CLINICAL STUDY PROTOCOL

Protocol Title:	A Randomized, Open-label, Phase 3 Study in Subjects with Relapsed and Refractory Multiple Myeloma Receiving Carfilzomib in Combination with Dexamethasone, Comparing Once-weekly versus Twice-weekly Carfilzomib Dosing
Protocol Number:	20140355 (Formerly CFZ014)
Name of Investigational Product:	Carfilzomib for Injection
IND Number:	IND 71,057
EudraCT Number:	2014-005325-12
Sponsor:	Onyx Therapeutics, Inc., an Amgen Inc. subsidiary One Amgen Center Drive Thousand Oaks, CA 91320 USA
Study Medical Monitor:	PPD, MD, MS One Amgen Center Drive, M/S 27-4-A Thousand Oaks, CA 91320 USA PPD
Investigator(s):	PPD, MD PPD, MD PPD MD
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Date of Protocol Amendment 3.0:	22 April 2016
Date of Protocol Amendment 4.0:	**08 February 2017**
Date of Superseding Protocol Amendment 4.0:	**07 March 2017**
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.

NCT Number: 02412878
This NCT number has been applied to the document
for purposes of posting on clinicaltrials.gov

Compliance Statement: This study will be conducted in accordance with Protocol 20140355, 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: 20140355 (**Superseding** Protocol Amendment **4**.0)/**07 March 2017**

I have read this protocol for Study 20140355 entitled: A Randomized, Open-label, Phase 3 Study in Subjects with Relapsed and Refractory Multiple Myeloma Receiving Carfilzomib in Combination with Dexamethasone, Comparing Once-weekly versus Twice-weekly Carfilzomib Dosing

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 or its designee (please retain a copy for your files).

SYNOPSIS

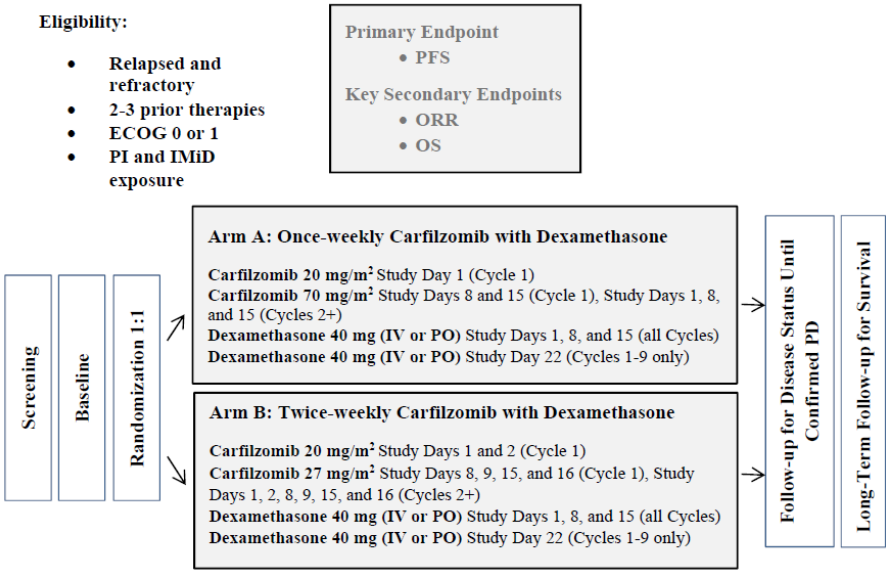
Name of sponsor/company:	Onyx Therapeutics, Inc.
Name of product:	Carfilzomib for Injection
Title of study and protocol number and phase:	A Randomized, Open-label, Phase 3 Study in Subjects with Relapsed and Refractory Multiple Myeloma Receiving Carfilzomib in Combination with Dexamethasone, Comparing Once-weekly versus Twice-weekly Carfilzomib Dosing / 20140355
Study objective(s):	**Primary Objective** To compare the **progression-free survival** (**PFS**) of once-weekly carfilzomib dosing in combination with dexamethasone to the **PFS** of twice-weekly carfilzomib dosing in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma who have received prior treatment with a proteasome inhibitor and an IMiD (immunomodulatory agent). **Secondary Objectives** To compare the following between treatment groups: • **Overall response rate** (**ORR**) • Overall survival (OS) • Safety and tolerability • Pharmacokinetics (PK) of carfilzomib using sparse sampling **Exploratory Objectives** • Intensive pharmacokinetics (PK) and pharmacodynamics (PDn) of carfilzomib in a subset of subjects (substudy) • All subscales of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Core Module (QLQ-C30), and the EORTC Quality of Life Multiple Myeloma Module 20 (QLQ-MY20) • European Quality of Life-5 Dimensions (EQ-5D-5L); a standardized measure of health status developed by the European Quality of Life (EuroQol) Group • Patient reported convenience and satisfaction with the carfilzomib schedule • Healthcare resource utilization
Study design:	This is an open-label, multicenter, randomized Phase 3 study comparing carfilzomib dosing in combination with dexamethasone administered once-weekly to twice-weekly carfilzomib dosing in subjects with relapsed and refractory multiple myeloma, previously treated with a proteasome inhibitor and an IMiD. The primary endpoint is **PFS**. The study design is illustrated in the schema below. Eligible subjects will be randomized in a 1:1 ratio to receive a regimen consisting of either once-weekly or twice-weekly carfilzomib in combination with dexamethasone. The randomization will be stratified by: • The International Staging System (ISS) at study entry (Stage 1 versus Stage 2 or 3) per International Myeloma Working Group (Greipp 2005). See Appendix H • Refractory to bortezomib treatment (Yes versus No) • Age (< 65 versus ≥ 65 years)

Study design (cont'd):

Study treatment will be administered in 28-day cycles. Subjects will receive study treatment determined by randomization until disease progression, unacceptable toxicity, withdrawal of consent, or death (whichever occurs first). No crossover between the 2 treatment groups will be allowed.

Following termination of study treatment all subjects will be followed for disease status (if progressive disease [PD] has not been reached), subsequent antimyeloma treatment, and survival. All subjects will be followed for safety at least 30 additional days after the last study treatment administration. All treatment-related adverse events (AEs) and serious adverse events (SAEs) will be followed until resolution or stabilization.

Study 20140355 Schema



ECOG = Eastern Cooperative Oncology Group; IMiD = immunomodulatory agents; IV = intravenous(ly); ORR = overall response rate; OS = overall survival; PD = **progressive disease**; PFS = progression-free survival; PI = proteasome inhibitor; PO = orally.

Subjects will be assessed for response using central laboratory results every 28 days (± 4 days). Subjects are followed for disease status until confirmed PD. Long-term follow-up (LTFU) for disease status (only in cases where subjects discontinued treatment prior to PD) and for survival (after reaching PD) will continue after treatment discontinuation or until the subject has withdrawn consent for further participation, is lost to follow-up, has died, or the sponsor makes a decision to close the study. For subjects who discontinued treatment before disease progression occurred (such as for an adverse event, noncompliance, etc.), disease response assessments will be performed using central laboratory results every 28 days until disease progression. Follow-up for survival will continue approximately every 12 weeks ± 28 days, or as needed, for all surviving subjects until study closure. For any subject who is lost to follow-up, the study site will attempt to ascertain survival information via public database search.

Number of investigational sites:	Approximately 150 sites worldwide
Planned number of subjects:	460 subjects 230 each arm
Sample size justification:	CCI **the sample size of 460 subjects (230 in each arm** CCI **a total of 350 PFS events for the final PFS analysis will provide 83% power to detect a significant difference in PFS between the 2 treatment groups with 1-sided overall Type-I error of 0.025 when 1 interim analysis is performed at approximately 75% information time (i.e., 263 events) using the O'Brien-Fleming type alpha spending function,** CCI CCI
Study population:	Adults with relapsed and refractory multiple myeloma will be considered for eligibility. Subjects must have had at least 2 but no more than 3 prior therapies for multiple myeloma.

Treatment regimen(s):	Carfilzomib and dexamethasone will be administered in 28-day cycles in 1 of 2 treatment regimens. All cycles will start 28 days (± 2 days) after the start of the prior cycle.
	Arm A: Once-weekly
	• Carfilzomib 20 mg/m^2
	  ○ Study Day 1 (Cycle 1)
	• Carfilzomib 70 mg/m^2
	  ○ Study Days 8 and 15 (Cycle 1)
	• Carfilzomib 70 mg/m^2
	  ○ Study Days 1, 8, and 15 (Cycles 2+)
	• Dexamethasone
	  ○ 40 mg (intravenously [IV] or orally [PO]) Study Days 1, 8, and 15 (all Cycles)
	  ○ 40 mg (IV or PO) Study Day 22 (Cycles 1 to 9 only)
	Arm B: Twice-weekly
	• Carfilzomib 20 mg/m^2
	  ○ Study Days 1 and 2 (Cycle 1)
	• Carfilzomib 27 mg/m^2
	  ○ Study Days 8, 9, 15, and 16 (Cycle 1)
	• Carfilzomib 27 mg/m^2
	  ○ Study Days 1, 2, 8, 9, 15, and 16 (Cycles 2+)
	• Dexamethasone
	  ○ 40 mg (IV or PO) Study Days 1, 8, and 15 (all Cycles)
	  ○ 40 mg (IV or PO) Study Day 22 (Cycles 1 to 9 only)

Subject selection:	Approximately 460 subjects will be randomized in this study. Subjects will be evaluated for study eligibility within the 21 days prior to randomization.

Inclusion criteria:

101. Age ≥ 18 years

102. Able to provide written informed consent in accordance with federal, local, and institutional guidelines

103. Relapsed multiple myeloma

104. Refractory multiple myeloma**,** defined as meeting 1 or more of the following:

a. Nonresponsive to most recent therapy (stable disease or PD while on treatment), or

b. Disease progression within 60 days of discontinuation from most recent therapy

105. At least 2 but no more than 3 prior lines of therapies for multiple myeloma

106. Prior exposure to an immunomodulatory agent (IMiD)

107. Prior exposure to a proteasome inhibitor (PI)

108. Documented response of at least partial response (PR) to at least 1 prior line of therapy

109. Measurable disease with at least 1 of the following assessed at a central laboratory within the 21 days prior to randomization:

a. Serum M-protein ≥ 0.5 g/dL

b. Urine M-protein ≥ 200 mg/24 hours

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

110. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1

111. Left ventricular ejection fraction (LVEF) ≥ 40% within the 21 days prior to randomization

112. Adequate organ and bone marrow function performed at a central laboratory within the 21 days prior to randomization**,** defined by:

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

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

c. Absolute neutrophil count (ANC) ≥ 1 x 10^9/L (screening ANC must be independent of growth factor support for ≥ 7 days)

d. Hemoglobin ≥ 8 g/dL (Use of erythropoietic stimulating factors and red blood cell [RBC] transfusion**s** per institutional guidelines are allowed, however the most recent RBC transfusion may not have been done within 7 days prior to obtaining the screening hemoglobin)

e. Platelet count ≥ 50,000/mm^3 (≥ 30,000/mm^3 if myeloma involvement in the bone marrow is > 50%. Subjects must not have received platelet transfusions for at least 7 days prior to obtaining the screening platelet count)

f. Calculated or measured creatinine clearance (CrCl) of ≥ 30 mL/min. Calculation must be based on the Cockcroft and Gault formula: [(140 – Age) × Mass (kg) / (72 × Creatinine mg/dL)]; multiply result by 0.85 if female

113. Females of childbearing potential (FCBP) must have a confirmed negative serum pregnancy test performed at a central laboratory within the 21 days prior to randomization and must not be breastfeeding

Inclusion criteria (cont'd):	**114.** Females of childbearing potential must agree to use highly effective method(s) of contraception during the study and for 30 days following the last study drug administration. (Refer to Appendix K for specific contraception requirements) **115.** Male subjects who are sexually active with an FCBP must agree to use condoms (unless they have had a vasectomy with medical confirmation of surgical success), during treatment and for an additional 90 days following the last study drug administration **116.** Male subjects must agree to not donate sperm, during treatment and for an additional 90 days following the last study drug administration
Exclusion criteria:	**201.** Waldenström macroglobulinemia **202.** Multiple myeloma of Immunoglobulin M (IgM) subtype **203.** POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) **204.** Plasma cell leukemia (> 2.0×10^9/L circulating plasma cells by standard differential) **205.** Myelodysplastic syndrome **206.** Second malignancy within the past 5 years except: a. Adequately treated basal cell or squamous cell skin cancer b. Carcinoma in situ of the cervix c. Prostate cancer < Gleason score 6 with stable prostate-specific antigen (PSA) over 12 months d. Ductal breast carcinoma in situ with full surgical resection (i.e., negative margins) e. Treated medullary or papillary thyroid cancer f. Similar condition with an expectation of > 95% five-year disease-free survival **207.** History of or current amyloidosis **208.** Cytotoxic chemotherapy or other antineoplastic therapy, aside from immunotherapy or proteasome inhibitors, within the 28 days prior to randomization **209.** Immunotherapy, such as an IMiD or a proteasome inhibitor within the 21 days prior to randomization **210.** Glucocorticoid therapy exceeding a cumulative dose of 160 mg of dexamethasone or equivalent within 14 days prior to randomization **211.** Radiation therapy: a. Focal therapy within the 7 days prior to randomization b. Extended field therapy within the 21 days prior to randomization **212.** Prior treatment with either carfilzomib or oprozomib **213.** Known history of allergy to Captisol (a cyclodextrin derivative used to solubilize carfilzomib) **214.** Contraindication to dexamethasone or any of the required concomitant medications or supportive treatments **215.** Active congestive heart failure (New York Heart Association [NYHA] Class III or IV, refer to Appendix F), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, acute diffuse infiltrative pulmonary disease, pericardial disease, or myocardial infarction within 6 months prior to randomization **216.** Active infection requiring systemic treatment within the 14 days prior to randomization

Exclusion criteria (cont'd):	**217.** Pleural effusions requiring thoracentesis within the 14 days prior to randomization **218.** Ascites requiring paracentesis within the 14 days prior to randomization **219.** Ongoing graft-versus-host disease **220.** Uncontrolled hypertension or diabetes mellitus **221.** Significant neuropathy (≥ Grade 3) within the 14 days prior to randomization **222.** Known cirrhosis **223.** Known human immunodeficiency virus (HIV) seropositivity, hepatitis C infection, or hepatitis B infection. Subjects with past hepatitis B virus (HBV) infection, defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen (anti HBc) antibody test, are eligible. Subjects positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA. **224.** Participation in another interventional study within the 28 days prior to randomization **225.** Major surgery (except kyphoplasty) within the 28 days prior to randomization **226.** 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, be compliant with study procedures, or provide accurate information
Efficacy variables:	The primary endpoint is **PFS**. Secondary endpoints are: **ORR**, overall survival (OS), safety and tolerability, and pharmacokinetics (sparse sampling) (PK). Disease assessments according to the International Myeloma Working Group-Uniform Response Criteria (IMWG-URC) will be conducted at baseline and then every 28 days (± 4 days) thereafter until progression.
PK (sparse sampling)	For both arms, blood samples will be collected from subjects who consent to the additional testing except for those participating in the intensive PK/PDn substudy for determination of plasma concentrations of carfilzomib on C2D1.
Intensive PK and PDn Substudy	Intensive pharmacokinetic (PK) and pharmacodynamic (PDn) samples will be obtained as a substudy (approximately n = 15 evaluable subjects in each arm) from subjects who consent to the additional testing at selected sites. Pharmacokinetic samples will be collected on Day 15 of Cycle 1 and PDn samples will be collected on Days 1, 15, 16, 17, and 22 of Cycle 1.
Health related Quality of Life (HRQL):	The following patient reported outcomes (PRO) will be collected in the study: • The EORTC 30-item QLQ-C30 questionnaire • The EORTC 20-item QLQ-MY20 module specifically designed to address the quality of life for those with multiple myeloma • The EQ-5D-5L and patient reported convenience and satisfaction questionnaire QLQ-C30, QLQ-MY20, and EQ-5D-5L questionnaires should be administered prior to study treatment on Day 1 of Cycle 1, then every second cycle (Cycle 1, 3, 5, etc) during treatment and every 12 weeks (every 84 days ± 4 days) until progression, or withdrawal of consent during LTFU. Patient convenience and satisfaction questionnaire will be collected at Day 1 Cycle 2 and end of treatment (EOT) only. Healthcare resource utilization will be collected for all subjects during the study. Details on hospitalizations (not related to adverse events) will also be collected.

Safety variables:	Safety and tolerability will be assessed by incidence and severity of adverse events and changes from baseline of all relevant parameters, including laboratory values, physical examination, vital signs**,** and electrocardiogram (ECG). Severity of adverse events will be assessed according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. All subjects will be monitored for adverse events for at least 30 days after the last administration of study treatment.
Statistical methods and analyses:	Efficacy analyses will be based on the ITT (Intent-To-Treat) Population, which includes all randomized subjects. The primary endpoint, **PFS**, **will be calculated from the time of randomization until PD or death due to any cause, whichever occurs first. If a subject is alive or lost to follow-up without experiencing documented disease progression by the data cutoff date, the PFS data for the subject will be censored at the date of last valid disease and response assessment. The distribution of PFS will be estimated using the Kaplan-Meier method. The inferential comparison between treatment groups will be made using the log-rank test stratified by the randomization stratification factors. The HR and its 95% CI will be estimated using a Cox proportional hazards model stratified by the same randomization stratification factors.** The **following** randomization stratification factors will be included in the model: • The ISS Stage at study entry (Stage 1 versus Stage 2 or 3) • Refractory to bortezomib treatment (Yes versus No) • Age (< 65 versus ≥ 65 years) **Response and disease progression will be determined using a validated computer algorithm (Onyx Response Computational Assessment [ORCA]), as well as by local investigators and by an Independent Review Committee (IRC). The primary analysis of PFS will be based on ORCA-assessed outcomes. The PFS outcomes assessed by the investigator will serve as a supportive analysis of PFS, as will IRC-assessed outcomes.** **The secondary endpoint ORR is defined as the proportion of subjects achieving a best overall response of PR, very good partial response (VGPR), complete response (CR), or stringent complete response (sCR), based on the IMWG-URC.** The ORR will be calculated by treatment group**,** and the associated 95% confidence interval [CI] will be estimated using the Clopper-Pearson method. The odds ratio (and its 95% CI) will be estimated using the logistic regression model. The duration of response (DOR), defined as time in months from the start date of the response to the earlier date of documented PD or death, will be calculated for subjects who achieve PR, VGPR, CR or sCR. The DOR will be censored at date of the last valid assessment for responders who have not experienced PD or death. The distribution of the DOR, including the median will be estimated using the Kaplan-Meier method based on the subjects who achieve overall response. The secondary endpoint of OS will be analyzed using the log-rank test stratified by the randomization stratification factors. The corresponding HRs will be estimated using a stratified Cox proportional hazards model. The distribution of OS including medians will be summarized using the Kaplan-Meier method.

