evaluated in NDMM subjects: carfilzomib will be given at 20 mg/m^2 on Day 1 of Cycle 1, 56 mg/m^2 on Days 8 and 15 of Cycle 1, then 70 mg/m^2 on Days 1, 8, and 15 beginning with Cycle 2 (Cohort 4; Table 2). This regimen was selected by the Cohort Safety Review Committee (CSRC) for Dose-evaluation in NDMM subjects, after the occurrence of 2 SAEs in NDMM subjects during Cycle 1 of treatment at Cohort 2 dose-level **(Arm 1)**.

Section: 5 STUDY DESIGN

Paragraph 7-10

Replace:

The first part is the Dose-evaluation Component during which carfilzomib combination regimens will be evaluated (Table 2 and Figure 1). Approximately 8 dose-limiting toxicity evaluable subjects will be enrolled into each opened Dose-evaluation cohort. Before opening Dose-expansion cohorts, it must be determined that there are not more than 2 dose-limiting toxicities in 8 DLT-evaluable subjects at the dose selected for Dose-expansion. Dose-expansion cohorts may open once all safety data for at least 1 cycle at maximal dose carfilzomib is reviewed by the CSRC.

The second part is the Dose-expansion Component.

Prior to protocol amendment 2, dose evaluation was performed on RRMM subjects treated at Cohort 1 and Cohort 2 dosing (Table 2). Cohort 2 dosing was selected for expansion with a plan for approximately 30 RRMM subjects and 30 NDMM subjects to be treated in the Dose-expansion Component (Appendix E; Figure 2 and Figure 3).

In the first 8 NDMM subjects treated in Dose-expansion at Cohort 2 dosing, 2 SAEs were observed during Cycle 1 (Table 2). Thus, per protocol amendment 2, a Dose-evaluation Cohort 4 is added for NDMM subjects (Table 2 and Figure 1). A Dose-expansion cohort for NDMM subjects may open once all safety data for at least 1 cycle at maximal planned carfilzomib dose is reviewed by the CSRC as described in Section 5.4.

With:

The first part is the Dose-evaluation Component during which carfilzomib combination regimens will be evaluated (Table 2 and Figure 1). Approximately 8 dose-limiting toxicity evaluable subjects will be enrolled into each opened Dose-evaluation cohort. Before opening Dose-expansion **arms**, it must be determined that there are not more than 2 dose-limiting toxicities in 8 DLT-evaluable subjects at the dose selected for Dose-expansion. Dose-expansion **arms** may open once all safety data for at least 1 cycle at maximal dose carfilzomib is reviewed by the CSRC.

The second part is the Dose-expansion Component.

Prior to protocol amendment 2, dose evaluation was performed on RRMM subjects treated at Cohort 1 and Cohort 2 dosing (Table 2). Cohort 2 dosing was selected for expansion with a plan for approximately 30 RRMM subjects and 30 NDMM subjects to be treated in the Dose-expansion Component (**Arms 1 and 2;** Appendix E; Figure 2 and Figure 3).

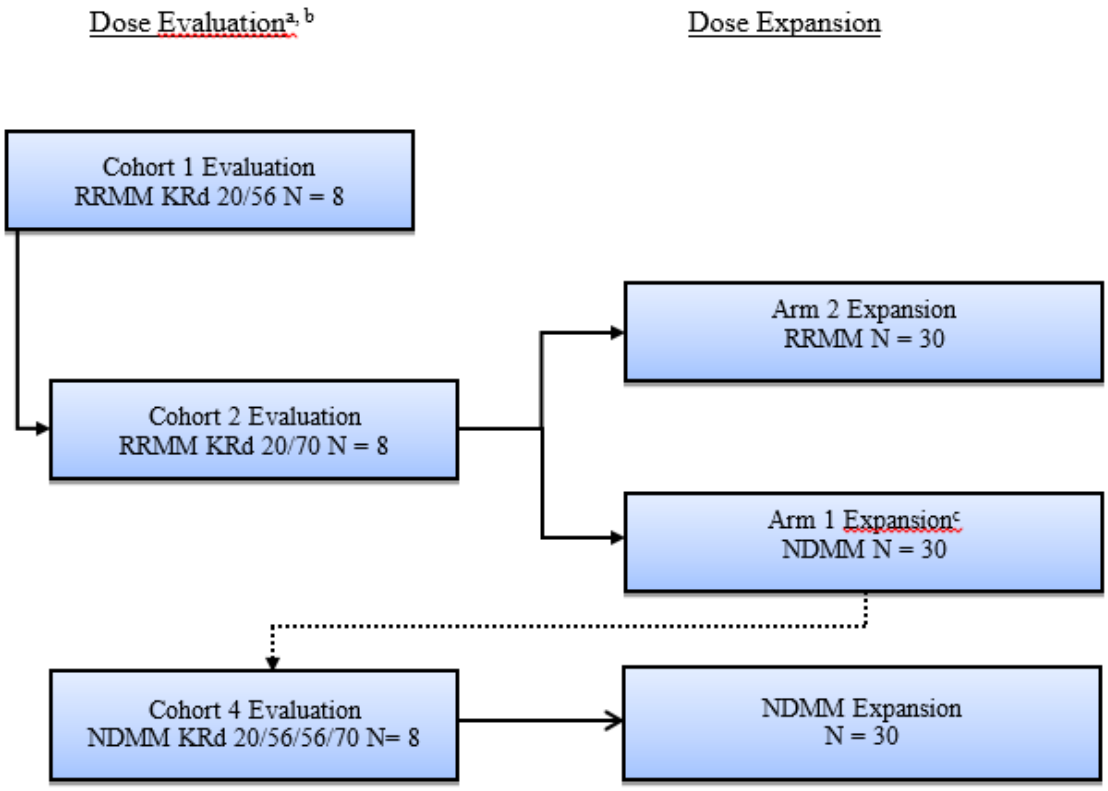
In the first 8 NDMM subjects treated in Dose-expansion **Arm 1** at Cohort 2 dosing, 2 SAEs were observed during Cycle 1 (Table 2). Thus, **with** protocol amendment 2, ~~a~~ Dose-evaluation Cohort 4 is added for NDMM subjects (Table 2 and Figure 1). A Dose-expansion **arm** for NDMM subjects may open once all safety data for at least 1 cycle at maximal planned carfilzomib dose is reviewed by the CSRC as described in Section 5.4.

Section: 5 STUDY DESIGN

Figure 1

Replace:

Figure 1 Study Schema



N = number; NDMM = newly diagnosed multiple myeloma; RRMM = relapsed refractory multiply myeloma; KRd = Kyprolis (carfilzomib)/Revlimid® (lenalidomide)/dexamethasone'

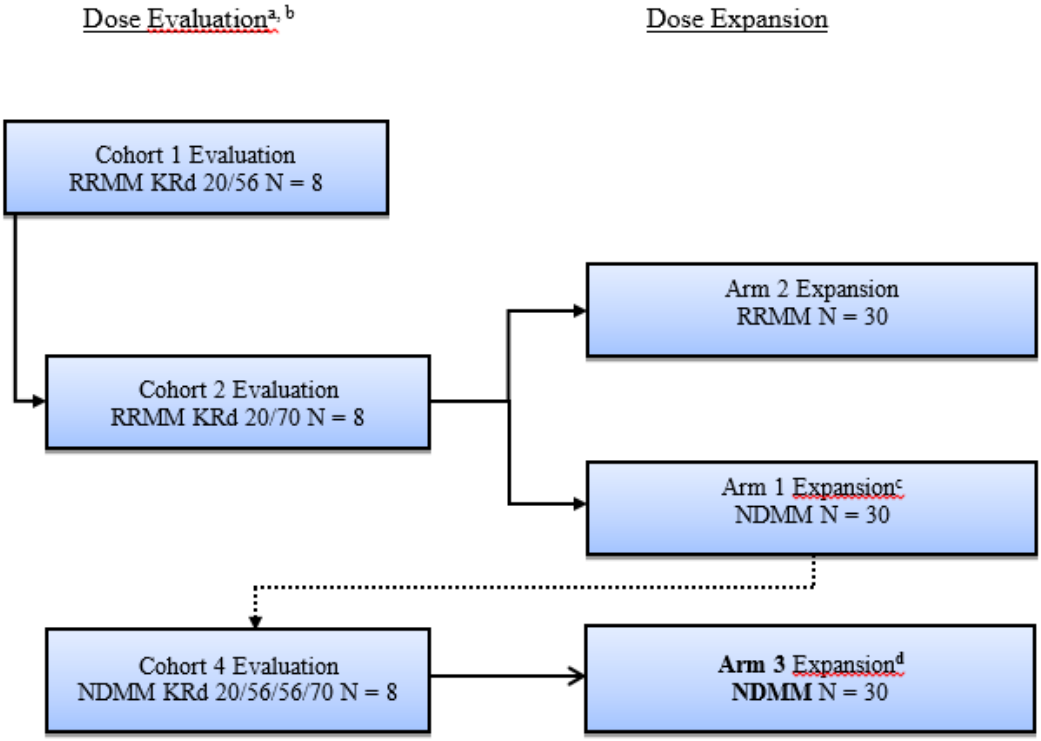
[a] Optional Cohort 3 was not opened.

[b] Full dosing information is presented in Table 2.

[c] Twenty out of 30 planned NDMM subjects were enrolled in Dose expansion, at cohort 2 dosing, prior to protocol amendment 2.

With:

Figure 1 Study Schema



Up to 18 Cycles -> Active Follow Up (all subjects)

N = number; NDMM = newly diagnosed multiple myeloma; RRMM = relapsed refractory multiply myeloma; KRd = Kyprolis (carfilzomib)/Revlimid® (lenalidomide)/dexamethasone'

[a] Optional Cohort 3 was not opened.
[b] Full dosing information is presented in Table 2.
[c] Twenty out of 30 planned NDMM subjects were enrolled in Dose expansion, at cohort 2 dosing, prior to protocol amendment 2.
[d] **Subjects in dose-expansion Arm 3 will be treated with KRd at 20/56 (full dosing regimen as shown for Cohort 1 in Table 2).**

Section: 5.1 STUDY POPULATION

Paragraph 2

Add:

Prior to protocol amendment 2, subjects with newly diagnosed, previously untreated multiple myeloma were included only in the Dose-expansion Component (Appendix E; Figure 2, Arm 1). After protocol amendment 2, NDMM subjects will be

enrolled into a NDMM Dose-evaluation cohort, which may be expanded after safety evaluation by the CSRC (**Arm 3,** Figure 1).

Section: 5.4 PART 1: DOSE-EVALUATION COMPONENT

Paragraph 4

Replace:

A 2-step-up KRd regimen will be evaluated in NDMM subjects: carfilzomib will be given at 20 mg/m^2 on Day 1 of Cycle 1, 56 mg/m^2 on Days 8 and 15 of Cycle 1, then at 70 mg/m^2 on Days 1, 8, and 15 beginning with Cycle 2 (Cohort 4; Table 2). This regimen was selected by the CSRC for dose-evaluation in NDMM subjects, after the occurrence of 2 SAEs in NDMM subjects during Cycle 1 of treatment at Cohort 2 dose level during the first NDMM Dose-expansion Component.

With:

A 2-step-up KRd regimen will be evaluated in NDMM subjects: carfilzomib will be given at 20 mg/m^2 on Day 1 of Cycle 1, 56 mg/m^2 on Days 8 and 15 of Cycle 1, then at 70 mg/m^2 on Days 1, 8, and 15 beginning with Cycle 2 (Cohort 4; Table 2). This regimen was selected by the CSRC for dose-evaluation in NDMM subjects, after the occurrence of 2 SAEs in NDMM subjects during Cycle 1 of treatment at Cohort 2 dose level during the **Arm 1** NDMM Dose-expansion **(Figure 1)**.

Section: 5.5 PART 2: DOSE-EXPANSION COMPONENT

Paragraph 3

Replace:

The CSRC will evaluate all safety data for all NDMM subjects following the rules above. The CSRC may elect to open an NDMM Dose-expansion cohort for 2-step-up KRd dosing, and may enroll an additional 30 NDMM subjects (Section 5.4).

With:

The CSRC will evaluate all safety data for all NDMM subjects**. F**ollowing the **DLT** rules above**, t**he CSRC may elect to open an NDMM Dose-expansion **arm**, and may enroll an additional 30 NDMM subjects (Section 5.4).

Section: 5.7 ESTIMATED STUDY DURATION AND STUDY CLOSURE

Paragraph 2

Replace:

It will take up to approximately 8 months to enroll NDMM subjects into Dose-evaluation Cohort 4, review the safety data, and enroll NDMM subjects into the NDMM Dose-expansion Component. Subjects will be followed for up to 17 months on treatment (with an allowed interruption of up to 4.5 months for ASCT), and for 12 months for Active Follow up.