Statistical methods and analyses (cont'd):	The hypotheses for the primary efficacy endpoint, **PFS**, and secondary efficacy endpoints (**ORR** and OS) will be tested using a fixed sequence hierarchical testing procedure to control the family-wise Type I error rate below 1-sided 0.025 level. The family of hypotheses is ordered as follows: **PFS**, **ORR**, and OS. Starting with the hypothesis of **PFS**, if any hypothesis in the sequence is rejected at a 1-sided significance level of 0.025, then the subsequent hypothesis will be tested; if any hypothesis is accepted, then the subsequent hypotheses will not be tested. Safety analyses will be based on the Safety Population (defined as all randomized subjects who have received at least 1 dose of study treatment). The number and percentage of subjects experiencing 1 or more AEs will be summarized by treatment group, relationship to study treatment, and severity. Changes from baseline and shift in toxicity grade in safety laboratory test results and vital signs will be summarized using descriptive statistics. Adverse events and safety laboratory test results will be graded for severity using the NCI-CTCAE Version 4.03. Subjects' demographics baseline, and disease characteristics, in addition to prior and concomitant medications and study treatment exposure will be summarized descriptively for each treatment group. **The final PFS analysis will be conducted when approximately 350 PFS events have occurred or by end of year 2018, whichever is earlier. A total of 350 PFS events will provide 83% power to detect a significant difference in PFS between the 2 treatment groups with 1 interim analysis** CCI [redacted] CCI **The interim analysis will be performed when approximately 75% of the total PFS events (i.e., 263 events) have occurred. The ORR and OS analyses will be performed at the same time as the primary PFS analysis (interim or final).**

TABLE OF CONTENTS

Page

CLINICAL STUDY PROTOCOL 1
PROTOCOL ACCEPTANCE PAGE 3
SYNOPSIS 4
TABLE OF CONTENTS 12
1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 19
2 BACKGROUND INFORMATION 23
2.1 Introduction 23
2.2 Multiple Myeloma 23
2.3 Proteasome Background 24
2.3.1 Carfilzomib Background (Nonclinical) 24
2.3.2 Carfilzomib Background (Clinical) 25
2.4 Study Rationale 27
2.5 Dose Rationale 28
2.5.1 Rationale for Once-weekly Dosing 29
2.5.2 Pharmacokinetics and Pharmacodynamics Data for Once-weekly Dosing 32
3 STUDY OBJECTIVES 35
3.1 Primary Objective 35
3.2 Secondary Objectives 35
3.3 Exploratory Objectives 35
4 EXPERIMENTAL PLAN 35
4.1 Study Design 35
4.2 Number of Centers 37
4.3 Number of Subjects 37
4.4 Estimated Study Duration and Closure 37
4.4.1 End of Study 37
5 SUBJECT ELIGIBILITY 38
5.1 Inclusion Criteria 38
5.2 Exclusion Criteria 40
6 SUBJECT SCREENING 41
7 SUBJECT RANDOMIZATION 42

8 STUDY DRUGS 43
8.1 Carfilzomib 43
8.1.1 Packaging and Labeling 43
8.1.2 Storage 43
8.2 Dexamethasone 43
8.3 Study Drug Accountability 43
8.4 PRODUCT COMPLAINTS 43
9 DOSAGE AND TREATMENT ADMINISTRATION 44
9.1 Treatment Regimen 44
9.2 Intravenous preHydration 45
9.2.1 Study Treatment Administration 45
9.2.1.1 Carfilzomib 47
9.2.1.2 Dexamethasone 47
9.3 Dose Modification RULES 47
9.3.1 Carfilzomib: RULES for Dose Modification 48
9.3.1.1 Hematologic Toxicity 48
9.3.1.2 Nonhematologic Toxicity 49
9.3.2 Dexamethasone: Guidelines for Toxicities and Dose Modification 52
9.3.3 Conditions not Requiring Dose Reduction 54
9.4 Concomitant Medications and Therapies 54
9.4.1 Required Concomitant Medications 54
9.4.1.1 Gastrointestinal Prophylaxis 54
9.4.1.2 Pregnancy and Contraception 55
9.4.2 Recommended Concomitant Medications 55
9.4.2.1 Antiviral Prophylaxis 55
9.4.2.2 Uric Acid-lowering Agents 55
9.4.2.3 Mycostatin or Oral Fluconazole 55
9.4.2.4 Antiemetics and Antidiarrheal Agents 55
9.4.2.5 Thrombophrophylaxis 55
Venous thromboembolism has been observed in patients receiving carfilzomib. Thromboprophylaxis may be considered on the basis of a benefit-risk assessment. 55
9.4.3 Excluded Concomitant Medications and Therapies 56

9.4.3.1 Anticancer Agents....56
9.4.3.2 Radiation Therapy....56
9.4.3.3 Myeloid Growth Factors....56
9.4.3.4 Corticosteroids....56
9.4.3.5 Plasmapheresis....56
9.4.3.6 Novel Agents for Non-neoplastic Conditions....57
10 STUDY ASSESSMENTS AND PROCEDURES....57
10.1 Study Specific Procedures....57
10.1.1 Multiple Myeloma History and Prior Lines of Therapy Assessment....57
10.1.2 Vital Signs....58
10.1.3 Complete Physical Examination....58
10.1.4 Eastern Cooperative Oncology Group Performance Status....59
10.1.5 International Staging System Stage Determination....59
10.2 Multiple Myeloma Disease Assessments....59
10.3 Multiple Myeloma Response Assessments....61
10.3.1 Disease Response and Progression Assessments....61
10.3.2 Tumor Response Assessment....61
10.3.3 Disease Progression....61
10.4 Laboratory Tests....62
10.4.1 Hematology....63
10.4.2 Serum Chemistry....63
10.4.3 Coagulation....64
10.4.4 Pregnancy Testing....64
10.5 Electrocardiogram....64
10.6 Echocardiogram....65
10.7 Patient Reported Outcomes....65
10.8 Healthcare Resource Utilization....67
10.9 Correlative Studies....67
10.9.1 Intensive Pharmacokinetics/Pharmacodynamics Substudy....67
10.9.2 Sparse Pharmacokinetic Sampling....68
10.10 Long-term Follow-up....68
10.10.1 Long-term Follow-up Before Disease Progression....69

10.10.2 Long-term Follow-up After Disease Progression (For Survival) 69
11 STUDY DISCONTINUATION 69
11.1 Withdrawal of Subjects from Study Treatment 69
11.2 Withdrawal of Subjects from Study 70
11.3 Study Termination 71
12 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS 71
12.1 Adverse Event Reporting 71
12.1.1 Adverse Event Terminology 71
12.1.2 Severity 72
12.1.3 Duration 73
12.1.4 Causality 73
12.2 Adverse Events Reporting Procedures 74
12.2.1 General 74
12.3 Serious Adverse Event Definition 75
12.4 Serious Adverse Event Reporting and Documentation Requirements 75
12.5 Pregnancy and Lactation Exposure Reporting 76
12.6 Death Reporting 77
13 STATISTICAL CONSIDERATIONS 77
13.1 Study Endpoints 78
13.1.1 Primary Endpoints 78
13.1.2 Secondary Endpoints 78
13.2 Study Populations 78
13.2.1 Intent-to-Treat Population 78
13.2.2 Safety Analysis Population 78
13.3 Statistical Methods 78
13.3.1 Analysis of the Conduct of the Study 78
13.3.2 Efficacy Analyses 79
13.3.2.1 Primary Efficacy Endpoint 79
13.3.2.2 Secondary Efficacy Endpoints 80
13.3.2.3 Control of Family-wise Type I Error Rate 81
13.3.3 Safety Analysis 81
13.3.3.1 Adverse Events 81
13.3.3.2 Safety Laboratory Values 82

13.3.3.3 Vital Signs....83
13.3.4 Sparse Pharmacokinetic Analyses....83
13.3.5 Exploratory Analyses....84
13.4 Handling of Data....85
13.4.1 Handling Missing Data in Descriptive Analyses....85
13.4.2 Handling Missing or Partially Missing Dates....85
13.4.3 Missing Grade or Relationship of Adverse Event to Study Treatments....86
13.4.4 Unscheduled Visits....86
13.5 Determination of Sample Size....86
13.6 Independent Review Committee....86
13.7 Data Monitoring Committee....87
13.8 Interim Analysis....87
14 REGULATORY OBLIGATIONS....88
14.1 Informed Consent....88
14.2 Compliance with Laws and Regulations....89
14.3 Subject Confidentiality....90
15 ADMINISTRATIVE AND LEGAL OBLIGATIONS....90
15.1 Protocol Amendments....90
15.2 Study Termination....91
15.3 Study Documentation and Archives....91
15.3.1 Source Documents....91
15.3.2 Archival of Records....91
15.4 Data Collection and Study Monitoring....91
15.4.1 Electronic Case Report Forms....91
15.4.2 Study Monitoring....92
15.4.3 Data Quality Assurance....92
15.5 Publication Policy....93
16 REFERENCES....94
APPENDIX A SCHEDULE OF ASSESSMENTS....97
APPENDIX B SCHEDULE OF DISEASE ASSESSMENTS....99
APPENDIX C SCHEDULE OF STUDY TREATMENT ADMINISTRATION....100

APPENDIX D SCHEDULE OF STUDY ASSESSMENTS FOR THE PHARMACOKINETIC SPARSE SAMPLING AND INTENSIVE PHARMACOKINETIC & PHARMACODYNAMIC SUB-STUDY 101

APPENDIX E ECOG PERFORMANCE STATUS.....103

APPENDIX F NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION 104

APPENDIX G SUMMARY OF INTERNATIONAL MYELOMA WORKING GROUP UNIFORM RESPONSE CRITERIA (IMWG-URC) 105

APPENDIX H INTERNATIONAL STAGING SYSTEM 107

APPENDIX I NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (NCI-CTCAE) GRADING SCALE.....108

APPENDIX J PATIENT REPORTED OUTCOMES 109

APPENDIX K COUNTRY SPECIFIC PREGNANCY AND CONTRACEPTIVE SUPPLEMENT 110

APPENDIX L SAMPLE SERIOUS ADVERSE EVENT REPORT FORM.....113

APPENDIX M PREGANCY NOTIFICATION FORM 118

APPENDIX N LACTATION NOTIFICATION FORM.....119

APPENDIX O SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 4 AND FOR SUPERSEDING PROTOCOL AMENDMENT 4 120

LIST OF TABLES

Table 1 Summary of Pharmacokinetic Parameters from CHAMPION 1 32

Table 2 Pharmacokinetic Parameters Comparison of CHAMPION 1 and PX-171-003 – Part 2 (A1).....33

Table 3 Carfilzomib Dose Decrements 48

Table 4 Carfilzomib Dose Modification Rules for Treatment-emergent Hematologic Toxicity 49

Table 5 Carfilzomib Dose Modifications for Nonhematologic Toxicity.....50

Table 6 Dose Decrements for Dexamethasone 52

Table 7 Treatment Rules for Dexamethasone-related Toxicities.....53

Table 8 Laboratory Tests: Hematology 63

Table 9 Laboratory Tests: Chemistry Panel.....64

Table 10 Study 20140355 Pharmacodynamics Sampling Timepoints 67

Table 11 Grading for Adverse Events not Covered in the NCI-CTCAE.....72

Table 12 Stopping Boundaries for Progression-free Survival 88

LIST OF FIGURES

Figure 1 Proteasome Percent Activity in Peripheral Blood Mononuclear Cells 34
Figure 2 Study 20140355 Schema.....36
Figure 3 Arm A and Arm B Carfilzomib with Dexamethasone Regimens.....46

1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADL	Activities of daily living
AE(s)	adverse event(s)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-last}}$	area under the curve from time 0 to last time measurable concentration
BSA	body surface area
BUN	blood urea nitrogen
CBR	clinical benefit rate
CFZ	carfilzomib
CI	confidence interval
C_{max}	maximum plasma concentration
C1D1	Cycle 1 Day 1
C2D1	Cycle 2 Day 1
CR	complete response
CrCl	creatinine clearance
CT	computed tomography
CT-L	chymotrypsin-like
D5W	5% Dextrose Injection
Dex	dexamethasone
DLT(s)	dose-limiting toxicity(ies)
DMC	Data Monitoring Committee
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organization for Research and Treatment of Cancer
eCRF	electronic Case Report Form
EDC	electronic data capture
EOT	End of Treatment
EQ VAS	EQ Visual Analogue scale
EuroQOL	European Quality of Life
EQ-5D-5L	European Quality of Life-5 Dimensions

Abbreviation	Definition
FDA	Food and Drug Administration
FCBP	females of childbearing potential
FISH	Fluorescence in situ hybridization
GCP	Good Clinical Practice
H2	histamine 2
HIV	human immunodeficiency virus
HR(s)	hazard ratio(s)
HRQL	health-related quality of life
HUS	hemolytic uremic syndrome
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgM	immunoglobulin M
IMiD(s)	immunomodulatory agent(s)
IMWG-URC	International Myeloma Working Group-Uniform Response Criteria
IND	Investigational New Drug
INR	international normalized ratio
IP(s)	investigational product(s)
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IRC	Independent Review Committee
ISRG	Independent Statistical Reporting Group
IST(s)	investigator-sponsored trial(s)
ISS	International Staging System
ITT	Intent-to-Treat
IUD	intrauterine device
IV	intravenous(ly)
IVR/IWR	Interactive Voice (IVR) and Web Response (IWR)
LDH	lactate dehydrogenase
LFT(s)	liver function test(s)
LMP2	latent membrane protein 2
LMP7	latent membrane protein 7
LTFU	Long-term follow-up
LVEF	left ventricular ejection fraction
MECL-1	multicatalytic endopeptidase complex-like 1
MedDRA	Medical Dictionary for Regulatory Activities
MR	minimal response

Abbreviation	Definition
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
ORCA	Onyx Response Computational Assessment
ORR	overall response rate
OS	overall survival
PBMC(s)	peripheral blood mononuclear cell(s)
PD	progressive disease
PDn	pharmacodynamics
PET	positron emission tomography
PK	pharmacokinetic
PFS	progression-free survival
PI	proteasome inhibitor
PN	peripheral neuropathy
prn	as needed
PO	orally
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes
PR	partial response
PRO(s)	patient reported outcome(s) (psychosocial measures)
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
QLQ-C30	Quality of Life Core Module
QLQ-MY20	Quality of Life Multiple Myeloma Module 20
QOL	Quality of Life
QTc	corrected QT-interval
RBC(s)	red blood cell(s)
SAE(s)	serious adverse event(s)
SAg	surface antigen
SAP	Statistical Analysis Plan
SBE-CD	sulfobutylether-beta-cyclodextrin (Captisol)
SOC	system organ class
SWI	Sterile Water for Injection
sCR	stringent complete response
SFLC	serum free light chain

Abbreviation	Definition
SOPs	Standard Operating Procedures
SPEP	serum protein electrophoresis
$t_{1/2}$	terminal half-life
TEAE(s)	treatment-emergent adverse event(s)
TLS	tumor lysis syndrome
t_{max}	time to maximum plasma concentration
TTP	thrombocytopenic thrombotic purpura
ULN	upper limit of normal
UPEP	urine protein electrophoresis
US	United States
USP	United States Pharmacopeia
VGPR	very good partial response
WBC(s)	white blood cell(s)
WOCBP	woman of childbearing potential

2 BACKGROUND INFORMATION

2.1 INTRODUCTION

Carfilzomib for Injection received accelerated approval from the United States Food and Drug Administration (US FDA) in July 2012 for the treatment of patients with multiple myeloma who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent (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 refractory multiple myeloma.

Per the 2012 approved label, carfilzomib is administered intravenously (IV) over 10 minutes, on 2 consecutive days each week for 3 weeks (Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle). The recommended Cycle 1 dose is 20 mg/m^2/day with an increase to 27 mg/m^2 on Cycle 2 Day 1 onwards.

This study will assess the superiority of a higher dose level of carfilzomib (70 mg/m^2) given once-weekly (Days 1, 8, and 15) over 30 minutes in combination with dexamethasone compared to the twice-weekly regimen at 20/27 mg/m^2 in combination with dexamethasone. Subjects will receive the study treatment determined by randomization until disease progression, unacceptable toxicity, withdrawal of consent, or mortality (whichever occurs first). Subjects will be evaluated in long-term follow-up (LTFU) for health status and survival.

2.2 MULTIPLE MYELOMA

Multiple myeloma, a clonal neoplastic proliferation of plasma cells, is the second most common hematologic malignancy and accounts 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.

Historically, multiple myeloma was treated with chemotherapy with the introduction of melphalan in the 1960s. Subsequent treatment paradigms for the next three decades relied largely on combination of chemotherapy regimens with corticosteroids, with minimal to no incremental improvements in survival. In the 1990s, the introduction of autologous stem cell transplantation (ASCT) after a conditioning regimen that incorporates high doses of melphalan resulted in improvements in survival. Additional improvements in survival followed the advent of the IMiDs, thalidomide (Thalomid) and lenalidomide (Revlimid) and the proteasome inhibitor (PI) bortezomib (Velcade) (Kumar 2008). Since then, these 3 agents have been used in combination with corticosteroids, and with chemotherapy agents (e.g., alkylating agents) (National Comprehensive Cancer Network 2014; Harousseau 2010).

Despite improvements in progression free survival (PFS) and overall survival (OS), patients who have received several lines of prior therapy experience progressively lower rates and durations of response as resistance emerges (Kumar 2004; Durie 2012; Kumar 2012)**;** and current therapeutic options for patients who have multiply relapsed and refractory disease, especially those refractory to both IMiDs and bortezomib, are limited. A recent retrospective review of 286 patients from treatment centers in the US, Europe, and Asia with a median of 4 prior therapies and 3.3 years since initial diagnosis of multiple myeloma, revealed that such patients with multiply relapsed multiple myeloma can anticipate a median OS of approximately 9 months (Kumar 2012).

2.3 PROTEASOME BACKGROUND

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 (CT-L) activity, a trypsin-like activity, and a caspase-like activity.

2.3.1 *CARFILZOMIB BACKGROUND (NONCLINICAL)*

Carfilzomib (formerly known as PR-171) is a tetrapeptide epoxyketone-based inhibitor of the 20S proteasome, primarily of the CT-L activity, and at higher concentrations,

of multiple 20S proteolytic activities. 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. Carfilzomib, which is structurally and mechanistically different from the dipeptide boronic acid PI bortezomib, 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 clinical and nonclinical studies comparing carfilzomib with bortezomib.

Carfilzomib primarily inhibits the CT-L activity of both the constitutive proteasome and the immunoproteasome (Kuhn 2007; Demo 2007). The importance for co-inhibition of multiple proteasome active sites for cytotoxicity (CT-L, trypsin-like, and/or caspase-like) has been demonstrated against multiple myeloma cell lines (Britton 2009; Geurink 2013).

Nonclinical work supported improved tolerability with increased infusion time, possibly because of the reduced maximum concentration (C_{max}) with a 30-minute IV infusion (Yang 2011). Correlative clinical pharmacodynamics (PDn) studies have confirmed that longer infusion times and higher doses of carfilzomib resulted in increased proteasome inhibition (Papadopoulos 2014; Lee 2012). Clinical evidence for carfilzomib dose response has been observed in a multivariable modeling analysis comparing 20 mg/m^2 with 27 mg/m^2, (Lonial 2011; Squifflet 2011) suggesting that more effective inhibition of proteasome activity may improve efficacy. An increased infusion time of 30 minutes enabled carfilzomib to be administered at a higher dose, with a maximum tolerated dose (MTD) of 56 mg/m^2 in Study PX-171-007**,** compared to 27 mg/m^2 over a 2 to 10-minute infusion as discussed in Section 2.3.2.

2.3.2 *CARFILZOMIB BACKGROUND (CLINICAL)*

As of 10 July 2015, approximately 2921 individual subjects have been treated with carfilzomib as participants in Onyx-sponsored clinical studies, and 89 subjects have been enrolled in studies in Japan sponsored by Ono Pharmaceutical Company. Approximately

3549 subjects have been treated with carfilzomib through the 76 completed or actively enrolling investigator-sponsored trials (ISTs) (Carfilzomib IB).