With:

It will take up to approximately **12** months to enroll NDMM subjects into Dose-evaluation Cohort 4, review the safety data, and enroll NDMM subjects into the NDMM Dose-expansion **Arm 3**. Subjects will be followed for up to 17 months on treatment (with an allowed interruption of up to 4.5 months for ASCT), and for 12 months for Active Follow up.

Section: 9.2.1.2 Lenalidomide

Paragraph 2

Replace:

For FCBP, nonpregnant state must be documented prior to the first dose of lenalidomide, every week for the first cycle, and prior to the start of each subsequent cycle.

With:

For FCBP, nonpregnant state must be documented prior to the first dose of lenalidomide, every week for the first cycle, ~~and~~ prior to the start of each subsequent cycle**, and at EOT**.

Section: 9.2.2.2 Nonhematologic Toxicity

Replace:

Table 9 Treatment Guidelines for Nonhematologic Toxicity

Symptom	Recommended Action	
	Lenalidomide	Carfilzomib
Blood and Lymphatic System		
Thrombotic microangiopathy (TMA) Fever, microangiopathic hemolytic anemia, thrombocytopenia, renal failure, neurologic changes	If the diagnosis is suspected, stop lenalidomide and carfilzomib and manage per standard of care including plasma exchange as clinically appropriate. If TMA is confirmed and related to lenalidomide or carfilzomib, permanently discontinue. If the diagnosis of TMA is excluded, lenalidomide and carfilzomib dosing may be resumed at full dose if clinically appropriate.	
Cardiac		
Congestive heart failure	Full dose	Any subject with symptoms of congestive heart failure, whether or not drug related, must have the dose held until resolution or return to baseline, after which treatment may continue at a reduced dose, or the subject may be permanently discontinued. If no resolution after 4 weeks, the subject will be withdrawn from all study treatment.
Hypertensive crisis Sustained or persistent SBP ≥ 180 mm Hg or DBP ≥ 110 mm Hg	Full dose	Hold carfilzomib until resolution to baseline, then resume at 1 dose decrement
LVEF Reduction < 40% or < 55% if the drop is greater than 20% from baseline	Full dose	Hold carfilzomib until LVEF returns to ≥ 40% or, if held due to a drop to < 55%, to within 15% of baseline. Resume at 1 dose decrement.
Infections and Infestations		
Infection Grade 3 or 4	Hold both lenalidomide and carfilzomib until systemic treatment for infection is complete. If ANC > 1,000/µL, resume both drugs at full dose. If ANC < 1,000/µL, follow hematologic toxicities dosage guidelines.	
Investigations		
Elevation of AST, ALT, or total bilirubin Grade 3 or 4	Hold lenalidomide until resolution to baseline, then resume at full dose.	Hold carfilzomib until resolution to baseline, then resume at 1 dose decrement.

Page 1 of 3

Footnotes defined on last page of table

Table 9 Treatment Guidelines for Nonhematologic Toxicity (cont'd)

Symptom	Recommended Action	
	Lenalidomide	Carfilzomib
Investigations (cont'd)		
CrCl[a] ≥ 30 and < 50 mL/min	Reduce dose to 10 mg once daily.	Full dose
CrCl[a] ≥ 15 and < 30 mL/min (NCI-CTCAE Grade 3)	Hold dose. If CrCl recovers resume dose at 1 dose decrement. If significant CrCl reduction reappears then reduce dose to 15 mg every 48 hours. Further dose modification will be based on individual subject treatment tolerance.	Full dose
CrCl[a] < 15 mL/min (NCI-CTCAE Grade 4)	Hold dose. If CrCl recovers to baseline, resume dose at 1 dose decrement. If significant CrCl reduction reappears reduce dose to 15 mg every 48 hours. If dialysis required, reduce dose to 5 mg once daily (administer the lenalidomide after dialysis on dialysis days). Further dose modification will be based on individual subject treatment tolerance.	Hold dose. When CrCl returns to ≥ 15 mL/ minute, resume same dose. If dialysis required, contact the medical monitor.
Metabolism		
Tumor Lysis Syndrome 3 or more of the following: • increase in creatinine of ≥ 50% • increase in uric acid, of ≥ 50% • increase in phosphate of ≥ 50% • increase in potassium of ≥ 30% • decrease in calcium, OR • increase in LDH of ≥ 2-fold from baseline	Hold both lenalidomide and carfilzomib until all abnormalities in serum chemistries have resolved; resume at full dose.	
Nervous System Disorders		
Neuropathy Treatment-emergent painful grade 2, or grade 3	Full dose	Hold carfilzomib until resolution to ≤ grade 2 without pain, then resume at 1 dose decrement
Neuropathy Grade 4	Discontinue	Discontinue

Page 2 of 3

Footnotes defined on last page of table

Table 9 Treatment Guidelines for Nonhematologic Toxicity (cont'd)

Symptom	Recommended Action	
	Lenalidomide	Carfilzomib
Nervous System Disorders (cont'd)		
Posterior Reversible Encephalopathy Syndrome (PRES) headaches, altered mental status, seizures, visual loss and hypertension	If PRES is suspected, hold lenalidomide and carfilzomib. Consider neuroradiographic imaging, specifically MRI, to evaluate onset of visual or neurological symptoms suggestive of PRES. If the diagnosis of PRES is excluded lenalidomide and carfilzomib dosing may resume at the same dose, if clinically appropriate. If condition recurs, permanently discontinue carfilzomib.	
Respiratory		
Dyspnea Grade 2, 3 or 4	Full dose	Hold carfilzomib until resolution to baseline, then resume at 1 dose decrement
Pulmonary hypertension: (≥Grade 3)	Full dose	Hold carfilzomib until resolution to baseline, then resume at 1 dose decrement
Pulmonary toxicity Interstitial lung disease, acute respiratory failure, ARDS (≥Grade 3)	Hold lenalidomide until resolution to baseline then resume full dose	Hold carfilzomib until resolution to baseline, then resume at 1 dose decrement
Other Symptoms Not Listed Above		
Any other drug-related nonhematologic toxicity ≥ Grade 3[b]	For lenalidomide attribution, hold dose. Resume at 1 dose decrement when toxicity has resolved to Grade 1 or less or to baseline grade.	For carfilzomib attribution, hold dose. Resume at 1 dose decrement when toxicity has resolved to Grade 1 or less or to baseline[c] grade.

Page 3 of 3

With:

Table 1 Treatment Guidelines for Nonhematologic Toxicity

Symptom	Recommended Action	
	Lenalidomide	Carfilzomib
Blood and Lymphatic System		
Thrombotic microangiopathy (TMA) Fever, microangiopathic hemolytic anemia, thrombocytopenia, renal failure, neurologic changes	If the diagnosis is suspected, stop lenalidomide and carfilzomib and manage per standard of care including plasma exchange as clinically appropriate. If TMA is confirmed and related to lenalidomide or carfilzomib, permanently discontinue. If the diagnosis of TMA is excluded, lenalidomide and carfilzomib dosing may be resumed at full dose if clinically appropriate.	
Cardiac		
Congestive heart failure	Full dose	Any subject with symptoms of congestive heart failure, whether or not drug related, must have the dose held until resolution or return to baseline, after which treatment may continue at a reduced dose, or the subject may be permanently discontinued. If no resolution after 4 weeks, the subject will be withdrawn from all study treatment.
Hypertensive crisis Sustained or persistent SBP ≥ 180 mm Hg or DBP ≥ 110 mm Hg	Full dose	Hold carfilzomib until resolution to baseline, then resume at 1 dose decrement
LVEF Reduction < 40% or < 55% if the drop is greater than 20% from baseline	Full dose	Hold carfilzomib until LVEF returns to ≥ 40% or, if held due to a drop to < 55%, to within 15% of baseline. Resume at 1 dose decrement.
Infections and Infestations		
Infection Grade 3 or 4	Hold both lenalidomide and carfilzomib until systemic treatment for infection is complete. If ANC > 1,000/μL, resume both drugs at full dose. If ANC < 1,000/μL, follow hematologic toxicities dosage guidelines.	
Hepatic Dysfunction and Related Investigations		
Mild liver dysfunction, defined as 2 consecutive values, at least 28 days apart, of: **(1) total bilirubin (> 33% direct) > 1x ULN to < 1.5x ULN** **OR** **(2) an elevation of AST and/or ALT with normal bilirubin**	**Full dose.**	**25% dose reduction.** **Dose may be re-escalated if liver function tests return to normal and drug-induced hepatotoxicity is excluded.**

Page 1 of 3

Footnotes defined on last page of table

Table 9 Treatment Guidelines for Nonhematologic Toxicity (cont'd)

Symptom	Recommended Action	
	Lenalidomide	Carfilzomib
Hepatic Dysfunction and Related Investigations (cont'd)		
Moderate liver dysfunction, defined as 2 consecutive values, at least 28 days apart, of total bilirubin (> 33% direct) > 1.5x ULN to < 3x ULN	**Hold lenalidomide until resolution to baseline, then resume at full dose.**	**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 lenalidomide until resolution to baseline, then resume at full dose.**	**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 lenalidomide until resolution to baseline, then resume at full dose.**	**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.**
Renal Dysfunction		
CrCl[a] ≥ 30 and < 50 mL/min	Reduce dose to 10 mg once daily.	Full dose
CrCl[a] ≥ 15 and < 30 mL/min (NCI-CTCAE Grade 3)	Hold dose. If CrCl recovers resume dose at 1 dose decrement. If significant CrCl reduction reappears then reduce dose to 15 mg every 48 hours. Further dose modification will be based on individual subject treatment tolerance.	Full dose
CrCl[a] < 15 mL/min (NCI-CTCAE Grade 4)	Hold dose. If CrCl recovers to baseline, resume dose at 1 dose decrement. If significant CrCl reduction reappears reduce dose to 15 mg every 48 hours. If dialysis required, reduce dose to 5 mg once daily (administer the lenalidomide after dialysis on dialysis days). Further dose modification will be based on individual subject treatment tolerance.	Hold dose. When CrCl returns to ≥ 15 mL/ minute, resume same dose. If dialysis required, contact the medical monitor.

Page 2 of 3

Footnotes defined on last page of table

Table 9 Treatment Guidelines for Nonhematologic Toxicity (cont'd)

Symptom	Recommended Action	
	Lenalidomide	Carfilzomib
Metabolism		
Tumor Lysis Syndrome 3 or more of the following: • increase in creatinine of ≥ 50% • increase in uric acid of ≥ 50% • increase in phosphate of ≥ 50% • increase in potassium of ≥ 30% • decrease in calcium, OR increase in LDH of ≥ 2-fold from baseline	Hold both lenalidomide and carfilzomib until all abnormalities in serum chemistries have resolved; resume at full dose.	
Nervous System Disorders		
Neuropathy Treatment-emergent painful grade 2, or grade 3	Full dose	Hold carfilzomib until resolution to ≤ grade 2 without pain, then resume at 1 dose decrement
Neuropathy Grade 4	Discontinue	Discontinue
Posterior Reversible Encephalopathy Syndrome (PRES) headaches, altered mental status, seizures, visual loss and hypertension	If PRES is suspected, hold lenalidomide and carfilzomib. Consider neuroradiographic imaging, specifically MRI, to evaluate onset of visual or neurological symptoms suggestive of PRES. If the diagnosis of PRES is excluded lenalidomide and carfilzomib dosing may resume at the same dose, if clinically appropriate. If condition recurs, permanently discontinue carfilzomib.	
Respiratory		
Dyspnea Grade 2, 3 or 4	Full dose	Hold carfilzomib until resolution to baseline, then resume at 1 dose decrement
Pulmonary hypertension: (≥Grade 3)	Full dose	Hold carfilzomib until resolution to baseline, then resume at 1 dose decrement
Pulmonary toxicity Interstitial lung disease, acute respiratory failure, ARDS (≥Grade 3)	Hold lenalidomide until resolution to baseline then resume full dose	Hold carfilzomib until resolution to baseline, then resume at 1 dose decrement
Other Symptoms Not Listed Above		
Any other drug-related nonhematologic toxicity ≥ Grade 3[b]	For lenalidomide attribution, hold dose. Resume at 1 dose decrement when toxicity has resolved to Grade 1 or less or to baseline grade.	For carfilzomib attribution, hold dose. Resume at 1 dose decrement when toxicity has resolved to Grade 1 or less or to baseline[c] grade.

Page 3 of 3

Section: 10.2.1 PHARMACOKINETIC MEASUREMENTS

Paragraph 1

Replace:

For both the Dose-evaluation and the Dose-expansion Components, blood samples will be collected from all subjects for determination of plasma concentrations of carfilzomib. Subjects enrolled prior to protocol amendment 2: PK samples will be collected on treatment Day 8 of Cycle 1. Subjects enrolled under protocol amendment 2: PK samples will be collected on Day 1 of Cycle 2.