There are five Phase 3 studies in multiple myeloma: PX-171-009 (ASPIRE), PX-171-011 (FOCUS), 2011-003 (ENDEAVOR), 2012-005 (CLARION), and this study, 20140355 (A.R.R.O.W.). Additionally, 137 subjects with solid tumors have been treated with carfilzomib.

These trials have explored various doses of carfilzomib either as monotherapy or in combination with other agents and in the majority of studies conducted to date, carfilzomib has been administered on 2 consecutive days for 3 weeks in a 28-day cycle. Carfilzomib clinical activity has been demonstrated in these studies along with an acceptable safety profile.

Higher doses of carfilzomib administered on a twice-weekly schedule have been studied. PX-171-007, a Phase 1b/2 study, was the first to establish the MTD of single agent carfilzomib administered as a 30-minute infusion in subjects with relapsed and/or refractory multiple myeloma (Papadopolous 2014). Subjects received carfilzomib monotherapy on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. Cycle 1 Day 1 and Day 2 doses were 20 mg/m^2 followed thereafter by dose escalation to 36, 45, 56, or 70 mg/m^2. Carfilzomib was administered later with low-dose dexamethasone (40 mg/week) at the 45 mg/m^2 and 56 mg/m^2 dose levels. Thirty-three subjects were treated**,** and there were dose-limiting toxicities (DLTs) in 2 subjects dosed at 70 mg/m^2 of renal tubular necrosis (Grade 3) and proteinuria (Grade 3). The MTD was determined to be 56 mg/m^2.

In the 56 mg/m^2 cohort (n = 24), the most common treatment-related adverse events (AEs) of any grade were nausea (54.2%)**,** dyspnea (50.0%), fatigue (45.8%), pyrexia (41.7%), and thrombocytopenia and chills (both 37.5%); a majority were Grade 1 or 2. At this dose, hematologic AEs of thrombocytopenia (37.5%) and anemia (16.7%) were the most common treatment-related AEs of ≥ Grade 3. When carfilzomib at 56 mg/m^2 was combined with dexamethasone (n = 8), nausea (25%), fatigue (25%), and dyspnea and chills (each 12.5%) occurred less frequently than with carfilzomib alone. The overall response rate (ORR) was 50% in the 56 mg/m^2 cohort where the majority of subjects were refractory to IMiDs and bortezomib. The Phase 2 PX-171-003 – Part 2 (A1) study

with single agent carfilzomib at 20/27 mg/m^2 in a similar population had an ORR of 22.9% in the Safety population.

As evidenced by Study PX-171-007, higher doses of carfilzomib on a twice-weekly schedule administered over 30 minutes were well tolerated and efficacious with an acceptable safety profile. This led the sponsor to investigate whether higher doses of carfilzomib could be tolerated and be efficacious on a more convenient weekly dosing schedule in the CHAMPION 1 study as discussed in Section 2.5.

Additional information on the safety and activity of carfilzomib is described in the Carfilzomib IB.

2.4 STUDY RATIONALE

Based on the aspiration of improving the convenience of the currently approved carfilzomib dosing regimen and the recognition that higher doses appeared active and tolerable when given over a longer infusion time, a Phase 1b/2 Study CHAMPION 1 was initiated to evaluate the safety and efficacy of once-weekly carfilzomib with dexamethasone in subjects with relapsed myeloma, who had received 1 to 3 prior therapies. The dose-escalation portion of the study has identified an MTD of 70 mg/m^2 administered once-weekly over 30 minutes on Days 1, 8, and 15 of a 28-day cycle. Preliminary results from the ongoing Phase 2 portion of this multicenter, single-arm study suggested that the dose and regimen of 70 mg/m^2 once-weekly appeared to be well tolerated, highly active, and able to offer a more convenient treatment regimen for subjects as discussed in Section 2.5.

The rationale for this study is to compare carfilzomib administered once weekly in combination with dexamethasone, based on the CHAMPION 1 results, to twice-weekly carfilzomib in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma, previously treated with **a proteasome inhibitor** and an IMiD. The hypothesis is that this regimen will have superior efficacy with an acceptable safety profile and a more convenient dosing regimen when compared with the US approved dose and schedule of carfilzomib administered at 20/27 mg/m^2 twice weekly.

The primary endpoint in this study is **PFS**. Response rates, especially high-quality responses of substantial duration**,** are important indicators of benefit in relapsed and refractory multiple myeloma (Anderson 2008). A number of studies have shown an association between deeper responses and improved survival in patients with multiple myeloma (Lonial 2014). **For these reasons, this study was originally designed with ORR as the primary endpoint and PFS as a key secondary endpoint. Although ORR remains a meaningful clinical endpoint, recent advances in antimyeloma therapy have altered the landscape such that PFS is now considered to be the more relevant regulatory endpoint in this setting. To support regulatory interactions and protect the integrity of the the PFS data, the primary endpoint has been amended to PFS, with ORR as a key secondary endpoint.**

2.5 DOSE RATIONALE

Carfilzomib 20/27 mg/m^2 twice-weekly is an approved monotherapy dose and 20/70 mg/m^2 once-weekly is the MTD that was determined in the CHAMPION 1 study described in Section 2.5.1.

In the proposed study, dexamethasone will be administered prior to carfilzomib administration at 40 mg weekly on Days 1, 8, and 15 in both arms during all Cycles and on Day 22 in both arms during Cycle 1 to 9 only. This dose and schedule of therapeutic dexamethasone was part of the once-weekly treatment regimen in Study CHAMPION 1. The equivalent weekly doses of dexamethasone in both treatment arms will enable a clear interpretation of the study's primary comparison between high-dose once-weekly carfilzomib and standard-dose twice-weekly carfilzomib.

Carfilzomib study treatment administration will use a step-up approach in which the first dose level for all subjects will be 20 mg/m^2 (Cycle 1 Day 1 for the once-weekly regimen and Cycle 1 Days 1 and 2 for the twice-weekly regimen) and the dose level will then increase to 70 mg/m^2 or 27 mg/m^2 respectively, beginning on Day 8 of Cycle 1.

The dose levels of carfilzomib and dexamethasone being evaluated in this study are:

Arm A: Once-weekly

- Carfilzomib 20 mg/m^2
  - Study Day 1 (Cycle 1)
- Carfilzomib 70 mg/m^2
  - Study Days 8 and 15 (Cycle 1)
- Carfilzomib 70 mg/m^2
  - Study Days 1, 8, and 15 (Cycles 2+)
- Dexamethasone
  - 40 mg (IV or PO [orally]) on Study Days 1, 8, and 15 (all Cycles)
  - 40 mg (IV or PO) Study Day 22 (Cycles 1 to 9 only)

Arm B: Twice-weekly

- Carfilzomib 20 mg/m^2
  - Study Days 1 and 2 (Cycle 1)
- Carfilzomib 27 mg/m^2
  - Study Days 8, 9, 15, and 16 (Cycle 1)
- Carfilzomib 27 mg/m^2
  - Study Days 1, 2, 8, 9, 15, and 16 (Cycles 2+)
- Dexamethasone
  - 40 mg (IV or PO) on Study Days 1, 8, and 15 (all Cycles)
  - 40 mg (IV or PO) on Study Day 22 (Cycles 1 to 9 only)

2.5.1 *RATIONALE FOR ONCE-WEEKLY DOSING*

CHAMPION 1, a Phase 1b/2 study in subjects with relapsed multiple myeloma who had received 1 to 3 prior therapies was initiated to investigate higher doses of carfilzomib given once-weekly in combination with dexamethasone, and preliminary results indicated that these modifications were well tolerated and active. In the Phase 1b dose-escalation portion of the study**,** all subjects received 20 mg/m^2 carfilzomib on Cycle 1 Day 1 and then received the cohort-assigned test dose on Cycle 1 Days 8 and 15. The initial dose level evaluated was 45 mg/m^2**,** with escalation to 56 mg/m^2, 70 mg/m^2, and 88 mg/m^2 in

successive cohorts. Subjects received 40 mg dexamethasone on Days 1, 8, 15, and 22 of Cycles 1 through 8 and on Days 1, 8, and 15**,** from Cycle 9 onward.

No DLTs were observed during dose escalation at the dose levels of 45 mg/m^2, 56 mg/m^2, or 70 mg/m^2. At the carfilzomib dose level of 88 mg/m^2, 2 DLTs were observed during Cycle 1:

- Dyspnea (Grade 3, Days 9 to 11)
- Vomiting (Grade 3, Day 15)

Per protocol, an expansion cohort of 9 additional subjects was enrolled at the 70 mg/m^2 dose. There was 1 DLT in the 70 mg/m^2 expansion cohort: Grade 3 dyspnea (Days 16 to 18). The MTD of once-weekly carfilzomib in combination with dexamethasone was determined to be 70 mg/m^2.

A total of 27 subjects were enrolled in the Phase 1 portion of the study with a median of 1 prior therapy. Fifteen subjects received study treatment at a dose of 70 mg/m^2. The majority of the 27 subjects (85%) received prior bortezomib and 63% of those were refractory to bortezomib. The ORR in the Phase 1 population was 81% with a clinical benefit rate (CBR) of 93%. The once-weekly treatment regimen of 70 mg/m^2 showed promising activity with an ORR of 93% (95% [confidence interval] CI: 68.1 to 99.8%), 4 subjects achieved a complete response (CR) and the CBR was 100% (95% CI: 78.2 to 100%). The median treatment duration was 8.3 months in this cohort (Berenson 2014).

All 27 subjects (100%) experienced at least 1 AE. The most common (≥ 20% of subjects) AEs were upper respiratory tract infection, fatigue (each 52%), insomnia (44%), diarrhea, nausea, headache (each 41%), anemia, decreased hematocrit (each 37%), pyrexia (33%), constipation (30%), back pain, cough, muscle spasms, dyspnea, decreased red blood cell count (each 26%), arthralgia, dizziness, and pain in extremity (each 22%).

Five serious adverse events (SAEs) were reported in the Phase 1 part of this ongoing study:

- One subject at 45 mg/m^2 had 2 SAEs; increased blood creatinine (Grade 3)**,** and hyponatremia (Grade 4).
- One subject at 70 mg/m^2 had pneumonia (Grade 3).

- One subject at 88 mg/m^2 had dyspnea (Grade 3).
- One subject at 70 mg/m^2 had chronic obstructive pulmonary disease (Grade 3).

All SAEs were determined to be unrelated to carfilzomib and dexamethasone**,** except for the Grade 3 dyspnea event, a DLT in a subject receiving the 88 mg/m^2 dose.

As of 01 May 2015, 104 subjects (Phase 1 n = 15, Phase 2 n = 89) have received at least 1 dose of carfilzomib at the MTD. The majority of subjects (82%) had received prior bortezomib. A total of 48% of subjects were bortezomib-refractory, 28% were lenalidomide-refractory, and 16% were refractory to both. The ORR to date was 77% (95% CI: 68% to 85%) with a CBR of 84% (95% CI: 75% to 90%). Median PFS was 10.6 months (95% CI: 9.0 to 16.1). Preliminary median carfilzomib treatment duration in the ongoing study is 8.3 months (range: > 1 to 20) for the Phase 1 portion of the study and 7.2 months (range: 0.03 to 22.6) for the Phase 2 portion of the study (Berenson 2015).

All 104 subjects experienced at least 1 AE. The most common AEs (≥ 15% of subjects) were fatigue (52%), nausea (35%), headache, diarrhea (each 31%), insomnia, upper respiratory tract infection (each 30%), cough (26%), dyspnea (25%), anemia (24%), thrombocytopenia, pyrexia (each 22%), peripheral edema (20%), and back pain (17%). A total of 64 subjects (62%) experienced at least 1 Grade 3 or higher AE. The most common (≥ 5% of subjects) Grade 3 or higher AEs were fatigue (11%), pneumonia (7%), thrombocytopenia, hypertension, acute renal failure (each 6%), dyspnea, anemia, back pain, asthenia, and chronic obstructive pulmonary disease (each 5%) (Carfilzomib IB).

The preliminary results from CHAMPION 1 demonstrated that once-weekly carfilzomib at 70 mg/m^2 administered as a 30-minute infusion in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma had an acceptable safety and tolerability profile and promising efficacy. Eighty-nine subjects were enrolled into the Phase 2 portion of the study.

2.5.2 *PHARMACOKINETICS AND PHARMACODYNAMICS DATA FOR ONCE-WEEKLY DOSING*

Pharmacokinetics (PK) and pharmacodynamics (PDn) results from CHAMPION 1 are supportive of the proposal to study the once-weekly 70 mg/m^2 regimen as an effective alternative regimen for carfilzomib.

Preliminary PK results from CHAMPION 1 indicated that a once-weekly 30-minute infusion of carfilzomib had a mean terminal half-life similar to the half-life of ≤ 1 hour following the approved twice-weekly dosing regimen (20/27 mg/m^2 over 2 to10 minutes). In addition, the data showed a dose-proportional increase in the mean C_{max} and area under the curve (AUC) from 20 to 88 mg/m^2, as indicated by the similar dose normalized values for C_{max} and AUC (refer to Table 1). The AUC following a 70 mg/m^2 dose was 1045 ng·h/mL, which is higher than the total weekly AUC following the twice-weekly of 27 mg/m^2 dose (758 ng·h/mL, refer to Table 2). The mean C_{max} following the 70 mg/m^2 dose administered as a 30-minute infusion is 2640 ng/mL, which is lower than the mean C_{max} of 4232 ng/mL in Study PX-171-003 – Part 2 (A1), following the IV infusion of 27 mg/m^2 over 2 to 10 minutes (Carfilzomib IB).

Table 1 Summary of Pharmacokinetic Parameters from CHAMPION 1

Dose (mg/m^2)	n	$t_{1/2}$ (%CV)	C_{max} (%CV)	C_{max}/Dose (ng/mL)/ mg/m^2	$AUC_{0\text{-last}}$ (%CV)	AUC/Dose (h.ng/mL)/m g/m^2
20	11	0.77 hr (37.4%)	703 ng/mL (16.0%)	35.0	283 ng·h/mL (17.6%)	14.2
70	5	0.91 hr (24.3%)	2640 ng/mL (24.9%)	37.7	1045 ng·h/mL (22.1%)	14.9
88	5	0.84 hr (11.3%)	3172 ng/mL (24.9%)	36.0	1247 ng·h/mL (31.3%)	14.2

$AUC_{0\text{-last}}$ = AUC from time 0 to last time measurable concentration, CV = coefficient of variation, $t_{1/2}$ = terminal half-life, C_{max} = maximum plasma concentration, AUC = area under the curve.

Table 2 Pharmacokinetic Parameters Comparison of CHAMPION 1 and PX-171-003 – Part 2 (A1)

Study	Cycle/Dose/Days	Infusion Duration	Total dose/week (mg/m^2)	Total AUC per week (ng·hr/mL)	Maximal concentration (ng/mL)
PX-171-003 – Part 2 (A1)	Cycle 1: 20 mg/m^2 Days 1, 2, 8, 9, 15, and 16	2–10 minutes	40	566[a]	3060
	Cycle 2: 27 mg/m^2 Days 1, 2, 8, 9, 15, and 16	2–10 minutes	54	758[a]	4232
2012-002 (CHAMPION 1)	Cycle 1 Day 1: 20 mg/m^2 Cycle 1 Days 8 and 15: 70 mg/m^2	30 minutes	70	1045[b]	2640
	Cycle 2: 70 mg/m^2 Days 1, 8, and 15	30 minutes			

AUC = area under the curve.
[a] AUC following a single 20 and 27 mg/m^2 dose (2–10 minutes infusion) is 283 and 379 ng·hr/mL, respectively. Total AUC per week is calculated by multiplying the single dose AUC by 2 (e.g., 379 × 2 = 758 ng·h/mL).
[b] Represents total AUC per week starting on Day 8.

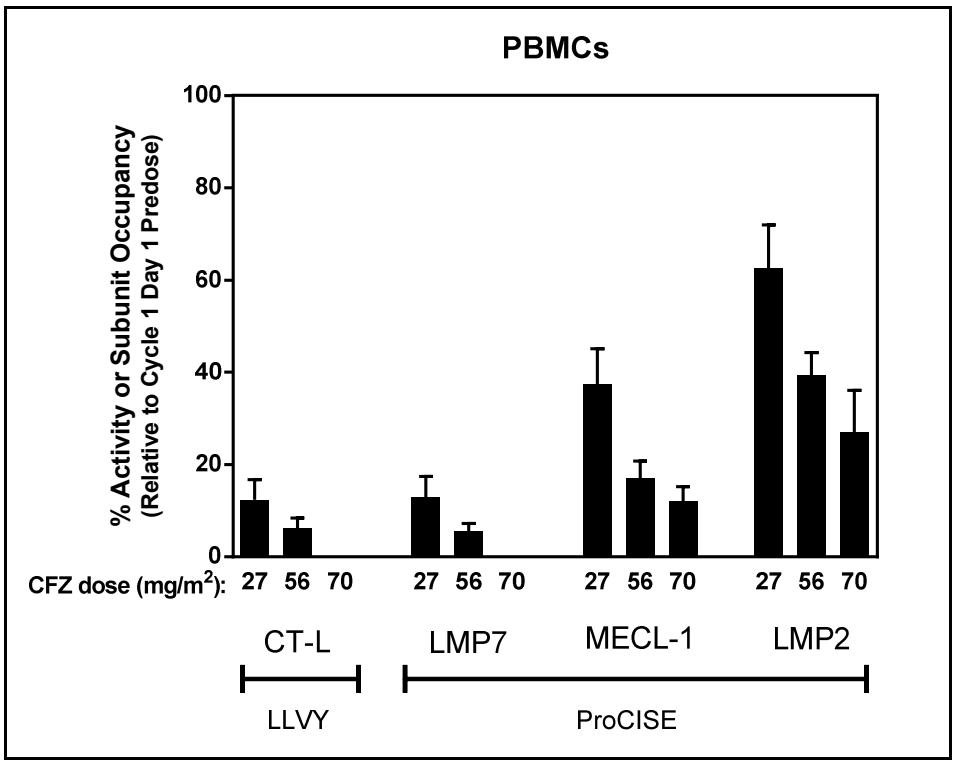
An exploratory exposure response analysis indicates a statistically significant relationship between the carfilzomib average AUC during Cycle 1 and response rates (ORR and CBR) with higher AUC exposures associated with improved responses in subjects with multiple myeloma (TR-1092-171). No statistically significant relationships between C_{max} and efficacy or safety endpoints were found.

Preliminary PDn data from CHAMPION 1 revealed that in blood and peripheral blood mononuclear cells (PBMCs) the 70 mg/m^2 dose level resulted in a greater depth of proteasome inhibition, at 1-hour post dose, compared to 1 hour after the Cycle 2 Day 1 dose in a twice-weekly schedule of 27 mg/m^2 and 56 mg/m^2 (as observed in the Phase 1b/2 PX-171-007 study). Chymotrypsin-like subunits (Beta 5 and latent membrane protein 7 [LMP7]) were inhibited most strongly, followed by trypsin-like (Beta 2 and multicatalytic endopeptidase complex-like 1 [MECL-1]), and caspase-like (Beta 1 and latent membrane protein 2 [LMP2]) subunits, respectively (refer to Figure 1).