With:

For both the Dose-evaluation and the Dose-expansion Components, blood samples will be collected from all subjects **on Day 8 of Cycle 1** for determination of plasma concentrations of carfilzomib. ~~Subjects enrolled prior to protocol amendment 2: PK samples will be collected on treatment Day 8 of Cycle 1. Subjects enrolled under protocol amendment 2: PK samples will be collected on Day 1 of Cycle 2.~~

Section: 10.2.2 PHARMACODYNAMIC MEASUREMENTS

Paragraphs 2 and 3

Replace:

For the Dose-evaluation component Cohorts 1 and 2 whole blood will be collected (pre-carfilzomib dose and post-carfilzomib dose) from all subjects on Days 1 and 8 of Cycle 1. On Days 9 and 11 of Cycle 1, when carfilzomib is not administered, one PDn sample will be collected at approximately the same time as when the pre-infusion sample was taken on Day 8.

For the first 8 NDMM subjects enrolled in Cohort 4 under protocol amendment 2, whole blood will be collected pre-carfilzomib dose and post-carfilzomib dose on Cycle 1 Day 1 and Cycle 2 Day 1; post-carfilzomib dose on Days 8 and 15 of Cycles 1 and 2.

With:

For the Dose-evaluation component Cohorts 1 and 2**, and the first 8 subjects enrolled into Dose-expansion Arm 3,** whole blood will be collected ~~(pre-carfilzomib dose and post-carfilzomib dose) from all subjects~~**.** **O**n Days 1 and 8 of Cycle 1**, whole blood will**

be collected pre-carfilzomib dose and post-carfilzomib dose. On Days 9 and 11 of Cycle 1, when carfilzomib is not administered, one PDn sample will be collected at approximately the same time as when the pre-infusion sample was taken on Day 8.

~~For the first 8 NDMM subjects enrolled in Cohort 4 under protocol amendment 2, whole blood will be collected pre-carfilzomib dose and post-carfilzomib dose on Cycle 1 Day 1 and Cycle 2 Day 1; post-carfilzomib dose on Days 8 and 15 of Cycles 1 and 2.~~

Section: 13.8 INTERIM ANALYSIS

Delete:

For subjects with relapsed disease, under the null hypothesis of ORR ≤ 55%, the alternative hypothesis of ORR ≥ 75%, and the beta (0.65, 0.35) prior distribution for the true ORR, the boundaries for number of subjects with overall responses based on Bayesian predictive probability (Lee 2008) are listed below in Table 13~~Table 13~~.

Section: 15 REFERENCES

Add:

Shibata S, Chung V, Synold TW, et al. Phase I study of pazopanib in patients with advanced solid tumors and hepatic dysfunction: a National Cancer Institute Organ Dysfunction Working Group study. Clin Cancer Res. 2013;19(13):3631-3639.

Section: Appendix A SCHEDULE OF STUDY ASSESSMENTS

Replace:

APPENDIX A SCHEDULE OF STUDY ASSESSMENTS

Assessment		Screening [a]	Baseline [b]	Cycles 1 through 18							EOT [c]	Active Follow-up
				D1	D8	D9	D11	D15	D21	D22		
Informed Consent		X										
Inclusion/exclusion criteria		X										
Medical and treatment history		X										
Time of pre-carfilzomib resting BP and time of dexamethasone administration (Cycles 1-6, 12, and 18)				X	X			X				
Vital signs		X		X	X			X			X	
Post-carfilzomib BP (Cycles 1-6, 12, and 18)				X	X			X				
Physical examination [d] and ECOG Performance Score		X		X							X	
Hematology		X		X	X			X			X	
Full serum chemistry panel [e]		X		X							X	
Abbreviated serum chemistry panel [f]					X			X				
Coagulation			X								X	
ECG (repeat if clinically indicated)		X										
ECHO/MUGA	Dose–evaluation cohorts (Cycle 2 and as clinically indicated)	X						X			X	
	Dose–expansion cohorts (repeat if clinically indicated)	X									X	

Footnotes defined on last page of table

APPENDIX A SCHEDULE OF STUDY ASSESSMENTS (CONT'D)

Assessment		Screening[a]	Baseline[b]	Cycles 1 through 18							EOT[c]	Active Follow-up
				D1	D8	D9	D11	D15	D21	D22		
Pregnancy testing (for FCBP)	Serum (10–14 days prior to C1D1)	X									X	
	Urine or serum Cycle 1 (predose)			X	X			X		X		
	Urine or serum Cycle 2–18 (predose; no menses)			X								
	Urine or serum Cycle 2–18 (predose; irregular menses)			X				X				
SPEP/UPEP/immunofixation (except Cycle 1)		X		X							X	X
Serumfree light chains (except Cycle 1)		X		X							X	X
Quantitative immunoglobulins (except Cycle 1)		X		X							X	X
Beta-2 microglobulin			X									
Skeletal survey (repeat if clinically indicated)			X									
Plasmacytoma evaluation (if clinically indicated at baseline and repeat to confirm response)			X									
Bone marrow aspirate	Percent plasma cell involvement (local lab): Baseline and upon CR		X									
	FISH testing (central lab): Baseline		X									
	MRD (central lab): Baseline; Cycle 8 Day 1; and upon achieving CR or sCR		X	X[g]								
	Genomics (optional; central lab; baseline is run on remaining sample after FISH): Baseline, EOT, and active follow-up, if PD in subjects consenting to genomics evaluation		X								X[h]	X[h]

Footnotes defined on last page of table

APPENDIX A SCHEDULE OF STUDY ASSESSMENTS (CONT'D)

Assessment		Screening[a]	Baseline[b]	Cycles 1 through 18							EOT[c]	Active Follow-up
				D1	D8	D9	D11	D15	D21	D22		
Blood for MRD/NGS (central lab): Baseline; Cycle 8 Day 1; and upon achieving CR or sCR			X	X[g]								
Genomic Biomarkers blood and saliva (optional)			X									
Plasma PK	Cohorts 1-2 NDMM subjects enrolled prior to protocol amendment 2 (Cycle 1)				X							
	Under protocol amendment 2: NDMM subjects (Cycle 2 only)			X								
Blood for PDn	Cohorts 1-2 (Cycle 1 only)			X[i]	X[i]	X[j]	X[j]					
	First 8 NDMM subjects enrolled under protocol amendment 2 (Cycle 1-2 only)			X[i]	X[k]			X[k]				
Questionnaire: patient convenience/satisfaction (Cycles 3 and 18 only)				X								
IV hydration (Cycle 1 only)				X	X			X				
Carfilzomib administration				X	X			X				
Dexamethasone administration[l]	Cycles 1 to 8			X	X			X		X		
	Cycles 9 to 18			X	X			X				
Lenalidomide administration				→								
Adverse events		→										
Concomitant medications		→										

Footnotes defined on last page of table

Page 3 of 3

BP = blood pressure; BSA = body surface area; CR = complete response; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FCBP = females of childbearing potential; FISH = fluorescent in situ hybridization; IV = intravenous (ly); MRD = minimal residual disease; MUGA = multigated acquisition; NDMM = newly diagnosed multiple myeloma; PD = progressive disease; PDn = pharmacodynamic(s); PK = pharmacokinetic(s); RRMM = relapsed and refractory multiple myeloma; sCR = stringent complete response; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis

Details of Assessments are in the protocol body.

[a] Screening samples can be collected within 21 days of Cycle 1 Day 1.

[b] It is recommended that baseline samples are collected only after subject is enrolled.

[c] EOT visit must be scheduled 28 ± 7 days after the last study treatment. EOT ECHO must be performed within 28 ± 7 days after the last study treatment.

[d] Height is only measured once at screening. BSA is not calculated on Day1 of Cycle 1 or at EOT visit.

[e] Full serum chemistry panel will also be collected on Days 8 and 15 of Cycle 1.

[f] Abbreviated serum chemistry panel will be collected Cycle 2 onwards, Days 8 and 15 (as listed in table).

[g] After baseline, collect aspirate and blood for MRD only on Day 1 Cycle 8, all subjects, and upon achieving a CR or sCR in all subjects.

[h] Optional bone marrow aspirate to be collected upon progression of disease in subjects consenting to optional genomic biomarker analysis.

[i] Predose and postdose.

[j] On Days 9 and 11, when carfilzomib is not administered, collect 1 PDn sample at approximately the same time as when the pre-infusion sample was taken on Day 8.

[k] Postdose only.

[l] Dexamethasone should be administered 30 minutes to 4 hours prior to initiation of carfilzomib infusion.

With:

APPENDIX A SCHEDULE OF STUDY ASSESSMENTS

Assessment		Screening [a]	Baseline [b]	Cycles 1 through 18							EOT [c]	Active Follow-up
				D1	D8	D9	D11	D15	D21	D22		
Informed Consent		X										
Inclusion/exclusion criteria		X										
Medical and treatment history		X										
Time of pre-carfilzomib resting BP and time of dexamethasone administration (Cycles 1-6, 12, and 18)				X	X			X				
Vital signs		X		X	X			X			X	
Post-carfilzomib BP (Cycles 1-6, 12, and 18)				X	X			X				
Physical examination [d] and ECOG Performance Score		X		X							X	
Hematology		X		X	X			X			X	
Full serum chemistry panel [e]		X		X							X	
Abbreviated serum chemistry panel [f]					X			X				
Coagulation			X								X	
ECG (repeat if clinically indicated)		X										
ECHO/MUGA	Dose–evaluation cohorts (Cycle 2 and as clinically indicated)	X						X			X	
	Dose–expansion **arms** (repeat if clinically indicated)	X									X	

Footnotes defined on last page of table

APPENDIX A SCHEDULE OF STUDY ASSESSMENTS (CONT'D)

Assessment		Screening[a]	Baseline[b]	Cycles 1 through 18							EOT[c]	Active Follow-up
				D1	D8	D9	D11	D15	D21	D22		
Pregnancy testing (for FCBP)	Serum (10–14 days prior to C1D1)	X									X	
	Urine or serum Cycle 1 (predose)			X	X			X		X		
	Urine or serum Cycle 2–18 (predose; no menses)			X								
	Urine or serum Cycle 2–18 (predose; irregular menses)			X				X				
SPEP/UPEP/immunofixation (except Cycle 1)		X		X							X	X
Serum free light chains (except Cycle 1)		X		X							X	X
Quantitative immunoglobulins (except Cycle 1)		X		X							X	X
Beta-2 microglobulin			X									
Skeletal survey (repeat if clinically indicated)			X									
Plasmacytoma evaluation (if clinically indicated at baseline and repeat to confirm response)			X									
Bone marrow aspirate	Percent plasma cell involvement (local lab): Baseline and upon CR		X									
	FISH testing (central lab): Baseline		X									
	MRD (central lab): Baseline; Cycle 8 Day 1; and upon achieving CR or sCR		X	X[g]								
	Genomics (optional; central lab; baseline is run on remaining sample after FISH): Baseline, EOT, and active follow-up, if PD in subjects consenting to genomics evaluation		X								X[h]	X[h]

Footnotes defined on last page of table

APPENDIX A SCHEDULE OF STUDY ASSESSMENTS (CONT'D)

Assessment		Screening [a]	Baseline [b]	Cycles 1 through 18							EOT [c]	Active Follow-up
				D1	D8	D9	D11	D15	D21	D22		
Blood for MRD/NGS (central lab): Baseline; Cycle 8 Day 1; and upon achieving CR or sCR			X	X[g]								
Genomic Biomarkers blood and saliva (optional)			X									
Plasma PK	~~Cohorts 1-2 NDMM subjects enrolled prior to protocol amendment 2~~ (Cycle 1 **only**)				X							
	~~Under protocol amendment 2: NDMM subjects (Cycle 2 only)~~			~~X~~								
Blood for PDn	Cohorts 1-2 **and first 8 subjects in Arm 3** (Cycle 1 only)			X[i]	X[i]	X[j]	X[j]					
	~~First 8 NDMM subjects enrolled under protocol amendment 2 (Cycle 1-2 only)~~			~~X~~[i]	~~X~~[k]			~~X~~[k]				
Questionnaire: patient convenience/satisfaction -(Cycles 3 and 18 only)				X								
IV hydration (Cycle 1 only)				X	X			X				
Carfilzomib administration				X	X			X				
Dexamethasone administration[k]	Cycles 1 to 8			X	X			X		X		
	Cycles 9 to 18			X	X			X				
Lenalidomide administration				→								

APPENDIX A SCHEDULE OF STUDY ASSESSMENTS (CONT'D)

Assessment	Screening [a]	Baseline [b]	Cycles 1 through 18							EOT [c]	Active Follow-up
			D1	D8	D9	D11	D15	D21	D22		
Adverse events	→	→	→	→	→	→	→	→	→	→	→
Concomitant medications	→	→	→	→	→	→	→	→	→	→	→

Footnotes defined on last page of table

Page 3 of 3

BP = blood pressure; BSA = body surface area; CR = complete response; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FCBP = females of childbearing potential; FISH = fluorescent in situ hybridization; IV = intravenous (ly); MRD = minimal residual disease; MUGA = multigated acquisition; ~~NDMM = newly diagnosed multiple myeloma;~~ PD = progressive disease; PDn = pharmacodynamic(s); PK = pharmacokinetic(s)~~; RRMM = relapsed and refractory multiple myeloma~~; sCR = stringent complete response; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis

Details of Assessments are in the protocol body.