Together, PK and PDn results from CHAMPION 1 support the investigation of once-weekly 70 mg/m^2 regimen as a potentially effective alternative regimen for

carfilzomib. The PK results from this study indicate that the total AUC per cycle delivered by the 70 mg/m^2 dose is expected to be higher compared to those of the 20/27 mg/m^2 regimen, consistent with the high ORR observed in the study (Berenson 2014) and exploratory exposure response analysis for carfilzomib (TR-1092-171). Pharmacodynamics data are consistent with a greater depth of proteasome inhibition with 70 mg/m^2 compared to those at 27 mg/m^2 and 56 mg/m^2 (as observed in the Phase 1b/2 PX-171-007 study).

Figure 1 Proteasome Percent Activity in Peripheral Blood Mononuclear Cells



C1D1 = Cycle 1 Day 1; CT-L = Chymotrypsin-like; LMP2 = latent membrane protein 2; LMP7 = latent membrane protein 7; MECL-1 = multicatalytic endopeptidase complex-like 1; PBMCs = peripheral blood mononuclear cells. 27 mg/m^2 (n = 3); 56 mg/m^2 (n = 5–13) and 70 mg/m^2 (n = 4). Values (relative to Cycle 1 Day 1 pre-dose) are presented as mean (±SEM). Chymotrypsin-like and relative active subunit concentration (LMP7, MECL-1, LMP2) were assessed from PBMCs 1 hour following the carfilzomib dose. 27 mg/m^2 and 56 mg/m^2 samples are from the PX-171-007 study, while 70 mg/m^2 data samples are preliminary data from the 2012-002 study. Chymotrypsin-like activity was measured by the fluorescent enzymatic Suc-LLVY-AMC assay, while subunit occupancy was measured by the ProCISE assay (Parlati 2009).

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVE

The primary objective of this study is to compare the **PFS** of once-weekly carfilzomib dosing in combination with dexamethasone to the **PFS** of twice-weekly carfilzomib dosing in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma who have received prior treatment with a proteasome inhibitor and an IMiD.

3.2 SECONDARY OBJECTIVES

The secondary objectives of the study are to compare the following between treatment groups:

- **ORR**
- Overall survival (OS)
- Safety and tolerability
- Pharmacokinetics (PK) of carfilzomib using sparse sampling

3.3 EXPLORATORY OBJECTIVES

The exploratory objectives are to evaluate the following between treatment groups:

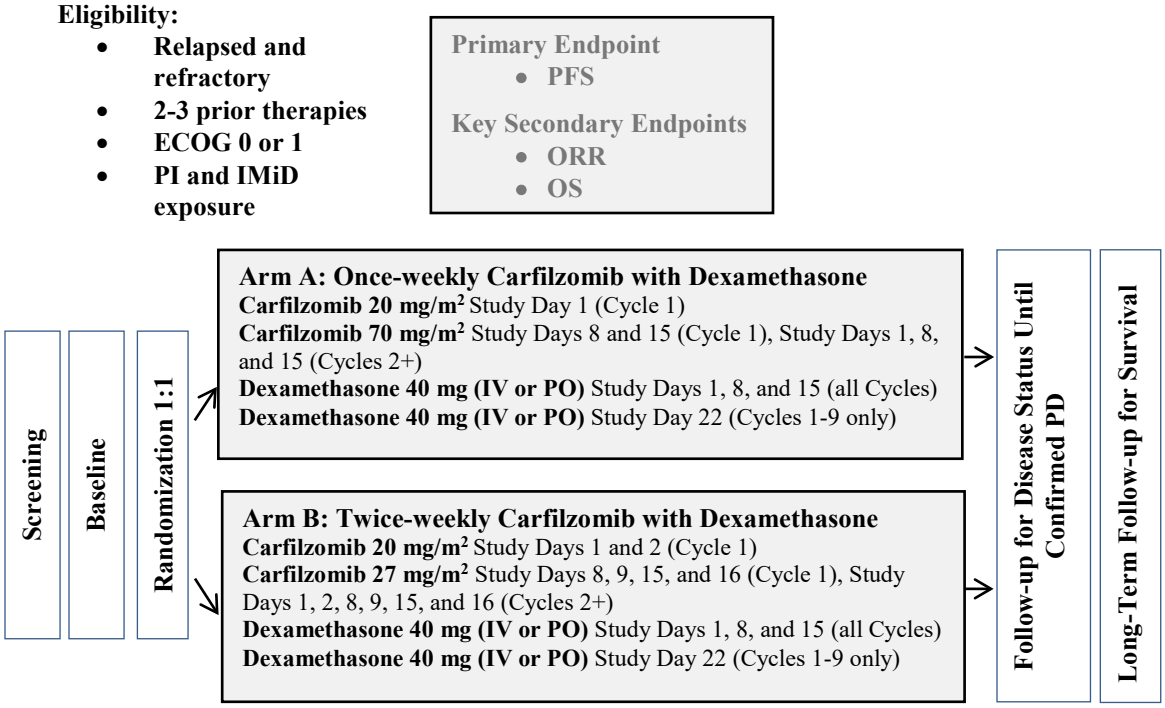
- Intensive pharmacokinetics (PK) and pharmacodynamics (PDn) of carfilzomib in a subset of subjects (substudy)
- All subscales of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Module (QLQ-C30), and the EORTC Quality of Life Multiple Myeloma Module 20 (QLQ-MY20)
- European Quality of Life-5 Dimensions (EQ-5D-5L); a standardized measure of health status developed by the European Quality of Life (EuroQol) Group
- Patient reported convenience and satisfaction with the carfilzomib dosing schedule
- Healthcare resource utilization

4 EXPERIMENTAL PLAN

4.1 STUDY DESIGN

This is an open-label, multicenter, Phase 3 study. The study design is illustrated in Figure 2.

Figure 2 Study 20140355 Schema



ECOG = Eastern Cooperative Oncology Group; IMiD = immunomodulatory agents; IV = intravenous(ly); ORR = overall response rate; OS = overall survival; PD = **progressive disease**; PFS = progression-free survival; PI = proteasome inhibitor; PO = orally.

Subjects with relapsed and refractory multiple myeloma will be screened for eligibility. Subjects must have had 2 or 3 prior therapies for multiple myeloma and received treatment with a proteasome inhibitor and an IMiD. Eligible subjects will be randomized in a 1:1 ratio to receive a regimen consisting of either once-weekly or twice-weekly carfilzomib in combination with dexamethasone.

Randomization will be stratified by:

- International Staging System (ISS) Stage at study entry (Stage 1 versus Stage 2 or 3) per International Myeloma Working Group (Greipp 2005). See Appendix H.
- Refractory to bortezomib treatment (Yes versus No)
- Age (< 65 versus ≥ 65 years)

The primary endpoint is **PFS**.

Study treatment will be administered in 28-day cycles. Subjects will receive the study treatment determined by randomization until disease progression, unacceptable toxicity,

withdrawal of consent, or death (whichever occurs first). No crossover between the 2 treatment groups before progression will be allowed.

Disease assessments will be conducted at Screening (within 21 days before randomization) and then every 28 days ± 4 days after Cycle 1 Day 1, End of Treatment (EOT)**,** and during LTFU every 28 days ± 4 days, until PD and/or administration of subsequent antimyeloma therapy. Response will be evaluated using the International Myeloma Working Group-Uniform Response Criteria (IMWG-URC).

Following termination of study treatment, all subjects will be followed for disease status (if PD has not been reached), subsequent antimyeloma treatment, and survival.

All subjects will be followed for AEs for at least 30 additional days after the last study treatment administration. All treatment-related AEs and SAEs will be followed until resolution or stabilization.

4.2 NUMBER OF CENTERS

Approximately 1**5**0 sites worldwide will participate.

4.3 NUMBER OF SUBJECTS

Approximately 460 subjects (230 subjects per treatment group) will take part in this study.

4.4 ESTIMATED STUDY DURATION AND CLOSURE

The total study accrual period is expected to be approximately 15 months. **The interim analysis of PFS will occur when approximately 263 PFS events are observed. If the interim analysis crosses the boundary, the trial may stop early for efficacy; otherwise s**ubjects will be followed for disease and survival status until approximately 350 PFS events are observed **or by end of year 2018, whichever is earlier**.

4.4.1 *END OF STUDY*

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for

the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

The primary completion is anticipated to occur when approximately 350 PFS events occur or end of year 2018, whichever is earlier. The primary completion date is the date when data for the primary endpoint are last collected for the purposes of conducting the primary analysis or the end of year 2018, whichever is earlier.

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

End of Study: The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (i.e., last subject last visit), following any additional parts in the study (e.g., long-term follow-up), as applicable.

5 SUBJECT ELIGIBILITY

5.1 INCLUSION CRITERIA

101. Age ≥ 18 years
102. Able to provide written informed consent in accordance with federal, local, and institutional guidelines
103. Relapsed multiple myeloma
104. Refractory multiple myeloma, defined as meeting 1 or more of the following:
    a. Nonresponsive to most recent therapy (stable disease or progressive disease [PD] while on treatment), or
    b. Disease progression within 60 days of discontinuation from most recent therapy
105. At least 2, but no more than 3, prior lines of therapy for multiple myeloma
106. Prior exposure to an IMiD
107. Prior exposure to a proteasome inhibitor (PI)
108. Documented response of at least partial response (PR) to at least 1 prior line of therapy

109. Measurable disease, with at least 1 of the following assessed at a central laboratory within the 21 days prior to randomization:

    a. Serum M-protein ≥ 0.5 g/dL

    b. Urine M-protein ≥ 200 mg/24 hours

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

110. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1

111. Left ventricular ejection fraction (LVEF) ≥ 40% within the 21 days prior to randomization

112. Adequate organ and bone marrow function performed at a central laboratory within the 21 days prior to randomization, defined by:

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

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

    c. Absolute neutrophil count (ANC) ≥ 1×10^9/L (screening ANC must be independent of growth factor support for ≥ 7 days)

    d. Hemoglobin ≥ 8 g/dL (Use of erythropoietic stimulating factors and red blood cell [RBC] transfusions per institutional guidelines are allowed**;** however the most recent RBC transfusion may not have been done within 7 days prior to obtaining the screening hemoglobin.)

    e. Platelet count ≥ 50,000/mm^3 (≥ 30,000/mm^3 if myeloma involvement in the bone marrow is > 50%. Subjects must not have received platelet transfusions for at least 7 days prior to obtaining the screening platelet count.)

    f. Calculated or measured creatinine clearance (CrCl) of ≥ 30 mL/min. Calculation must be based on the Cockcroft and Gault formula: [(140 – Age) × Mass (kg) / (72 × Creatinine mg/dL)]; multiply result by 0.85 if female

113. Females of childbearing potential (FCBP) must have a confirmed negative serum pregnancy test performed at a central laboratory, within the 21 days prior to randomization, and must not be breastfeeding.

114. Females of childbearing potential must agree to use highly effective method(s) of contraception, during the study and for 30 days following the last study drug administration. (Refer to Appendix K for specific contraceptive requirements).

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

116. Male subjects must agree to not donate sperm, during treatment and for an additional 90 days following the last study drug administration.

5.2 EXCLUSION CRITERIA

201. Waldenström macroglobulinemia
202. Multiple myeloma of Immunoglobulin M (IgM) subtype
203. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
204. Plasma cell leukemia (> 2.0×10^9/L circulating plasma cells by standard differential)
205. Myelodysplastic syndrome
206. Second malignancy within the past 5 years except:
    a. Adequately treated basal cell or squamous cell skin cancer
    b. Carcinoma in situ of the cervix
    c. Prostate cancer < Gleason score 6 with stable prostate-specific antigen (PSA) over 12 months
    d. Ductal breast carcinoma in situ with full surgical resection (i.e., negative margins)
    e. Treated medullary or papillary thyroid cancer
    f. Similar condition with an expectation of > 95% five-year disease-free survival
207. History of or current amyloidosis
208. Cytotoxic chemotherapy or other antineoplastic therapy, aside from immunotherapy or proteasome inhibitors, within the 28 days prior to randomization
209. Immunotherapy, such as an IMiD, or a proteasome inhibitor, within the 21 days prior to randomization
210. Glucocorticoid therapy exceeding a cumulative dose of 160 mg dexamethasone or equivalent, within the 14 days prior to randomization
211. Radiation therapy:
    a. Focal therapy within the 7 days prior to randomization
    b. Extended field therapy within the 21 days prior to randomization
212. Prior treatment with either carfilzomib or oprozomib
213. Known history of allergy to Captisol (a cyclodextrin derivative used to solubilize carfilzomib)

214. Contraindication to dexamethasone or any of the required concomitant medications or supportive treatments

215. Active congestive heart failure (New York Heart Association [NYHA] Class III or IV, refer to Appendix F), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, acute diffuse infiltrative pulmonary disease, pericardial disease, or myocardial infarction within 6 months prior to randomization

216. Active infection requiring systemic treatment within the 14 days prior to randomization

217. Pleural effusions requiring thoracentesis within the 14 days prior to randomization

218. Ascites requiring paracentesis within the 14 days prior to randomization

219. Ongoing graft-versus-host disease

220. Uncontrolled hypertension or diabetes mellitus

221. Significant neuropathy (≥ Grade 3) within the 14 days prior to randomization

222. Known cirrhosis

223. Known human immunodeficiency virus (HIV) seropositivity, hepatitis C infection, or hepatitis B infection. Subjects with past hepatitis B virus infection, defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen (anti-HBc) antibody test, are eligible. Subjects positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

224. Participation in another interventional study within the 28 days prior to randomization

225. Major surgery (except kyphoplasty) within the 28 days prior to randomization

227. 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, be compliant with study procedures, or provide accurate information.

6 SUBJECT SCREENING

A signed and dated informed consent form (ICF) must be obtained before any screening procedures or study-specific tests are performed. Evaluations obtained as part of routine medical care prior to signing of the ICF may be used to satisfy the screening requirements, provided that these evaluations were obtained within the required screening period and do not require analysis at a central laboratory.

All subjects who provide 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 commences when the subject or a legally-authorized representative signs the ICF. Screening must be completed within the 21 days prior to randomization.

7 SUBJECT RANDOMIZATION

The primary investigator will determine the subject's eligibility, ensuring that the results of the required screening procedures are consistent with all of the eligibility criteria presented in Section 5. No eligibility waivers will be permitted. Randomization will be carried out centrally through an interactive voice and web response (IVR/IWR) system. Please refer to the separate study reference manual.

Eligible subjects will be randomized in a 1:1 ratio to either:

- Arm A: Once-weekly carfilzomib with dexamethasone regimen
- Arm B: Twice-weekly carfilzomib with dexamethasone regimen

The randomization will be stratified by the following factors:

- International Staging System (ISS) at study entry (Stage 1 versus Stage 2 or 3) (Appendix H)
- Refractory to bortezomib treatment (Yes versus No)
- Age (< 65 versus ≥ 65 years)

Within each stratum defined by the stratification factors, subjects will be randomized according to a randomly permuted blocked randomization scheme.

Study treatment will ideally commence on the day of randomization, but at least within 5 calendar days of randomization. Initiation of study treatment (Cycle 1 Day 1) > 5 calendar days after randomization must be approved by the study medical monitor.

8 STUDY DRUGS

8.1 CARFILZOMIB

8.1.1 *PACKAGING AND LABELING*

Carfilzomib is supplied as a lyophilized parenteral product in single-use vials packaged in multi-vial cartons. Institutional pharmacies will be supplied with open stock vials with full-disclosure labels. Additional details are provided in the Investigational Product Instruction Manual (IPIM).

8.1.2 *STORAGE*

Study treatments should be stored in a securely locked area with access limited to appropriate study personnel. Carfilzomib must be stored at [redacted]°C to [redacted]°C ([redacted]°F–[redacted]°F) in a refrigerator.

Please refer to the IPIM for further storage information.

8.2 DEXAMETHASONE

Dexamethasone is commercially available and will be obtained by the investigational site. Sponsor (and/or designee) may provide dexamethasone, if the investigational site is unable to obtain adequate supply. Details regarding the description, supply, and storage instructions for dexamethasone are found in the prescribing information. Sites are advised to refer to the prescribing information for information that is specific to the brand or formulation of the drug product in use.

8.3 STUDY DRUG ACCOUNTABILITY

Please refer to the IPIM for details on study drug accountability.

8.4 PRODUCT COMPLAINTS

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

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

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

9 DOSAGE AND TREATMENT ADMINISTRATION

9.1 TREATMENT REGIMEN

Carfilzomib and dexamethasone will be administered in 28-day cycles. All cycles will start 28 days (± 2 days) after the start of the prior cycle.

In the once-weekly carfilzomib arm, intra-cycle doses of carfilzomib and dexamethasone may be administered within ± 2 days of the scheduled dose. However, carfilzomib must not be administered within the 5 days following a previous carfilzomib infusion. Dose delays > 2 days are only permitted during the start of a new cycle.

In the twice-weekly carfilzomib arm, every effort should be made to maintain the Days 1, 2, 8, 9, 15, and 16, every 28-day schedule. If this is not possible, then priority should be to maintain consecutive dosing days. For example, if Day 1 of a new cycle is started 2 days later than originally scheduled, the entire cycle should shift by 2 days, such that the new Days 1, 2, 8, 9, 15, and 16 of the next cycle are maintained. Dosing on nonconsecutive days should only occur under exceptional circumstances, such as interruptions due to national holidays. There must always be at least 5 days between the second dose of 1 week and the first dose of the following week (ie, between Days 2 and 8, and Days 9 and 15). Mid-cycle doses that are missed should not be made up, unless these parameters are maintained.

The reasons for all cycle delays, schedule changes, missed doses, and dose interruptions will be reported.

9.2 INTRAVENOUS PREHYDRATION

Subjects will receive IV prehydration prior to each carfilzomib infusion during Cycle 1. Prehydration will consist of 250 to 500 mL normal saline or other appropriate IV fluid. Thereafter, carfilzomib prehydration should only be administered if the subject's condition and/or risk factors require it. The total volume of prehydration and the reason for prehydration after Cycle 1 will be recorded.

9.2.1 *STUDY TREATMENT ADMINISTRATION*

Carfilzomib and dexamethasone will be administered in 28-day cycles in regimens of either once-weekly carfilzomib or twice-weekly carfilzomib as described in detail below in Figure 3

.

Figure 3 Arm A and Arm B Carfilzomib with Dexamethasone Regimens

Arm A: Once-weekly Carfilzomib with Dexamethasone Regimen (28-day Cycles)																											
Week	1							2							3							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
CFZ	20[a]							70							70													
Dex	40							40							40							40[c]						
Arm B: Twice-weekly Carfilzomib with Dexamethasone Regimen (28-day Cycles)																											
Week	1							2							3							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
CFZ	20[b]	20[b]						27	27						27	27												
Dex	40							40							40							40[c]						

CFZ = carfilzomib, Dex = dexamethasone; PO = oral(ly).

[a] Cycle 1 Day 1 carfilzomib dose level will be 20 mg/m^2; all other dose levels will be 70 mg/m^2.

[b] Cycle 1 Days 1 and 2 carfilzomib dose level**s** will be 20 mg/m^2; all other dose levels will be 27 mg/m^2.

[c] Dexamethasone on Day 22 in both treatment arms will be administered only during Cycles 1 to 9 and should be given PO, whenever possible.

9.2.1.1 Carfilzomib

Carfilzomib will be administered as an IV infusion over approximately 30 minutes in the once-weekly arm and over approximately 10 minutes in the twice-weekly arm.

Carfilzomib for Injection is supplied as a lyophilized parenteral product in single-use vials. The lyophilized product is reconstituted with Sterile Water for Injection (SWI), United States Pharmacopeia (USP), to a final carfilzomib concentration of 2 mg/mL.

Mechanical infusion pumps are recommended, but gravity-dependent infusions are permitted, if the infusion duration can be reliably maintained. 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. Carfilzomib should be administered via a dedicated IV line**,** whenever possible. Refer to the IPIM for detailed information regarding equipment and flush requirements.

9.2.1.2 Dexamethasone

Dexamethasone will be taken PO or administered by IV infusion. Dexamethasone will be administered at least 30 minutes (but no more than 4 hours) prior to carfilzomib infusion on Days 1, 8, and 15 in both treatment arms. Dexamethasone on Day 22 should be taken PO, whenever possible. Note: Dexamethasone on Day 22 in both treatment arms will only be administered during Cycles 1 to 9.

9.3 DOSE MODIFICATION RULES

In the event of a possible study treatment-related AE, the clinical investigator should assess, to the best of his/her ability, its relationship to carfilzomib and/or dexamethasone. Dose reduction rules for carfilzomib are presented in Table 4 and Table 5 and are often event-specific.

- If a subject requires interruption of carfilzomib for more than 28 days, the subject should be removed from study treatment. Exceptions must first be approved by the study medical monitor.
- If a subject requires carfilzomib dose reduction, the reduced dose level will be continued for at least 1 complete cycle. After that, if the reduced dose level has

been well tolerated, the previous dose level may be resumed at the investigator's discretion.

- If carfilzomib is temporarily held due to an AE, dexamethasone should be continued, unless the investigator determines that criteria for interrupting dexamethasone have also been met.
- If carfilzomib is permanently discontinued due to toxicity, dexamethasone must also be discontinued and the subject will be followed for disease progression per the guidelines in Section 10.10.1.
- If dexamethasone is permanently discontinued due to toxicity, the subject may continue to receive study treatment with carfilzomib at the investigator's discretion.

9.3.1 *CARFILZOMIB: RULES FOR DOSE MODIFICATION*

Dose decrements for carfilzomib are provided in Table 3.

Table 3 Carfilzomib Dose Decrements

Dose [a]	Carfilzomib Dose Decrements		
	First Dose Reduction Dose -1	Second Dose Reduction Dose -2	Third Dose Reduction Dose -3
70 mg/m^2	56 mg/m^2	45 mg/m^2	36 mg/m^2
27 mg/m^2	20 mg/m^2	15 mg/m^2	11 mg/m^2

[a] Note: If dose reduction of carfilzomib is required on C1D1 (Arm A) or C1D1 or D2 (Arm B), the investigator should contact the medical monitor to discuss the situation, before any additional doses of carfilzomib are administered.

The requirements for carfilzomib dose modification for specific hematologic and nonhematologic toxicities are outlined in Sections 9.3.1.1 and 9.3.1.2, respectively.

9.3.1.1 Hematologic Toxicity

Requirements for dose modification of carfilzomib in the events of thrombocytopenia, neutropenia, or neutropenic fever are summarized in Table 4.

Table 4 Carfilzomib Dose Modification Rules for Treatment-emergent Hematologic Toxicity

Hematologic Toxicity	Required Action[a]	
Thrombocytopenia		
• Platelets ≤ 10×10^9/L, OR • Platelets ≤ 30×10^9/L with evidence of bleeding/bruising	1st episode	• Withhold doses • Resume at the same dose level when platelets ≥ 10×10^9/L and bleeding is controlled
	Subsequent episodes	• Withhold doses • Resume at 1 dose decrement when platelets ≥ 10×10^9/L and bleeding is controlled
Neutropenia		
• ANC < 0.5×10^9/L	1st episode	• Withhold doses • Resume at the same dose level when ANC ≥ 0.5×10^9/L
	Subsequent episodes	• Withhold doses • Resume at 1 dose decrement when ANC ≥ 0.5×10^9/L
Febrile neutropenia		
• ANC < 0.5 x 10^9/L and oral temperature either: ○ > 38.5°C, OR ○ > 38.0°C on 2 consecutive measurements over 2 hours	1st and subsequent episodes	• Withhold doses • Resume at the same dose level when ANC returns to baseline grade and fever resolves

ANC = absolute neutrophil count; NA = not applicable.

9.3.1.2 Nonhematologic Toxicity

Requirements for dose modification of carfilzomib in the event of nonhematologic toxicities are summarized in Table 5.

Table 5 Carfilzomib Dose Modifications for Nonhematologic Toxicity

Nonhematologic Toxicity	Required Action[a]
Renal Dysfunction	
• Serum creatinine ≥ 2 × baseline, OR • CrCl < 15 mL/min, OR • CrCl decr*eases to ≤ 50%* of baseline, OR • Requirement for dialysis	• Withhold doses while the cause of renal dysfunction is being assessed • If attributable to carfilzomib, resume at 1 dose decrement when CrCl has recovered to within 25% of baseline • If not attributable to carfilzomib, resume the same dose or reduce by 1 dose decrement, at the investigator's discretion, when CrCl has recovered to within 25% of baseline • For patients on dialysis receiving carfilzomib, the dose is to be administered after the dialysis procedure
Hepatic Dysfunction	
• **Mild to moderate liver dysfunction: defined as 2 consecutive values, at least 28 days apart, of:** **(1) Total bilirubmin (> 33% direct) > 1 x ULN to < 3 x ULN** **OR** **(2) An elevation of AST and/or ALT with normal bilirubin**	• **25% dose reduction.** • **Dose may be re-escalated if liver function tests return to normal and drug-induced hepatotoxicity is excluded.**
• Grade 3 **elevation in ALT and/or AST (> 5 x ULN)**	• **Hold carfilzomib until resolution to baseline.** • **Monitor any abnormality weekly. Resume carfilzomib with a 25% dose reduction if drug-induced hepatoxicity is excluded.**
• **Grade 3 elevation in total bilirubin**	• **Hold carfilzomib until resolution to baseline. Monitor total bilirubin and direct bilirubin weekly.** • **Upon resolution of total bilirubin to normal, resume carfilzomib dosing with at 25% dose reduction if drug-induced hepatotoxicity is excluded.**
• **Drug-induced hepatoxicity attributable to carfilzomib**	• **Discontinue carfilzomib.**
Infection	
• ≥ Grade 3 Infection	• Withhold doses • Resume at the same dose level, when the infection is controlled

Nonhematologic Toxicity	Required Action[a]
Cardiovascular Dysfunction	
• Congestive Heart Failure	• Withhold doses for any subject with symptomatic heart failure, whether or not it is attributed to carfilzomib • Resume at 1 dose decrement, when symptoms have resolved or returned to baseline
• LVEF < 40%, OR • LVEF < 55%, if decreased > 20% from baseline	• Withhold doses • Resume at 1 dose decrement, when LVEF returns to ≥ 40%, or to within 15% of baseline, if carfilzomib was held due to a drop to < 55%
• **≥ Grade 2** Pulmonary Hypertension	• Withhold doses • **Carfilzomib** may be resumed at 1 dose decrement **when pulmonary hypertension resolves to grade ≤ 1**
Thrombotic Microangiopathy	
• Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS)	• Withhold doses when TTP/HUS is suspected • If the diagnosis is excluded, resume at the same dose level • If the diagnosis is confirmed, **discontinue carfilzomib. Subjects should not be rechallenged.** • Manage symptoms per standard of care including, plasma exchange as clinically indicated [b]
Venous Thrombosis	
• **≥ Grade 3**	• **Hold carfilzomib and adjust anticoagulation regimen.** • **Resume at full dose once anticoagulation has been optimized per treating investigator's discretion.**
Encephalopathy	
• Posterior reversible encephalopathy syndrome (PRES)	• Withhold doses • Consider evaluation with neuroradiological imaging for onset of visual or neurological symptoms suggestive of PRES • If the diagnosis is excluded, resume at the same dose level • If the diagnosis is confirmed, **discontinue carfilzomib. Subjects should not be rechallenged.**
Other Nonhematologic Toxicity	
• ≥ Grade 3 and attributed to carfilzomib	• Withhold doses • Resume at 1 dose decrement, when toxicity has resolved to Grade ≤ 2 or to baseline

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CrCl = creatinine clearance; eCRF = electronic Case Report Form; IB = Investigator's Brochure; IMWG = International Myeloma Working Group; LFTs = liver function tests; LVEF = left ventricular ejection fraction; mL = milliliter(s); PRES = posterior reversible encephalopathy syndrome; ULN = upper limit of normal.

Note: Carfilzomib dose schedule does not need to be adjusted for baseline renal dysfunction.

[a] The maximum allowed dose interruption is 4 weeks, except with approval by the medical monitor.

[b] Subjects requiring plasma exchange must be withdrawn from study treatment. Every effort should be made to assess disease status in accordance with IMWG criteria, before plasma exchange is initiated.

9.3.2 *DEXAMETHASONE: GUIDELINES FOR TOXICITIES AND DOSE MODIFICATION*

Dose decrements for dexamethasone are provided in Table 6.

Table 6 Dose Decrements for Dexamethasone

Nominal Dose	Dexamethasone Dose Decrements	
	Dose -1	Dose -2
40 mg	20 mg	12 mg

Dexamethasone will be permanently discontinued, if toxicity persists following 2 dose level reductions. At the investigator's discretion, dexamethasone may be tapered, prior to complete discontinuation, according to institutional practice. The requirements for dose modification due to dexamethasone-related toxicities are summarized in Table 7.

Table 7 Treatment Rules for Dexamethasone-related Toxicities

Toxicity	Required Action
Edema	
≥ Grade 3: • Limb edema • Truncal edema	• Withhold doses and diurese as needed • Resume at 1 dose decrement when Grade ≤ 1 or baseline
Gastrointestinal Distress	
Grade 1 or 2: • Dyspepsia, OR • Gastritis, OR • Gastric or duodenal ulcer	• Continue doses while attempting medical management • If symptoms persist, reduce by 1 dose decrement
≥ Grade 3: • Dyspepsia, OR • Gastritis, OR • Gastric or duodenal ulcer	• Withhold doses • Resume at 1 dose decrement, when symptoms return to baseline • If symptoms recur despite appropriate medical management, discontinue dexamethasone permanently
• Acute pancreatitis	• Discontinue dexamethasone permanently
Psychiatric Disorders	
≥ Grade 2: • Confusion, OR • Mood alteration	• Withhold doses • Resume at 1 dose decrement, when symptoms return to baseline
Other Toxicities	
• ≥ Grade 3 and attributed to dexamethasone	• Withhold doses • Resume at 1 dose decrement, when toxicity has resolved to ≤ Grade 2

9.3.3 *CONDITIONS NOT REQUIRING DOSE REDUCTION*

The following conditions are exceptions to the requirements presented above.

Carfilzomib and dexamethasone do not require dose modification in the following cases:

- Grade 3 nausea, vomiting, or diarrhea (unless persisting more than 3 days despite appropriate use of antiemetics or antidiarrheal agents)
- Grade 3 hyperglycemia
- Grade 3 fatigue (unless persisting for > 14 days)
- Alopecia

9.4 CONCOMITANT MEDICATIONS AND THERAPIES

A concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. For all randomized subjects, all administered concomitant medications and therapies, from signing of the informed consent until 30 days after the last dose of study treatment, must be recorded in the designated electronic case report form (eCRF).

Concomitant medications required for the study or used prophylactically should be described as such in the designated eCRF. Concomitant medications prescribed for "prn" or "as needed" use should not be reported, unless actually administered.

Blood and blood products are not considered concomitant medications and must be recorded on the appropriate eCRF.

9.4.1 *REQUIRED CONCOMITANT MEDICATIONS*

Required prophylactic medications should be initiated at least 1 day prior to the first administration of carfilzomib.

9.4.1.1 Gastrointestinal Prophylaxis

Lansoprazole or other oral proton-pump inhibitor, dosed according to institutional practice, is required to prevent peptic ulcer disease throughout the duration of treatment with dexamethasone.

9.4.1.2 Pregnancy and Contraception

Contraception must continue during study**, during** drug dose interruption intervals**, and** until 30 days (females) or 90 days (males) after the last study drug administration. If applicable, refer to the Country Specific Pregnancy and Contraceptive Supplement (refer to Appendix K).

If a subject thinks she may be pregnant (e.g., if a menstrual period in an FCBP does not occur at the anticipated time), study drug treatment must be interrupted, and a urine or serum pregnancy test must be performed locally. Study drug administration may resume after documentation of a nonpregnant state.

9.4.2 *RECOMMENDED CONCOMITANT MEDICATIONS*

9.4.2.1 Antiviral Prophylaxis

Valacyclovir (or an equivalent antiviral agent) is recommended for prophylaxis against herpes zoster reactivation.

9.4.2.2 Uric Acid-lowering Agents

Allopurinol or other approved uric acid-lowering agent are recommended for subjects at high risk for tumor lysis syndrome (TLS) due to high tumor burden. Refer to the current Carfilzomib IB for safety guidance regarding TLS.

9.4.2.3 Mycostatin or Oral Fluconazole

Mycostatin or oral fluconazole may be given to prevent oral thrush throughout the duration of treatment with dexamethasone.

9.4.2.4 Antiemetics and Antidiarrheal Agents

Antiemetics and antidiarrheal agents are recommended for prophylaxis and/or management of treatment-related gastrointestinal symptoms.

9.4.2.5 Thrombophrophylaxis

Venous thromboembolism has been observed in patients receiving carfilzomib. Thromboprophylaxis may be considered on the basis of a benefit-risk assessment.

9.4.3 *EXCLUDED CONCOMITANT MEDICATIONS AND THERAPIES*

If an investigator deems that use of an excluded concomitant medication or therapy is required but does not believe that withdrawal from study treatment is indicated, he/she must contact the study medical monitor to determine if continued study treatment is acceptable.

9.4.3.1 Anticancer Agents

Therapy with a marketed or investigational anticancer agent that is not required per this protocol is prohibited, while subjects remain on study treatment, and should be avoided prior to documentation of disease progression.

9.4.3.2 Radiation Therapy

Radiation to large marrow reserves is prohibited**;** however, focal palliative radiation is allowed with permission from the study medical monitor.

9.4.3.3 Myeloid Growth Factors

Prophylactic use of myeloid growth factors is prohibited, but they may be used for management of neutropenia, in accordance with American Society of Clinical Oncology (ASCO) Guidelines (Smith 2006).

9.4.3.4 Corticosteroids

Corticosteroids should not be used to treat concurrent medical conditions, unless the dose remains less than the equivalent of 4 mg/day of dexamethasone. Short term use of higher doses may be permitted to treat acute exacerbations of concurrent medical conditions, but this must be discussed with the study medical monitor as soon as is possible.

9.4.3.5 Plasmapheresis

Plasmapheresis is not permitted at any time during the Screening period or while the subject is receiving study treatment. If a subject who has started screening procedures requires plasmapheresis or is anticipated to require plasmapheresis during or after the Screening period, this subject will be considered ineligible.

For subjects requiring plasmapheresis while on study treatment**,** every attempt should be made to document disease status by IMWG criteria first. Study treatment must be discontinued and the subject will enter LTFU.

9.4.3.6 Novel Agents for Non-neoplastic Conditions

The use of novel agents for non-neoplastic conditions is prohibited throughout the duration of treatment and for 30 days following the last dose of study treatment.

10 STUDY ASSESSMENTS AND PROCEDURES

All protocol-required tests and observations, along with their chronology, are outlined in the Schedule of Assessments (refer to Appendix A). Protocol-specified assessments and procedures are summarized below.

10.1 STUDY SPECIFIC PROCEDURES

10.1.1 *MULTIPLE MYELOMA HISTORY AND PRIOR LINES OF THERAPY ASSESSMENT*

When documenting prior therapies for multiple myeloma, the following guidelines should be used:

- A new line of therapy is considered to start when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of lack of adequate response, PD (even if the level of progression has not yet met IMWG criteria for PD), relapse, or toxicity. A new therapy is also considered to start when a planned period of observation off-therapy is interrupted by a need for additional lines of therapy.
- An increase in treatment administration, with the intention of recapturing response in a patient with evidence of disease progression on that line of therapy, is considered to be a new line of therapy.

Examples of a line of therapy include:

- Induction therapy and stem cell transplant followed by planned maintenance therapy (provided there is no intervening PD)
- Induction therapy followed by maintenance therapy (provided there is no intervening PD)

If available, historical FISH data should be entered into the eCRF. The following results should be captured:

- t(4;14)
- t(6;14)
- t(11;14)
- t(14;16)
- t(14;20)
- Del 17p
- Del 13
- Chromosome 1 abnormalities

10.1.2 *VITAL SIGNS*

Vital signs will include heart rate, blood pressure, respiratory rate, and temperature and will be assessed at Screening, prior to each administration of carfilzomib, EOT, and as needed to assess potential AEs. Clinically significant abnormal vital signs will be reported as AEs.

10.1.3 *COMPLETE PHYSICAL EXAMINATION*

A physical examination will be performed during Screening, prior to dosing on Day 1 of each cycle, and at the EOT. For Cycle 1 Day 1, the screening physical examination may be used if performed within 7 days prior to Cycle 1 Day 1. Physical exam may be completed up to 3 days prior to Day 1 of each cycle. At a minimum, the physical exam should include constitutional, abdominal, cardiovascular, and respiratory assessments.

Clinically significant abnormal findings identified after the signing of informed consent must be reported as AEs and examined more frequently, as clinically indicated. Note: Clinically significant abnormal physical examination findings identified prior to the signing of informed consent should be reported as part of Medical History, not as AEs.

BSA is to be determined by a standard formula, such as the Mosteller Formula (Mosteller 1987): body surface area (BSA) (m^2) = ([Height (cm) × Weight (kg)]/ 3600)½. Body surface area must be recalculated and used for subsequent dose determinations, if the subject experiences a weight change of ≥ 20%. Recalculations of BSA must be made using the same technique as used at baseline.

10.1.4 *EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS*

Eastern Cooperative Oncology Group Performance Status will be assessed at Screening and at the EOT visit. Eastern Cooperative Oncology Group Performance Status grades and descriptions are tabulated in Appendix E.

10.1.5 *INTERNATIONAL STAGING SYSTEM STAGE DETERMINATION*

Beta-2 microglobulin and albumin will be assessed at the central laboratory during Screening to determine ISS Stage (refer to Appendix B and Appendix H). These results must be available, prior to randomization.

10.2 MULTIPLE MYELOMA DISEASE ASSESSMENTS

Disease response and progression assessments include (but are not limited to): SPEP, urine protein electrophoresis (UPEP), immunofixation, SFLC, bone marrow sample evaluation, serum calcium, plasmacytoma evaluation, and skeletal survey. Multiple myeloma assessment should be based on calendar day, regardless of cycle delay. SPEP, UPEP, immunofixation, SFLC, bone marrow evaluation, and serum calcium will all be conducted at the central laboratory.

The following disease assessments must be performed at Screening:

- SPEP, UPEP (24-hour assessment, no substitute method is acceptable), and immunofixation
- SFLC
- Quantitative immunoglobulins
- Beta-2 microglobulin

Cycle 1 Day 1 before treatment begins (Screening values may be used if obtained within 7 days prior to Cycle 1 Day 1), and every 28 days (± 4 days) thereafter, at EOT**,** and during LTFU if disease progression has not already been documented (every 28 days ± 4 days, until PD and/or started a subsequent antimyeloma therapy):

- SPEP, immunofixation
- UPEP (24-hour assessment, no substitute method is acceptable), and immunofixation: post-Cycle 1 Day 1 measurements required only if Cycle 1

Day 1 UPEP ≥ 200 mg/24 hours or to confirm a disease response (for very good partial response [VGPR] or better) or progression (if applicable)

- SFLC: post-Cycle 1 Day 1 measurements required only for SFLC measurable disease or to confirm stringent complete response (sCR)
- Quantitative immunoglobulins

Subjects will be instructed to collect 24-hour urine samples for assessment of UPEP at Screening and as required during the study. This collection will occur over 2 days and will be assessed at the central laboratory. For further instructions, refer to the Central Laboratory Services Manual.