[a] Screening samples can be collected within 21 days of Cycle 1 Day 1.

[b] It is recommended that baseline samples are collected only after subject is enrolled.

[c] EOT visit must be scheduled 28 ± 7 days after the last study treatment. EOT ECHO must be performed within 28 ± 7 days after the last study treatment.

[d] Height is only measured once at screening. BSA is not calculated on Day1 of Cycle 1 or at EOT visit.

[e] Full serum chemistry panel will also be collected on Days 8 and 15 of Cycle 1.

[f] Abbreviated serum chemistry panel will be collected Cycle 2 onwards, Days 8 and 15 (as listed in table).

[g] After baseline, collect aspirate and blood for MRD only on Day 1 Cycle 8, all subjects, and upon achieving a CR or sCR in all subjects.

[h] Optional bone marrow aspirate to be collected upon progression of disease in subjects consenting to optional genomic biomarker analysis.

[i] Predose and postdose.

[j] On Days 9 and 11, when carfilzomib is not administered, collect 1 PDn sample at approximately the same time as when the pre-infusion sample was taken on Day 8.

~~[k] Postdose only.~~

[k] Dexamethasone should be administered 30 minutes to 4 hours prior to initiation of carfilzomib infusion.

Section: Appendix I

Replace:

APPENDIX I SUMMARY OF CHANGES IN STUDY CFZ013 AMENDMENT 2

This Summary of Changes outlines noteworthy changes from protocol amendment 1.0 to protocol amendment 2.0, and includes rationales for the changes. Administrative updates, typographical and formatting changes were made throughout the protocol. Updates have been implemented to align with the current template. The main purposes for revising the CFZ013 (20140241) protocol are as follows:

A Dose-evaluation Component is added for newly diagnosed multiple myeloma (NDMM) subjects. During the conduct of the trial, NDMM subjects were enrolled into Dose-expansion Arm 1 (treated at Cohort 2 dosing; Table 2 and Appendix E).

- When 2 serious adverse events were seen during Cycle 1 in the first 8 NDMM subjects, an ad hoc Cohort Safety Review Committee (CSRC) meeting was held. The CSRC elected to:
  - continue the study
  - evaluate NDMM subjects in Dose-evaluation cohorts prior to opening additional NDMM Dose-expansion cohorts
  - modify Cycle 1 dosing for NDMM subjects as shown in Table 2, Cohort 4. After the ad hoc CSRC meeting, investigators were instructed to treat NDMM subjects at dosing herein referred to as Cohort 4 dosing.
- Dose-evaluation enrollment guideline text is modified. The language was broadened, to apply to both relapsed and refractory multiple myeloma RRMM Dose-evaluation and the newly added NDMM Dose-evaluation components of the trial
- Autologous stem cell transplant (ASCT) is now allowed for NDMM subjects while remaining on trial. The previous version allowed enrollment of transplant-eligible NDMM subjects and stem cell harvest but did not allow ASCT for subjects on trial.
- Simplified study schema (Figure 1)
- Revised blood collection schedule for pharmacokinetics and pharmacodynamics for NDMM cohort, to reflect dosing schedule
- Added dose rationale for new dosing regimen
- Modified study duration, given delay in enrollment of NDMM subjects

- For treatment guidelines:
  - modified guidelines for thrombotic microangiopathy and Posterior Reversible Encephalopathy Syndrome to align with the current Carfilzomib Investigator's Brochure Amgen/Onyx. Carfilzomib Investigator's Brochure. Onyx Therapeutics, Inc. (a wholly owned subsidiary of Onyx Pharmaceuticals, Inc., an Amgen Inc. subsidiary).
  - specified guidelines for pulmonary hypertension to align with the current Carfilzomib IB

- For study procedures:
  - Added Section 10.1.1 Baseline Procedures
  - revised vital signs collection text to clarify post-dose blood pressure collection on treatment days
  - removed peripheral neuropathy assessment from physical examination assessments
  - required urine protein electrophoresis with immunofixation for every disease assessment
  - specified that local bone marrow pathology assessment will be done to evaluate for complete response
- Modified Appendix C: removed text referring to subjects without measurable serum M-protein, urine M-protein or serum free light chains at baseline, as these subjects are not eligible for enrollment.
- To clarify changes to the protocol, added Appendix E APPENDIX E Figures from protocol amendment 1

The following changes were done to align the protocol with the current Amgen Clinical Protocol Template:

- Changed the language in Section 12 (Adverse Events and Serious Adverse Events)
- Modified analysis of the conduct of the study
- Added publication policy section
- Added APPENDIX F Additional Safety Assessment Information
- Added: APPENDIX G Sample eSerious Event Contingency Form
- Added APPENDIX H Pregnancy and Lactation Notification Worksheets

With:

APPENDIX I SUMMARY OF CHANGES IN STUDY CFZ013 AMENDMENT **3**

-This Summary of Changes outlines noteworthy changes from protocol amendment **2**.0 to protocol amendment **3**.0, and includes rationales for the changes. Administrative updates, typographical and formatting changes were made throughout the protocol. ~~Updates have been implemented to align with the current template.~~ The main purposes for revising the CFZ013 (20140241) protocol are **listed below**:

Protocol amendment 3 specifies the dosing selected for newly diagnosed multiple myeloma (NDMM) Dose-expansion Arm 3. The carfilzomib, lenalidomide, and dexamethasone (KRd) dosing for Arm 3 is as follows: carfilzomib 20 mg/m^2 on Day 1 of Cycle 1, then 56 mg/m^2 on Days 8 and 15 of Cycle 1, and Days 1, 8, and 15 of Cycles 2-18. Lenalidomide will be given at 25 mg on Days 1-21, and dexamethasone at 40 mg on Days 1, 8, 15, 22 of Cycles 1-8, and on Days 1, 8, and 15 of Cycles 9-18 (see Cohort 1 dosing in Table 2).