Radiological disease assessments at baseline are collected after subject eligibility is confirmed and may be done after randomization (as long as they are done before the start of treatment). Radiological disease assessments that were done per standard of care within 30 days before Cycle 1 Day 1 can be used as study baseline disease assessments. They include:

Extramedullary Plasmacytoma Assessment

- A plasmacytoma evaluation will be conducted at baseline, only if a lesion is suspected clinically.
- If an extramedullary plasmacytoma is detected, evaluation will be repeated during treatment to confirm a response of PR or better or to assess for PD based on plasmacytoma.
- Plasmacytomas are considered measurable if they have a longest diameter of at least 1 cm and the product of cross diameter measurements is at least 1 cm^2. Plasmacytomas of lesser size are considered unmeasurable. Bidimensional measurements must be recorded in the designated eCRF. The same technique must be used to evaluate plasmacytomas throughout the duration of study participation and may include: palpation, ultrasound, x-ray, computed tomography (CT) scan, magnetic resonance imaging (MRI), positron emission tomography (PET), or any other technique that is considered to be standard of care.

Skeletal Survey

- Skeletal survey will include lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. The skeletal survey will be conducted at baseline and will be repeated if worsening clinical symptoms suggest PD, or as clinically indicated.
- Other radiologic modalities for performing skeletal assessment (eg, low-dose CT scan) are acceptable, in accordance with regional standards.

10.3 MULTIPLE MYELOMA RESPONSE ASSESSMENTS

10.3.1 *DISEASE RESPONSE AND PROGRESSION ASSESSMENTS*

Determination of disease response must be based on the reported values from the central laboratory. Local laboratory results may be used for hypercalcemia (corrected calcium based on albumin), but a confirmatory sample should be collected and sent to the central laboratory for documentation.

Investigator-determined responses must be based on results from the central laboratory and must be consistent with the IMWG-URC (see definitions in Appendix G).

10.3.2 *TUMOR RESPONSE ASSESSMENT*

The following confirmatory assessments are required for all response categories (sCR, CR, VGPR, PR, minimal response [MR] and PD; refer to definitions in Appendix G:

- All laboratory-based PD (except bone marrow sample) and all response categories require 2 consecutive assessments made at any time before initiation of new therapy.
- All response categories require that there be no evidence of disease progression, including confirmation of no new bone lesions, if radiographic studies were performed.
- The preferred method of confirming CR or sCR is a bone marrow biopsy; however, a bone marrow aspirate is also acceptable for confirmation of CR.
- Extramedullary plasmacytoma evaluation (if present at Screening). Two consecutive radiographic tests are not required to confirm response or progression of extramedullary plasmacytoma.
- In the case where a patient does not have measurable M-protein by UPEP at baseline (i.e., baseline UPEP < 200 mg/24 hours), when SPEP is consistent with response (i.e., ≥ PR), 2 consecutive UPEP measurements must be performed to confirm response.

10.3.3 *DISEASE PROGRESSION*

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 (e.g., pathologic fracture in a subject with progressive multiple myeloma) should be reported in the appropriate eCRF 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.

Study treatment should not be discontinued on the basis of disease progression, until PD has been appropriately confirmed per IMWG-URC. Disease progression during LTFU must also be confirmed by these same criteria. Confirmation of PD will require 2 consecutive central laboratory evaluations that indicate PD, except in cases where PD is based on extramedullary lesions or hypercalcemia that is attributed solely to PD. These assessments should be separated in time by at least 1 calendar day, but no more than 28 ± 4 calendar days. Local laboratory results may not be used to determine or confirm disease progression, except when PD is based on hypercalcemia. The assessments outlined in Appendix B are required for PD determination.

10.4 LABORATORY TESTS

Laboratory tests for efficacy and safety during scheduled and unscheduled study visits, including screening will be performed at a central laboratory. Additional safety laboratory samples must also be collected and analyzed by local laboratories if the results are necessary to determine the appropriateness of dose administration. In rare circumstances, when the central laboratory is unable to provide results for tests that are needed to determine eligibility, the study medical monitor may grant permission for local laboratory results to be applied to the screening requirements. Local labs may also be required for management of treatment-emergent adverse events (TEAEs). Laboratory tests for disease assessment are described in Section 10.2.

Safety samples must be obtained within the 1 day prior to carfilzomib administration and the results must be reviewed prior to the start of the carfilzomib infusions on Days 1, 8, and 15 of Cycles 1 to 4. Beyond Cycle 4, these labs are only required on Days 1 and 15 of each cycle.

10.4.1 *HEMATOLOGY*

Hematology assessments (Table 8) will be performed during Screening, on Days 1, 8, and 15 for Cycles 1 to 4 and EOT. Beyond Cycle 4 labs will be performed on Days 1 and 15 of each cycle. For Cycle 1 Day 1, hematology assessments from Screening can be used, if they were obtained within 3 days prior to carfilzomib administration. For subsequent visits, hematology assessments may be completed up to 1 day prior to the scheduled dose.

Table 8 Laboratory Tests: Hematology

Hematology Panel
Hemoglobin
Hematocrit
WBC count with complete differential to include: [a] Neutrophils Lymphocytes Monocytes Eosinophils Basophils
RBC count
Platelet count

RBC = red blood cells; WBC = white blood cells.

[a] Absolute **counts** or percentage will be acceptable.

10.4.2 *SERUM CHEMISTRY*

A serum chemistry panel (Table 9) will be performed during Screening, on Days 1, 8, and 15 for Cycles 1 to 4 and EOT. Beyond Cycle 4, labs will be performed on Days 1 and 15 of each cycle. For Cycle 1 Day 1, serum chemistry assessments from Screening can be used, if performed within 3 days prior to carfilzomib administration. For subsequent visits, serum chemistries may be completed up to 1 day prior to the scheduled carfilzomib dose.

Table 9 Laboratory Tests: Chemistry Panel

Chemistry Panel	
Albumin	Glucose
Alkaline Phosphatase	LDH
ALT	Magnesium
AST	Phosphorus
Bicarbonate	Potassium
BUN	Sodium
Calcium	Total Bilirubin
Chloride	Total Protein
Creatinine	Uric Acid

ALT= alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, eCRF = electronic Case Report Form; LDH = lactate dehydrogenase; ULN = upper limit of normal

10.4.3 *COAGULATION*

Coagulation tests will be performed at a central laboratory at Screening and at EOT:

- Prothrombin time (PT)
- Activated partial thromboplastin time (PTT)
- International normalized ratio (INR)

10.4.4 *PREGNANCY TESTING*

For FCBP, a serum pregnancy test that is confirmed negative is required for eligibility determination and is to be performed at the central laboratory; FCBP is defined in Appendix K. In addition to the pregnancy tests conducted for eligibility, a serum or urine pregnancy test must be confirmed negative locally on Day 1 of each cycle and at EOT. A negative pregnancy test result must be available prior to the first dose of study treatment. More frequent pregnancy tests may be conducted if required per local regulations or investigational sites.

10.5 ELECTROCARDIOGRAM

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

10.6 ECHOCARDIOGRAM

A 2-D transthoracic echocardiogram (ECHO) is required to assess LVEF during Screening and will also serve as the baseline ECHO. If transthoracic ECHO is not available, multigated acquisition (MUGA) will be acceptable for LVEF evaluation.

Any subject with a clinically significant cardiac AE should be evaluated by a cardiologist and must have a follow-up ECHO, if medically indicated.

10.7 PATIENT REPORTED OUTCOMES

Patient reported outcomes (PRO) are based on the following questionnaires (refer to Appendix J).

All questionnaires should be collected on Day 1 of Cycle 1, then every second cycle (Cycle 1, 3, 5, etc) during treatment. The questionnaires listed below should be completed by the subject prior to drug administration during treatment cycles:

- EORTC QLQ-C30
- EORTC QLQ-MY20
- EQ-5D-5L
- Patient reported convenience and satisfaction (collected Day 1 Cycle 2 and EOT only)

Health-related Quality of Life (HRQL) will be assessed by the EORTC 30-item QLQ-C30 questionnaire and by the 20-item QLQ-MY20 module specifically designed to address the quality of life for those with multiple myeloma (Aaronson 1993; Fayers 2001; Cocks 2007). The primary constructed scales from the QLC-C30 are:

- Global Health Status/Quality of Life
- Physical functioning
- Role functioning
- Emotional functioning
- Cognitive functioning
- Social functioning
- Nine additional scales can be derived:
- Fatigue

- Nausea and vomiting
- Pain
- Dyspnea
- Insomnia
- Appetite loss
- Constipation
- Diarrhea
- Financial difficulties

The primary scales from the QLQ-MY20 include disease symptoms, side effects of treatment, body image and future perspectives.

The EQ-5D-5L is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol Group 1990). The EQ-5D-5L version will be used in this study. The EQ-5D-5L consists of a 1-page descriptive system and a 1-page EQ Visual Analogue scale (EQ VAS). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is then scored on 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'. This information can be used as a quantitative measure of health as judged by the individual respondents.

Patient reported convenience and satisfaction with the carfilzomib dosing schedule will be provided as a 1-page questionnaire on the tablet. Subjects will be instructed to fill out the questionnaires to the best of his/her abilities. The study coordinator will be responsible for signing off that the subject has completed the questionnaires.

10.8 HEALTHCARE RESOURCE UTILIZATION

Healthcare resource utilization data related to AEs will be collected for each subject. These data may include inpatient care, outpatient care, surgery, and use of other medications and therapeutic procedures related to AEs. Details on hospitalizations (not related to AEs) will also be collected.

10.9 CORRELATIVE STUDIES

Samples for correlative studies will be collected only after confirmation of study eligibility. Intensive PK and PDn will be conducted as a substudy at selected sites. Sparse PK samples will be collected at all other sites from subjects who consent to the additional testing.

10.9.1 *INTENSIVE PHARMACOKINETICS/PHARMACODYNAMICS SUBSTUDY*

Approximately 15 evaluable subjects in each arm will participate in the intensive PK/PDn substudy at select sites. On both arms, whole blood and PBMCs will be collected from all subjects on Days 1, 15, 16, 17, and 22 of Cycle 1 at the timepoints (summarized in Table 10). Directions for collection, processing, and shipping of PDn blood samples are provided in the Central Laboratory Services Manual. The actual time of when the PDn sample was collected will be recorded.

Table 10 Study 20140355 Pharmacodynamics Sampling Timepoints

	Arm A **Once-weekly carfilzomib**	**Arm B** **Twice-weekly carfilzomib**
Cycle 1 Day 1	Predose	Predose
Cycle 1 Day 15	Predose and 1 hour after the end of infusion	Predose and 1 hour after the end of infusion
Cycle 1 Day 16	24 hours ± 2 hours after the end of the Day 15 infusion	Predose and 1 hour after the end of infusion
Cycle 1 Day 17	48 hours ± 2 hours after the end of the Day 15 infusion	24 hours ± 2 hours after the end of the Day 16 infusion
Cycle 1 Day 22	168 hours ± 2 hours after the end of the Day 15 infusion	144 hours ± 2 hours after the end of the Day 16 infusion

For both treatment arms, PK samples will be collected from all subjects for determination of plasma concentrations of carfilzomib on treatment Day 15 of Cycle 1 at the following time points:

- Predose (within 5 minutes before the start of infusion)
- 15 minutes (± 5 minutes) after the start of infusion for Arm A only (once-weekly carfilzomib)
- Immediately prior to (within 2 minutes before) the end of infusion
- 15 minutes (± 5 minutes) after the end of infusion
- 60 minutes (± 5 minutes) after the end of infusion
- 2 hours (± 5 minutes) after the end of infusion

The actual time of PK sample collection will be recorded. Samples will be collected within ± 5 minute time windows around the nominal time points (except for the time point immediately prior to the end of infusion, for which the PK collection needs to occur prior to the end of infusion). Directions for collection, processing, and shipping of PK samples are provided in the Central Laboratory Services Manual.

10.9.2 *SPARSE PHARMACOKINETIC SAMPLING*

Sparse PK samples will be collected from subjects who do not participate in the intensive PK/PDn substudy and who consent to the additional testing. The actual time of the PK sample collection will be recorded. These samples will be assessed at a central laboratory. Directions for collection, processing, and shipping of PK samples are provided in the Central Laboratory Services Manual.

The sparse PK samples will be collected on Cycle 2 Day 1 at the following time points:

- Predose (within 5 minutes before the start of infusion)
- 15 minutes (± 5 minutes) after the start of infusion for Arm A only (once-weekly carfilzomib)
- Immediately prior to (within 2 minutes before) the end of infusion
- 30 minutes (± 5 minutes) after the end of infusion

10.10 LONG-TERM FOLLOW-UP

There are 2 criteria which mark when subjects may enter LTFU. Subjects may enter into LTFU when discontinuing treatment before disease progression occurs (refer to

Section 10.10.1, below), or, subjects may enter into LTFU when discontinuing due to disease progression (outlined in Section 10.10.2).

10.10.1 *LONG-TERM FOLLOW-UP BEFORE DISEASE PROGRESSION*

For subjects who discontinue treatment before disease progression occurs, disease assessments will be performed (using the central laboratory results) every 28 days ± 4 days until the subject has PD or until withdrawal of consent (Appendix B). Confirmatory PD results (refer to Appendix G) must be obtained prior to the initiation of new antimyeloma therapy. Subject reported outcomes (PROs) including the EORTC QLQ-C30 and QLQ-MY20, EQ-5D-5L and Healthcare Resource Utilization will be collected for these subjects who discontinue therapy prior to progression; assessments will be conducted every 12 weeks (every 84 days ± 4 days) until progression, or withdrawal of consent during LTFU (Appendix A). Long-term follow-up will continue until the subject has withdrawn consent for further participation, is lost to follow-up, has died, or the sponsor makes a decision to close the study. For any subject who is lost to follow-up, the study site will attempt to ascertain survival information via public database search.

10.10.2 *LONG-TERM FOLLOW-UP AFTER DISEASE PROGRESSION (FOR SURVIVAL)*

After completion of the EOT visit, subjects who have discontinued due to disease progression will be followed for survival status, queried by telephone contact or other method, approximately every 12 weeks ± 28 days, or as needed until study closure.

11 STUDY DISCONTINUATION

11.1 WITHDRAWAL OF SUBJECTS FROM STUDY TREATMENT

Subjects may withdraw from study treatment at any time. Reasons for discontinuation include**,** but are not limited to:

- Adverse event
- Pregnancy
- Death
- Lost to follow-up

- Non-compliance with study requirements
- Withdrawal of consent by subject
- Study termination by Sponsor
- Investigator decision
- Progression of disease

The primary reason for study 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 study treatment discontinuation is the occurrence of an AE, the subject will be followed by the investigator until such event(s) resolves, stabilizes, or, according to the investigator's judgment, no longer requires follow-up.

Study treatment discontinuation due to PD should be recorded as "disease progression."

All subjects who are withdrawn from study treatment will be encouraged to complete all relevant safety assessments and continue in the LTFU period. Subjects who discontinue study treatment will be followed for survival and disease status (if discontinuation is prior to progression) until study closure (refer to Appendix B, footnote d).

11.2 WITHDRAWAL OF SUBJECTS FROM STUDY

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

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

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

11.3 STUDY TERMINATION

Sponsor has the right to terminate this study or to terminate a study site from participating in the study at any time. Reasons for study or site termination may include, but are not limited to:

- 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
- Investigational site non-compliance with International Conference on Harmonisation/Good Clinical Practice (ICH/GCP)

12 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

An AE is any untoward medical occurrence in a subject administered a study drug and which is not necessarily caused by the study drug. An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, combination product, or medical device, whether or not considered related to the product. In addition to new events, any worsening of a pre-existing condition that occurs after the subject signs the ICF for participation is considered an AE. Worsening indicates that the pre-existing medical condition or underlying disease 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. This includes any side effect, injury, toxicity, or sensitivity reaction. All reported AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA).

12.1 ADVERSE EVENT REPORTING

12.1.1 *ADVERSE EVENT TERMINOLOGY*

When reporting an AE, accurate and standard medical terminology should be used that clearly identifies the event and the affected body system. Use of non-standard terminology and/or abbreviations should be avoided to ensure accurate and complete

reporting of AEs. Individual signs and symptoms should be reported unless they result in a definitive diagnosis of an event or represent a well-recognized syndrome.

12.1.2 *SEVERITY*

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 to assess the severity of AEs (NCI 2010). For AEs not adequately addressed in the NCI-CTCAE Version 4.03, the following criteria should be used (see Table 11).

Table 11 Grading for Adverse Events not Covered in the NCI-CTCAE

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 activities of daily living (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

NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events.

An AE or suspected adverse reaction (ADR) is considered "unexpected" if it is not listed in the current Carfilzomib IB or is not listed at the specificity or severity that has been observed. Adverse events or suspected ADRs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with particular study drug are considered "unexpected." For example, an event more specific or more severe than described in the IB would be considered "unexpected." Any condition, laboratory abnormality, or physical finding with an onset date prior to the subject signing the ICF is considered to be pre-existing in nature and part of the subject's medical history and should not be considered an AE.

Abnormal laboratory findings should be reported as AEs if medical intervention or corrective action (e.g., transfusions, initiation of antibiotics or other treatment regimens, hydration, study drug placed on hold) is required or the event is deemed clinically

significant by the treating physician. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

12.1.3 *DURATION*

The start and stop date**s** for all AEs will be recorded. The start date is the first date that the subject was aware of the AE and the end date is the date that the event has changed in grade, totally resolved, or returned to baseline. Any changes in grade should be recorded as a separate event. Terms such as "intermittent" or "occasional" are not appropriate descriptions of AEs; each time a full calendar day elapses without the subject experiencing the event should result in the event stop date recorded and a new event reported if the event recurs.

12.1.4 *CAUSALITY*

A relationship between study drug and an adverse event is considered causal if there is at least a reasonable possibility the adverse event was caused by carfilzomib administration, i.e., the relationship cannot be ruled out. The relationship of the AE to the study drug should be assessed by the investigator taking into account the totality of the evidence and in considering the variables listed below.

The following criteria should be considered and would support a positive assessment of causality:

- Time to onset plausible: There is a clinically plausible time sequence between the AE onset and administration of study treatment.
- Biologic plausibility: There is a biologically plausible mechanism for the study treatment to cause or contribute to the AE. Biologic plausibility should be evaluated but is not required for a positive causality assessment. For example, if there is lack of an alternative explanation for the adverse event, then a causal relationship may be positive pending a complete causality assessment.
- Positive dechallenge or rechallenge: The event improves or diminishes upon withdrawal of the study drug without the initiation of any specific treatment for the event (dechallenge) and/or recurs or worsens with rechallenge (when clinically feasible).
- Alternative explanation or confounding factors do not suggest another etiology for the AE: The role of concurrent or underlying illness, co-medication, procedures or other events need to be evaluated as possible causes of or contributing to the adverse event.

The following criteria should be considered and would support a non-causal association between drug administration and the adverse event.

- The AE is more likely to be explained by the subject's clinical state, underlying disease, concomitant medication, study or non-study procedure.
- The amount, duration of exposure**,** or time of last dose prior to the event suggests the AE is not reasonably related to administration of study treatment.