The pharmacokinetics (PK) and pharmacodynamics (PDn) sample collection schedule was modified to reflect the dosing selected. Cycle 2 sampling that was introduced in protocol amendment 2, in anticipation of a 2-step-up dosing regimen, has been removed as it is not required for the dosing selected for Dose-expansion Arm 3.

Two revisions were made in response to the carfilzomib US Prescribing Information (USPI) labelling change approved by FDA in November 2016, which required a 25% dose reduction in patients with mild or moderate hepatic impairment:

- **Table 9 (Treatment Guidelines for Nonhematologic Toxicity) has been modified to align with requested changes. Specifically, NCI Organ Dysfunction Working Group definition of mild, moderate and severe hepatic impairment were used (Shibata et al, 2013):**
  - **mild: total bilirubin (>33% direct) > the upper limit of normal (ULN) and ≤ 1.5x ULN OR total bilirubin (>33% direct) ≤ ULN and alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > ULN;**
  - **moderate: total bilirubin .5x ULN and ≤ 3x ULN, any ALT or AST;**
  - **severe: total bilirubin > 3x ULN, any ALT or AST.**

  Subjects with treatment-emergent mild or moderate hepatic impairment, per this definition, are to have a 25% carfilzomib dose reduction. In cases of severe hepatic impairment, carfilzomib is to be held. In moderate or severe hepatic impairment, lenalidomide is to be held.
- **Inclusion criteria have been modified in Section 6.1. Previous protocol amendments allowed enrollment of subjects with baseline mild hepatic insufficiency. With protocol amendment 3 (under which only the NDMM Dose-expansion Arm 3 subjects will be enrolled), subjects will be required to have normal hepatic function. The intent of this modification is to maximize the ability to give full, protocol-specified 20/56 mg/m^2 carfilzomib dosing to the enrolled NDMM subjects.**

Other minor changes:

- **To maintain internal consistency of the document, Dose-expansion groups are uniformly referred to "Arms" with the term "Cohort" reserved for Dose-evaluation groups.**
- **Changed the duration of enrollment from 8 to 12 months.**

APPENDIX I SUMMARY OF CHANGES IN STUDY CFZ013

AMENDMENT 2

This Summary of Changes outlines noteworthy changes from protocol amendment 1.0 to protocol amendment 2.0, and includes rationales for the changes. Administrative updates, typographical and formatting changes were made throughout the protocol. Updates have been implemented to align with the current template. The main purposes for revising the CFZ013 (20140241) protocol are as follows:

A Dose-evaluation Component is added for newly diagnosed multiple myeloma (NDMM) subjects. During the conduct of the trial, NDMM subjects were enrolled into Dose-expansion Arm 1 (treated at Cohort 2 dosing; Table 2 and Appendix E).

- **When 2 serious adverse events were seen during Cycle 1 in the first 8 NDMM subjects, an ad hoc Cohort Safety Review Committee (CSRC) meeting was held. The CSRC elected to:**
  - **continue the study**
  - **evaluate NDMM subjects in Dose-evaluation cohorts prior to opening additional NDMM Dose-expansion cohorts**
  - **modify Cycle 1 dosing for NDMM subjects as shown in Table 2, Cohort 4. After the ad hoc CSRC meeting, investigators were instructed to treat NDMM subjects at dosing herein referred to as Cohort 4 dosing.**
- **Dose-evaluation enrollment guideline text is modified. The language was broadened, to apply to both relapsed and refractory multiple myeloma RRMM Dose-evaluation and the newly added NDMM Dose-evaluation components of the trial**
- **Autologous stem cell transplant (ASCT) is now allowed for NDMM subjects while remaining on trial. The previous version allowed enrollment of transplant-eligible NDMM subjects and stem cell harvest but did not allow ASCT for subjects on trial.**
- **Simplified study schema (Figure 1)**
- **Revised blood collection schedule for pharmacokinetics and pharmacodynamics for NDMM cohort, to reflect dosing schedule**
- **Added dose rationale for new dosing regimen**
- **Modified study duration, given delay in enrollment of NDMM subjects**

- **For treatment guidelines:**
  - **modified guidelines for thrombotic microangiopathy and Posterior Reversible Encephalopathy Syndrome to align with the current Carfilzomib Investigator's Brochure Amgen/Onyx. Carfilzomib Investigator's Brochure. Onyx Therapeutics, Inc. (a wholly owned subsidiary of Onyx Pharmaceuticals, Inc., an Amgen Inc. subsidiary).**
  - **specified guidelines for pulmonary hypertension to align with the current Carfilzomib IB**

- **For study procedures:**
  - **Added Section 10.1.1 Baseline Procedures**
  - **revised vital signs collection text to clarify post-dose blood pressure collection on treatment days**
  - **removed peripheral neuropathy assessment from physical examination assessments**
  - **required urine protein electrophoresis with immunofixation for every disease assessment**
  - **specified that local bone marrow pathology assessment will be done to evaluate for complete response**
- **Modified Appendix C: removed text referring to subjects without measurable serum M-protein, urine M-protein or serum free light chains at baseline, as these subjects are not eligible for enrollment.**
- **To clarify changes to the protocol, added Appendix E APPENDIX E** Figures from protocol amendment 1

The following changes were done to align the protocol with the current Amgen Clinical Protocol Template:

- **Changed the language in Section 12 (Adverse Events and Serious Adverse Events)**
- **Modified analysis of the conduct of the study**
- **Added publication policy section**
- **Added APPENDIX F Additional Safety Assessment Information**
- **Added: APPENDIX G Sample eSerious Event Contingency Form**
- **Added APPENDIX H Pregnancy and Lactation Notification Worksheets**

APPENDIX E SUMMARY OF CHANGES IN STUDY CFZ013

AMENDMENT 1

Administrative updates, editorial changes, and style and formatting revisions have been made to improve clarity and consistency throughout the document. Significant changes and their rationale are described in the table below.

Main changes include the following:

- Allow for replacement of non-DLT evaluable subjects
- Define EOT visit window
- Include information distributed in former “Protocol Clarification Letters”
- Align with current Core Risk and Discomforts language
- Update subject questionnaire forms
- Align with current sponsor protocol SOP