12.2 ADVERSE EVENTS REPORTING PROCEDURES

12.2.1 *GENERAL*

All AEs (e.g., any new event or worsening in severity or frequency of a pre-existing condition or laboratory finding) with an onset date after the subject signs the informed consent for participation in the clinical trial must be promptly documented on the AE eCRF via the electronic data capture (EDC) system. Details of the event must include severity, relationship to study drug(s), duration, action taken, and, for SAEs only, outcome. Whenever possible, reporting specific diagnoses is preferred when reporting AEs in the AE eCRF rather than reporting individual signs and symptoms.

All AEs will be collected from the time the subject signs informed consent through 30 days after receiving the last dose of study drug(s). If initiation of new anticancer therapy occurs within 30 days following the last dose of study drug(s), 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.

All AEs that are considered related to study drug and all SAEs regardless of relationship to study drug must be followed to resolution or stabilization if improvement is not expected. Adverse events which completely resolve and then recur should be recorded as new AEs. 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 documented in the subject's source file. Adverse events 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 is responsible for evaluating all AEs, obtaining supporting source documents, and determining that documentation of the event is adequate. The investigator may delegate these duties to subinvestigators and must ensure that these subinvestigators are qualified to perform these duties under the supervision of the investigator and that they are listed on the FDA Form 1572.

12.3 SERIOUS ADVERSE EVENT DEFINITION

An SAE is an AE that meets 1 or more of the following criteria:

- Death
- Life-threatening experience defined as any adverse experience that places the subject, in the view of the Sponsor or investigator, at immediate risk of death at the time of occurrence (i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death).
- Requires in-subject hospitalization or prolongation of an existing hospitalization (except scheduled hospitalizations for a nonacute, unrelated cause such as elective surgery).
- Results in persistent or significant disability/incapacity (i.e., substantial disruption in a subject's ability to conduct normal activities of daily living [ADL]).
- Is a congenital anomaly/birth defect in the offspring of an exposed female subject or offspring of a female partner of a male subject.
- Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered a SAE when, based upon appropriate medical judgment, jeopardizes the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.

12.4 SERIOUS ADVERSE EVENT REPORTING AND DOCUMENTATION REQUIREMENTS

Amgen Global Patient Safety must be notified of the occurrence of any SAE within 24 hours of the investigator, designee, or site personnel's knowledge of the event. The SAE will be reported by completing and submitting the SAE report form through the EDC system. In the event that the EDC system is not available, paper SAE report forms may be used to report the SAE to Amgen Global Patient Safety (**Appendix L**). Please refer to the SAE Reporting Guidelines in the study reference manual.

Follow-up reports must be submitted in a timely fashion as additional information becomes available.

The investigator is responsible for notifying the Institutional Review Board (IRB) or Independent Ethics Committees (IEC), in accordance with local regulations, of all SAEs. The Sponsor may request for additional source documentation pertaining to the SAE from the investigational site. If a subject is permanently withdrawn from the study due to an SAE, this information must be included in the initial or follow-up SAE report in the eCRF.

The Sponsor is responsible for notifying the appropriate global health authorities of SAEs, when required, in accordance with applicable laws and regulations.

Properly anonymized and de-identified documents (e.g., hospital discharge summaries, autopsy reports, and/or death certificates), as available will be provided to Amgen Global Patient Safety.

12.5 PREGNANCY AND LACTATION EXPOSURE REPORTING

Pregnancy, although not considered an SAE, must be reported to Amgen Global Patient Safety within 24 hours of the investigator's awareness, if the pregnancy has occurred within 30 days of study treatment (for female participants) or within 90 days of study treatment (for female partners of male participants). The pregnancy will be reported on a Pregnancy Notification Worksheet (APPENDIX M). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a subject becomes pregnant while taking an Amgen drug, the study treatment will be immediately discontinued. The investigator will discuss the risks and concerns of investigational drug exposure to a developing fetus and counsel the subject and/or pregnant partner (or ensure that such counseling is provided).

Pregnancies will be followed through the outcome of the pregnancy.

If the outcome of the pregnancy meets a criterion for immediate classification as an SAE (e.g., spontaneous abortion, stillbirth, neonatal death, fetal or neonatal congenital anomaly), the investigator will report the event as an SAE.

With authorization of the subject or female partner, newborns should be followed-up at 6 and 12 months of age.

If a female subject breastfeeds during treatment with carfilzomib or up to 30 days following the last dose of study drug administration, the investigator will notify Amgen Global Patient Safety within 24 hours of learning of her breastfeeding. The investigator will discuss the risks and concerns of breastfeeding while taking an IP. The subject will be required to either discontinue breastfeeding or study treatment. The investigator will complete a Lactation Notification Worksheet (APPENDIX N). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

12.6 DEATH REPORTING

All deaths that occur from signing of informed consent until 30 days after the last dose of study drug are to be reported as SAEs (unless due to PD - refer to Section 12.4). Deaths occurring after the EOT visit do not need to be reported as SAEs. Additional details of the event (such as the primary and contributory causes of death) should be reported on the end of study eCRF.

13 STATISTICAL CONSIDERATIONS

This section describes the statistical considerations of the study design and summarizes the statistical analyses that will be conducted to assess the efficacy and safety endpoints in the study. Further details will be provided separately in the Statistical Analysis Plan (SAP). If, after the study has begun, but prior to the final analysis, important changes are made to the primary or key secondary analyses, then the changes will be reflected in the SAP or its amendment where applicable. The study protocol may be amended as appropriate. Any other changes made to the planned analyses after the protocol and SAP have been finalized, along with an explanation as to when and why they occurred, will be described in the clinical study report, in which any post hoc exploratory analyses also will be clearly identified. Any changes made in the analysis plan, after the primary inferential comparisons between treatment groups are performed, will be exploratory in nature.

13.1 STUDY ENDPOINTS

13.1.1 *PRIMARY ENDPOINTS*

The primary endpoint is **PFS**, which is defined as **the time in months from randomization to the earlier of disease progression or death due to any cause**.

13.1.2 *SECONDARY ENDPOINTS*

The secondary endpoints of the study are as follows:

- **ORR,** defined as the **proportion of subjects who achieved a confirmed PR, VGPR, CR, or sCR, according to the IMWG-URC**.
- OS defined as the time in months from randomization to death due to any cause.
- Safety and tolerability
- Sparse PK

13.2 STUDY POPULATIONS

13.2.1 *INTENT-TO-TREAT POPULATION*

The Intent-to-Treat (ITT) Population consists of all randomized subjects. It will be the basis for the analysis of efficacy endpoints in this study. Subjects in the analysis based on the ITT Population will be included in the treatment group to which they were randomized.

13.2.2 *SAFETY ANALYSIS POPULATION*

The Safety Population is defined as all randomized subjects who received at least 1 dose of any study drug (i.e., carfilzomib, dexamethasone). Subjects in the analysis based on the Safety Population will be included in the treatment group corresponding to the actual treatment received.

13.3 STATISTICAL METHODS

13.3.1 *ANALYSIS OF THE CONDUCT OF THE STUDY*

The number of subjects screened, randomized, and treated will be presented. The number and percentage of subjects excluded from each analysis population will be summarized with reason**s** for exclusion. The number of subjects who discontinue study treatment will be tabulated, along with the reason for discontinuation.

Subjects' demographics and baseline characteristics, disease characteristics, prior and concomitant medications, and study drug exposure and treatment compliance will be summarized descriptively for each treatment group.

The number and percentage of subjects with important protocol deviations will be summarized by treatment group.

13.3.2 *EFFICACY ANALYSES*

All efficacy analyses will be based on the ITT Population, which consists of all subjects randomized.

13.3.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is PFS. Progression-free survival will be calculated from the time of randomization until disease progression or death due to any cause, whichever occurs first. If a subject is alive or lost to follow-up without experiencing documented disease progression by the data cutoff date, the PFS data for the subject will be censored at the date of last valid disease and response assessment. Detailed PFS data censoring rules will be described in the SAP.

The distribution of PFS, including median, will be estimated using the Kaplan-Meier method. Progression-free survival rates at selected time points will be reported by treatment group. The 95% CI for the median and other percentiles of PFS will be constructed using the method of Klein and Moeschberger (1997) with log-log transformation. The 95% CIs for PFS rates were estimated using the method by Kalbfleisch and Prentice (1980) with log-log transformation. The inferential comparison between treatment groups will be made using the log-rank test stratified by the randomization stratification factors specified in Section 7. The hazard ratio (HR) and its 95% CI will be estimated using a Cox proportional hazards model stratified by the same randomization stratification factors. Duration of follow up for PFS will be estimated using the reverse Kaplan-Meier method (Schemper 1996; Smith 2006).

Response and disease progression will be determined using a validated computer algorithm (Onyx Response Computational Assessment; [ORCA]), as well as by local

investigators **and an Independent Review Committee (IRC). The primary analysis of PFS will be based on ORCA-assessed outcomes. The PFS outcomes assessed by the investigator will serve as a supportive analysis of PFS, as will IRC-assessed outcomes.**

The final PFS analysis will be conducted when approximately 350 PFS events have occurred or by end of year 2018, whichever is earlier. A total of 350 PFS events will provide 83% power to detect a significant difference in PFS between the 2 treatment groups with 1 interim analysis CCI [redacted] **. The interim analysis will be performed when 75% of the total PFS events (i.e., 263 events) have occurred. See also Section 13.8 for the interim analysis plan for PFS.**

13.3.2.2 Secondary Efficacy Endpoints

13.3.2.2.1 Overall Response Rate

The ORR will be analyzed at the time of the PFS analysis (interim or final), only if the PFS analysis crosses the boundary. The inferential comparison of ORR between treatment groups will be made using a logistic regression model-based test against the null hypothesis that the odds ratio is ≤ 1 at a 1-sided significance level of 0.025. The regression model will include the randomization stratification factors as covariates. The ORR will be calculated by treatment group and the associated 95% CI will be estimated using the Clopper-Pearson method. The odds ratio (and its 95% CI) will be estimated using the logistic regression model.

The primary analysis of ORR will be based on the ORCA-assessed responses. Investigator assessed responses will be analyzed as a supportive analysis of ORR, as will IRC-assessed responses.

The duration of response (DOR), defined as time in months from the start date of the response to the earlier date of documented disease progression or death, will be calculated for subjects who achieve sCR, CR, VGPR, or PR. The DOR will be censored at date of the last valid assessment for responders who have not experienced disease progression or death. The distribution of DOR, including the

median, will be estimated using the Kaplan-Meier method on the basis of subjects who achieve overall response.

13.3.2.2.2 Overall Survival

Overall Survival will be analyzed using the same methods as for PFS.

Overall Survival data will be right-censored at the earlier of last known alive date or data cutoff date for subjects who are still alive.

The analysis of OS will **be conducted at the time of the PFS analysis (interim or final), only if both PFS and ORR analyses are positive, per hierarchical testing procedures. There will be no interim analysis for OS. Additional follow-up for OS may be performed.**

13.3.2.3 Control of Family-wise Type I Error Rate

The **null** hypotheses for the primary efficacy endpoint, **PFS**, and secondary efficacy endpoints (**ORR** and OS) will be tested using a fixed sequence hierarchical testing procedure to control the family-wise Type I Error rate below 1-sided 0.025 level. The family of hypotheses is ordered as follows: 1) **PFS**, 2) **ORR**, and 3) OS. Starting with the hypothesis of **PFS**, if any hypothesis in the sequence is rejected at a 1-sided significance level of 0.025, then the subsequent hypothesis will be tested; if any hypothesis is accepted, then the subsequent hypotheses will not be tested.

13.3.3 *SAFETY ANALYSIS*

Safety analyses will be based on the Safety Population (defined as all randomized subjects who have received at least 1 dose of study treatment).

13.3.3.1 Adverse Events

Treatment-emergent adverse events are defined as AEs that start on or after the first day study treatment is administered and within 30 days of the last administration of study treatment. The reported AE term will be coded using MedDRA and will be graded for severity using NCI-CTCAE Version 4.03. The causal relationship between the occurrence of an AE and each treatment will be assessed by the investigator as related or not related.

Treatment-emergent adverse events will be summarized based on the number and percentage of subjects experiencing events by treatment group and by MedDRA system organ class (SOC) and preferred term. In the event that a patient experiences repeated episodes of the same AE, the subject will be counted once within each SOC and similarly counted once within each preferred term and the event with the highest severity grade and/or strongest causal relationship to each treatment will be used for purposes of incidence tabulations.

Tabular summaries of the following will be provided:

- All TEAEs by SOC
- All TEAEs in decreasing order of frequency
- TEAEs by causal relationship to study drug
- TEAEs by maximum severity grade
- All SAEs by SOC
- All SAEs in decreasing order of frequency
- TEAEs resulting in modification (i.e., dose reduction or dose interruption) of study treatment
- TEAEs resulting in discontinuation of study treatment
- Deaths within 30 days of the last administration of study treatment
- All AEs, including TEAEs, will be included in individual patient listings.

13.3.3.2 Safety Laboratory Values

For hematology, chemistry, and other laboratory values, the baseline values, changes from baseline by visit, the minimum, maximum, and last observed values will be summarized descriptively.

For the summary of changes from baseline by visit, subjects without a baseline and/or post baseline value will be excluded; values from unscheduled assessments will be excluded. Subjects with missing data for a scheduled assessment time point will be excluded from the summary for that time point. Laboratory results from samples taken > 30 days after the last administration of protocol therapy will be excluded from the laboratory summaries.

All available laboratory data, including those excluded from summary tabulations, will be included in individual patient listings.

Laboratory test results will be graded using the NCI-CTCAE (Version 4.03). Shifts in laboratory toxicity grades to outside the normal range will be evaluated for selected laboratory parameters by assessing the maximum increase and/or decrease observed during the course of study treatment relative to the baseline toxicity grade.

The subject incidence of Grade 3 and 4 hematological laboratory abnormalities (including neutropenia, thrombocytopenia, and anemia) will be provided by treatment group.

The subject incidence of Grade 3 and 4 nonhematological laboratory abnormalities (including liver function test [LFT], CrCl) will be provided by treatment group. Similar analyses will be done for selected chemistry tests.

13.3.3.3 Vital Signs

Vital sign results (systolic and diastolic blood pressure, pulse, respiratory rate, and temperature) will be summarized descriptively for baseline values and changes from baseline to the minimum, maximum, and last observed values.

For the summary of changes from baseline by visit, subjects without a baseline and/or past-baseline value will be excluded; values from unscheduled assessments will be excluded. Vital sign results taken > 30 days after the last administration of protocol therapy will be excluded from all vital sign summaries.

13.3.4 *SPARSE PHARMACOKINETIC ANALYSES*

A sparse PK sampling strategy will be employed in this study, at a subset of study sites. Blood samples will be collected at specified times, processed and stored until analysis. Concentrations of carfilzomib will be measured in plasma using a validated assay method.

The population pharmacokinetic analysis will be a cumulative analysis that will include population pharmacokinetic data obtained from previous Phase 2 and Phase 3 studies that

used intensive or sparse PK sampling. The analysis plan as well as a stand-alone pharmacokinetic analysis report will be prepared separately. 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 who participate in the sparse PK sampling, along with results from the intensive PK/PDn substudy 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.

Additional analyses may be performed to evaluate the relationship between the estimated PK parameters and selected safety or clinical effect endpoints.

13.3.5 *EXPLORATORY ANALYSES*

Exploratory analyses will be performed for the following endpoints:

- PDn and PK endpoints
    - To characterize the PK and PDn of proteasome inhibition in both treatment groups in a subset of subjects. Actual collection times will be recorded and used in the analysis. For the intensive PK/PDn substudy, individual and mean plasma concentration versus time data will be tabulated and plotted by dose level. The PK parameter will be estimated based on noncompartmental methods. The PK parameter estimates for carfilzomib will be summarized, including total plasma exposure (AUC, Cmax, time to maximum plasma concentration [tmax], total plasma clearance, and t1/2 [as appropriate for data collected]). Estimates for these parameters will be tabulated and summarized (i.e., mean, standard deviation). These estimates will be summarized descriptively by each arm.
- Patient-reported outcomes
    - All subscales of the EORTC QLQ-C30, and the EORTC QLQ-MY20
    - EQ-5D-5L: a standardized measure of health status developed by the EuroQol Group
    - Patient-reported convenience and satisfaction
- Healthcare resource utilization

13.4 HANDLING OF DATA

13.4.1 *HANDLING MISSING DATA IN DESCRIPTIVE ANALYSES*

When summarizing categorical variables, subjects with missing data are generally not included in calculations of percentages unless otherwise specified. When needed, the category of "Missing" is created and the number of subjects with missing data is presented.

When summarizing continuous variables, subjects with missing data are not included in calculations. No imputations are made.

13.4.2 *HANDLING MISSING OR PARTIALLY MISSING DATES*

Missing or partially missing dates will not be imputed at data level. However, assumptions for missing or partially missing dates for important variables will be made to allow inclusion of appropriate data records in the analyses. In general, the assumptions about the missing or partially missing dates, when needed, are made conservative to avoid overestimation of treatment effect and underestimation of adverse effects.

If a medication date or time is missing or partially missing, and it cannot be determined whether it was taken prior or concomitantly, it will be considered as a prior, concomitant, and a post-treatment medication.

If the partial AE onset date information does not indicate whether the AE started prior to treatment or after the TEAE period, the AE will be classified as treatment-emergent.

If the start day of subsequent anticancer therapy is missing, it will be assumed to be the first day of the month.

If only the day of a death date is missing, the death will be assumed to be on the first day of the month if the last known alive date is earlier. If the last known alive date is later than the first day of the month, then the death date will be assumed to be the last known alive date plus 1 day.

13.4.3 *MISSING GRADE OR RELATIONSHIP OF ADVERSE EVENT TO STUDY TREATMENTS*

No imputation of AE grades will be performed. Treatment-emergent adverse events with missing CTCAE grade will only be summarized in the all-grades column.

If the assessment of the relationship of an AE to study treatments is missing, then the AE is assumed to be related to the study treatments in the safety analysis, but no imputation should be done at the data level.

13.4.4 *UNSCHEDULED VISITS*

Unscheduled visit measurements of laboratory data and vital signs will be included for computing worst values and/or grades.

13.5 DETERMINATION OF SAMPLE SIZE

CCI [redacted] **the sample size of 460 subjects (230 in each arm) was calculated** CCI [redacted] **a total of 350 PFS events for the final PFS analysis will provide 83% power to detect a significant difference in PFS between the 2 treatment groups with 1-sided overall Type-I error of 0.025 when 1 interim analysis is performed at approximately75% information time (i.e., 263 PFS events) using the O'Brien-Fleming type alpha spending function,** CCI [redacted]

13.6 INDEPENDENT REVIEW COMMITTEE

An IRC **will** be convened for this study to support the ORCA-determined results**. The IRC will centrally review the disease-related tests and assessments (Multiple Myeloma Disease Assessments 10.2) to evaluate disease progression and responses without knowledge of the randomization assignments. The details of the IRC,**

including the roles and responsibilities of the involved parties, will be described in the IRC Charter.

13.7 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be convened for this study and will act in an advisory capacity to the sponsor with respect to safeguarding the interests of study subjects through periodic safety data reviews, assessments of interim safety and efficacy data, and monitoring of the overall conduct of the study. To enhance the integrity of the study, the DMC may also formulate recommendations relating to the selection, recruitment, and retention of subjects, their management, improving adherence to protocol treatment, and the procedures for data management and quality control.

An Independent Statistical Reporting Group (ISRG) will function independently of the Sponsor study team**,** in support of the DMC. The ISRG will conduct unblinded analyses, generate the open and closed reports to be reviewed at the DMC meetings, and serve as the liaison between the Sponsor and the DMC.

The details of the DMC, including the roles and responsibilities of the involved parties, will be described in the DMC Charter.

The DMC will meet to review safety data on a periodic basis, including after approximately 40 subjects have completed ≥ 1 cycle and no less frequently than approximately every 6 months thereafter. Unplanned safety review meetings of the DMC may be called at any time**,** if warranted, for an earlier review of safety data. **The DMC will also review the interim PFS analysis results and recommend whether the study should stop early for efficacy.**

13.8 INTERIM ANALYSIS

Periodic safety review will be conducted by the DMC.

One interim analysis will be conducted for PFS **when** approximately 26**3** (75% of total 350) PFS events **are** observed. The objective of the interim analysis is to **monitor for differences between treatment arms for evidence of a substantial benefit in the carfilzomib once-weekly with dexamethasone arm**.

To ensure proper control of type I error rate, the interim and final analysis of PFS will be analyzed under a group sequential design framework with the stopping boundaries constructed using the **O'Brien-Fleming type** alpha-spending function approach. CCI

[redacted]

CCI

[redacted]

14 REGULATORY OBLIGATIONS

14.1 INFORMED CONSENT

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 will 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 will be in a language understandable to the subject and/or representative as applicable.

The Sponsor or its designated representative will provide the investigator with a sample ICF. Local and/or institutional requirements may require disclosure of additional information in the ICF. Any changes to the ICF must be submitted to the sponsor or its designated representative for approval, prior to submission to the IRB/IEC. The IRB/IEC

will review the ICF for approval. A copy of the approved form must be submitted to the sponsor or its designated representative prior to initiation of the study.

Before implementing any study procedure, informed consent will be documented in the subject's case history and by the use of a written ICF approved by 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.

14.2 COMPLIANCE WITH LAWS AND REGULATIONS

The study will be conducted in accordance with US FDA and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), the Declaration of Helsinki, any applicable local health authority, and IRB or IEC requirements.

This study must have the approval of a properly constituted IRB/IEC. Before the investigational drug is shipped to the investigator, the investigator or designee will provide the Sponsor with a copy of the IRB/IEC approval letter stating that the study protocol and any subsequent amendments and the ICF have been reviewed and approved.

The investigator or designee will be responsible for obtaining annual IRB/IEC re-approval throughout the duration of the study. Copies of the investigator's annual report to the IRB/IEC and copies of the IRB/IEC continuance of approval must be submitted to the Sponsor or designee.

The investigator is also responsible for notifying their IRB/IEC of any significant AEs that are serious and/or unexpected.

The Sponsor will provide study sites with any Investigational New Drug (IND) safety reports, changes to the IB, and any safety updates. The investigator is responsible for immediately notifying their IRB/IEC of any such updates.

14.3 SUBJECT CONFIDENTIALITY

Subject medical information obtained as part of this study is confidential, and must not be disclosed to third parties, except as noted below. The subject may request in writing that medical information be given to his/her personal physician.

The investigator/institution will permit direct access to source data and documents by the Sponsor, its designee, the US FDA, and other applicable regulatory authorities. The access may consist of study-related monitoring, audits, IRB/IEC reviews, and US FDA/regulatory authority inspections.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with US Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508 and, if and to the extent applicable, the principles set out in Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, and national legislation with regard to data privacy.

15 ADMINISTRATIVE AND LEGAL OBLIGATIONS

15.1 PROTOCOL AMENDMENTS

The Sponsor will implement in writing any substantive changes to this protocol as a protocol amendment. The amendment will be submitted to the applicable local regulatory health authority and IRB/IEC, together with a revised ICF, if applicable. Amendments must be submitted to the applicable local regulatory health authority and IRB/IEC approval must be received, signed, and dated by the subject or the subject's legally authorized representative at the time of consent before the amendment is implemented. The investigator or designee must send a copy of the approval letter from the IRB/IEC, along with the revised ICF, to the Sponsor or designee. Upon completion of the study, the investigator must provide the IRB/IEC with a summary of the study's outcome.

15.2 STUDY TERMINATION

The Sponsor reserves the right to terminate the study at any time. The investigator or designee should notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to the Sponsor or designee.

15.3 STUDY DOCUMENTATION AND ARCHIVES

15.3.1 *SOURCE DOCUMENTS*

Source records are original documents, data, and records (e.g., medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical study. The investigator will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject randomized in this clinical study. Source records must be adequate to reconstruct all data entered in the designated eCRF.

15.3.2 *ARCHIVAL OF RECORDS*

According to 21 CFR 312.62(c), the investigators will retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such indication, the investigator will retain these records until 2 years after the investigation is discontinued and the US FDA or applicable regulatory authorities are notified.

The investigator must retain protocols, amendments, IRB/IEC approvals, copies of the Form FDA 1572 or Canadian Quality Investigator Undertaking, signed and dated consent forms, medical records, eCRFs, drug accountability records, all correspondence, and any other documents pertaining to the conduct of the study.

15.4 DATA COLLECTION AND STUDY MONITORING

15.4.1 *ELECTRONIC CASE REPORT FORMS*

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, etc. (refer to Section 15.3.1). The Sponsor will supply the eCRF, which must be completed in English.

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; however, they can authorize listed sub-investigators to sign/approve the data.

15.4.2 *STUDY MONITORING*

The clinical research associate or study monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator(s) and study facility at periodic intervals, in addition to maintaining necessary telephone and letter contacts. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, discussion of the conduct of the study with the investigators and study site personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current SOPs.

15.4.3 *DATA QUALITY ASSURANCE*

The clinical research associates will visit each study site, at a frequency documented in the monitoring plan, to review eCRFs for completeness and accuracy. Any discrepancies noted between source documents and completed eCRFs will be entered as a discrepancy in the EDC system by the clinical research associate, which will then be addressed by the study site personnel. Uniform procedures for eCRF correction (queries) will be discussed at the investigator meeting, and during the study site initiation visits. Data from eCRFs and other external data sources will be entered into a clinical database as specified in the

data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

15.5 PUBLICATION POLICY

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

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

[Additional information on the current guidelines for publications can be found at the following location: http://www.icmje.org/.]

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.

16 REFERENCES

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APPENDIX A SCHEDULE OF ASSESSMENTS

Assessment[a]	Screening[b]	Baseline[c]	All Cycles								LTFU
			D1	D2	D8	D9	D15	D16	D22	EOT	
Informed Consent	X										
Demographics	X										
Medical and treatment history	X										
Vital signs	X		X	X[d]	X	X[d]	X	X[d]		X	
Physical examination[e]	X		X							X	
ECOG Performance Status	X									X	
12 lead ECG with QTc interval	X									X	
ECHO/MUGA	X										
Full hematology panel[f]	X		X		X		X			X	
Full serum chemistry panel[f]	X		X		X		X			X	
Coagulation	X									X	
QLQ-C30, QLQ-MY20, EQ-5D-5L, and Patient Convenience and Satisfaction[g]			X							X	X

APPENDIX A SCHEDULE OF ASSESSMENTS (CONT'D)

Assessment	Screening[b]	Baseline[c]	All Cycles								LTFU
			D1	D2	D8	D9	D15	D16	D22	EOT	
AEs and Survival Status	→	→	→	→	→	→	→	→	→	→	
Concomitant medications	→	→	→	→	→	→	→	→	→	→	
Pregnancy Test (FCBP)[h]	X		X							X	
Survival											X

AEs = adverse events; C1D1 = Cycle 1 Day 1; C2D1 = Cycle 2 Day 1; ECHO = echocardiogram; ECG = electrocardiogram; LTFU = long-term follow-up; EOT = End of Treatment; FCBP = females of childbearing potential; MUGA = multigated acquisition; QLQ-C30 = Quality of Life Core Module; QLQ-MY20 = Quality of Life Multiple Myeloma Module; QT_C = corrected QT-interval; EQ-5D-5L = European Quality of Life-5 Dimensions.

Details of Assessments are in the protocol body.

[a] Refer to Section 9.1 for study treatment related assessment window.

[b] Screening samples can be collected within 21 days of randomization. Refer to Section 10.1.

[c] Baseline samples are collected only after subject eligibility is confirmed. Refer to Section 10.2.

[d] Arm B only (twice-weekly regimen).

[e] The physical examination Screening may be used if within 7 days prior to C1D1. Refer to Section 10.1.3.

[f] Full hematology and serum chemistry samples from Screening may be used for C1D1 if taken within 3 days prior to C1D1. Refer to Section 10.4.1 and Section 10.4.2. Beyond Cycle 4, labs will be performed on Days 1 and 15 of each cycle in both arms.

[g] Questionnaires to be collected on Day 1 of Cycle 1, then every second cycle (Cycle 1, 3, 5, etc) during treatment and every 12 weeks (every 84 days ± 4 days) until progression, or withdrawal of consent during LTFU. Questionnaires should be completed by the subject prior to drug administration during treatment cycles. Patient convenience and satisfaction collected at Cycle 2 and EOT only. Refer to Sections 10.7 and 10.10.1.

[h] Urine or serum pregnancy test must be confirmed negative locally on Day 1 of each Cycle prior to dosing and at EOT. At Screening, a confirmed negative serum pregnancy test that is performed centrally is required. Refer to Section 10.4.4.

APPENDIX B SCHEDULE OF DISEASE ASSESSMENTS

Disease Assessment	Screening (within 21 days of randomization)	Baseline (predose-C1D1)	C1D1	Disease Assessment repeated every 28 days (± 4 days)	EOT[c]	LTFU
SPEP/UPEP/immunofixation[a,b]	X		X[b]	X	X	X[d]
SFLC[a,b]	X		X[b]	X	X	X[d]
Quantitative immunoglobulins[a,b]	X		X[b]	X	X	X[d]
Beta-2 microglobulin[e]	X					
Plasmacytoma Evaluation		X[f]				
Skeletal Survey		X[f]				
Bone Marrow Sample[g]						

C1D1 = Cycle 1 Day 1; C2D1 = Cycle 2 Day 1; LTFU = Long-Term Follow-Up; PD = progressive disease; SFLC = serum free light chain; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; EOT = End of Treatment.

[a] C1D1 before treatment begins (Screening values may be used if obtained within 7 days prior to C1D1) and every 28 days (± 4 days) thereafter, at EOT and during LTFU if disease progression has not already been documented, (every 28 days ± 4 days) until PD and/or start of a subsequent antimyeloma therapy. Refer to Section 10.2.

[b] Screening values may be used if within 7 days prior to C1D1. Refer to Section 7 for allowable window between randomization and C1D1.

[c] EOT will be upon treatment discontinuation or early study withdrawal. Refer to Section 11.

[d] For subjects who did not progress during treatment, SPEP, UPEP, SFLC, and quantitative immunoglobulins will continue to be measured (by the central laboratory) every 4 weeks (every 28 days ± 4 days) until PD. All subjects will be followed for survival and disease status (if discontinuation is prior to progression) by telephone contact or other method every 12 weeks ± 28 days for until study closure. Refer to Sections 10.10.1, 10.10.2 and 11.1.

[e] Must be obtained by central laboratory within 21 days prior to randomization.

[f] Extramedullary plasmacytoma assessments will be performed if clinically indicated at baseline and repeated during treatment only to confirm a response of PR or better, or to confirm PD, or as clinically indicated. A skeletal survey will be repeated if worsening clinical symptoms suggest PD, or as clinically indicated. Historical plasmacytoma evaluation and a skeletal survey performed within 30 days prior to C1D1 may be used for baseline assessments.

[g] Bone marrow samples: Bone marrow biopsy or bone marrow aspirate will be obtained to confirm sCR or CR, or as clinically indicated. The preferred method for a confirmation of CR or sCR is bone marrow biopsy. However, an aspirate slide is acceptable for confirmation of CR (a confirmatory bone marrow sample is not required).

APPENDIX C SCHEDULE OF STUDY TREATMENT ADMINISTRATION

	Cycle 1							Cycles 2+						
	D1	D2	D8	D9	D15	D16	D22	D1	D2	D8	D9	D15	D16	D22
Arm A[a] Once-weekly Carfilzomib with Dexamethasone Regimen														
Carfilzomib (20 mg/m^2)	X													
Carfilzomib (70 mg/m^2)			X		X			X		X		X		
Dexamethasone 40 mg[b] (Day 22 administration should be given PO, Cycles 1−9)	X		X		X		X	X		X		X		X
IV Hydration (Cycle 1 Only)	X		X		X									
Arm B[a] Twice-weekly Carfilzomib with Dexamethasone Regimen														
Carfilzomib (20 mg/m^2)	X	X												
Carfilzomib (27 mg/m^2)			X	X	X	X		X	X	X	X	X	X	
Dexamethasone 40 mg[b] (Day 22 administration should be given PO, Cycles 1−9)	X		X		X		X	X		X		X		X
IV Hydration (Cycle 1 Only)	X	X	X	X	X	X								

D = Day; IV = intravenous(ly); PO = oral(ly).

[a] Study treatment will commence on the day of randomization or at least within 5 calendar days of randomization according to treatment group assignment. Refer to Sections 7 and 9.1 for study treatment related assessment window.

[b] Within 4 hours prior to carfilzomib on Days 1, 8, and 15 in both arms.

APPENDIX D SCHEDULE OF STUDY ASSESSMENTS FOR THE PHARMACOKINETIC SPARSE SAMPLING AND INTENSIVE PHARMACOKINETIC & PHARMACODYNAMIC SUB-STUDY

INTENSIVE PK/PDn SUBSTUDY SAMPLING *Optional*	**Cycle 1**							
	D1	**D2**	**D8**	**D9**	**D15**	**D16**	**D17**	**D22**
Arm A								
PDn substudy/whole blood/PBMCs • Predose	X				X			
PDn substudy/whole blood/PBMCs • 1 hour after dose or equivalent time on non-dosing day					X	X[a]	X[b]	X[c]
PK plasma samples • Predose (within 5 minutes before the start of infusion) • 15 minutes after the start of infusion (± 5 minutes) • Immediately prior to (within 2 minutes before) the end of infusion • 15 minutes, 60 minutes, and 2 hours after the end of infusion (± 5 minutes)					X			
Arm B								
PDn sub-study/whole blood/PMBCs • Predose	X				X	X		
PDn sub-study/whole blood/PBMCs • 1 hour after dose or equivalent time on non-dosing day					X	X	X[d]	X[e]
PK plasma samples • Predose (within 5 minutes before the start of infusion) • Immediately prior to (within 2 minutes before) the end of infusion • 15 minutes, 60 minutes, and 2 hours after the end of infusion (± 5 minutes)					X			
D = Day; PBMC(s) = Peripheral blood mononuclear cell(s); PDn = Pharmacodynamics; PK = Pharmacokinetics.								

a. 24 hours ± 2 hours after the end of the Day 15 infusion
b. 48 hours ± 2 hours after the end of the Day 15 infusion
c. 168 hours ± 2 hours after the end of the Day 15 infusion
d. 24 hours ± 2 hours after the end of the Day 16 infusion
e. 144 hours ± 2 hours after the end of the Day 16 infusion

SPARSE PK SAMPLING *Optional* (ALL SUBJECTS NOT IN THE ABOVE SUBSTUDY)	Cycle 2							
	D 1	D 2	D 8	D 9	D1 5	D1 6	D1 7	D2 2
Arm A • Predose (within 5 minutes before the start of infusion) • 15 minutes after the start of infusion (± 5 minutes) • Immediately prior to (within 2 minutes before) the end of infusion • 30 minutes after the end of infusion (± 5 minutes)	X							
Arm B • Predose (within 5 minutes before the start of infusion) • Immediately prior to (within 2 minutes before) the end of infusion • 30 minutes after the end of infusion (± 5 minutes)	X							

D = Day; PK = Pharmacokinetics.

APPENDIX E 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 (e.g., 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, PPD MD, Group Chair.

APPENDIX F NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

Class I:	Patients with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II:	Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III:	Patients with marked limitation of activity; they are comfortable only at rest.
Class IV:	Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

APPENDIX G SUMMARY OF INTERNATIONAL MYELOMA WORKING GROUP UNIFORM RESPONSE CRITERIA (IMWG-URC)

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

Response Subcategory[a]	Multiple Myeloma Response Criteria
sCR[b]	• CR as defined below and • Normal SFLC ratio and • Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence[c]
CR[b, h]	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow
VGPR[b]	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-protein with urine M-protein level< 100 mg/24 hours • If the serum and urine M-protein are not measurable, a decrease of ≥ 90% in the difference between the involved and uninvolved FLC levels required in place of the M-protein criteria. However, documentation of VGPR requires collection and analysis of 24 hour urine sample for UPEP and immunofixation and confirmed to be negative. • If present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.
PR[b]	• ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/ 24 h • If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • If serum and urine M-protein are not measureable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow cell percentage was ≥ 30% • If present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
MR	• 25%–49% reduction in the level of serum M-protein and a 50%–89% reduction in 24 hour urinary M-protein, which still exceeds 200 mg per 24 hours • If the serum and urine M-protein are not measurable, a decrease of 25%–49% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • If present at baseline, a 25%–49% reduction in the size of soft tissue plasmacytomas is also required
Stable disease	• Not meeting criteria for sCR, CR, VGPR, PR, MR, or PD

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

Response Subcategory[a]	Multiple Myeloma Response Criteria

PD[b]	Any one or more of the following:
	• Increase of ≥ 25% from lowest response value in:
	  ○ Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)
	  ○ Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h)
	  ○ Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dL
	  ○ Bone marrow plasma cell percentages (absolute percentage must be ≥ 10%)
	• Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas[e, f, g]
	• Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65mmol/L) that can be attributed solely to the plasma cell proliferative disorder

Source: Durie 2006; Rajkumar 2011 (*modified for protocol purposes*).

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

Note: For patients without measurable protein on UPEP at baseline, UPEP will need to be repeated to confirm a response of VGPR or better.

[a] Patients with measurable disease in both serum (SPEP) and urine (UPEP) at study entry are required to meet response criteria in both UPEP and SPEP in order to qualify for a MR or better. Conversely, it should be noted that criteria for PD only needs to be met, and confirmed, in one parameter.

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

[c] Presence/absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of > 4:1 or < 1:2.

[d] 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.

[e] Plasmacytomas: A definite increase in the size is defined as a ≥ 50% increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion. A plasmacytoma is considered measurable if the longest diameter is at least 1 cm and the product of the cross diameters is at least 1 cm^2. Plasmacytomas of lesser size will be considered non-measurable.

[f] The requirement for bi-directional measurements applies only to plasmacytomas.

[g] The plasmacytoma specifications for PD are based on the Sponsor's interpretation of the IMWG-URC and practical considerations for study execution.

[h] In patients with sFLC measurable disease only, normal sFLC ratio is required for CR.

APPENDIX H INTERNATIONAL STAGING SYSTEM

The International Staging System (ISS) for myeloma was published by the International Myeloma Working Group (Greipp 2005):

Stage	Criteria
I	Serum beta-2 microglobulin < 3.5 mg/L and serum albumin ≥ 3.5 g/dL
II	Serum beta-2 microglobulin < 3.5 mg/L and serum albumin < 3.5 g/dL or Serum beta-2 microglobulin 3.5–5.5 mg/L irrespective of the serum albumin
III	Serum beta-2 microglobulin ≥ 5.5 mg/L

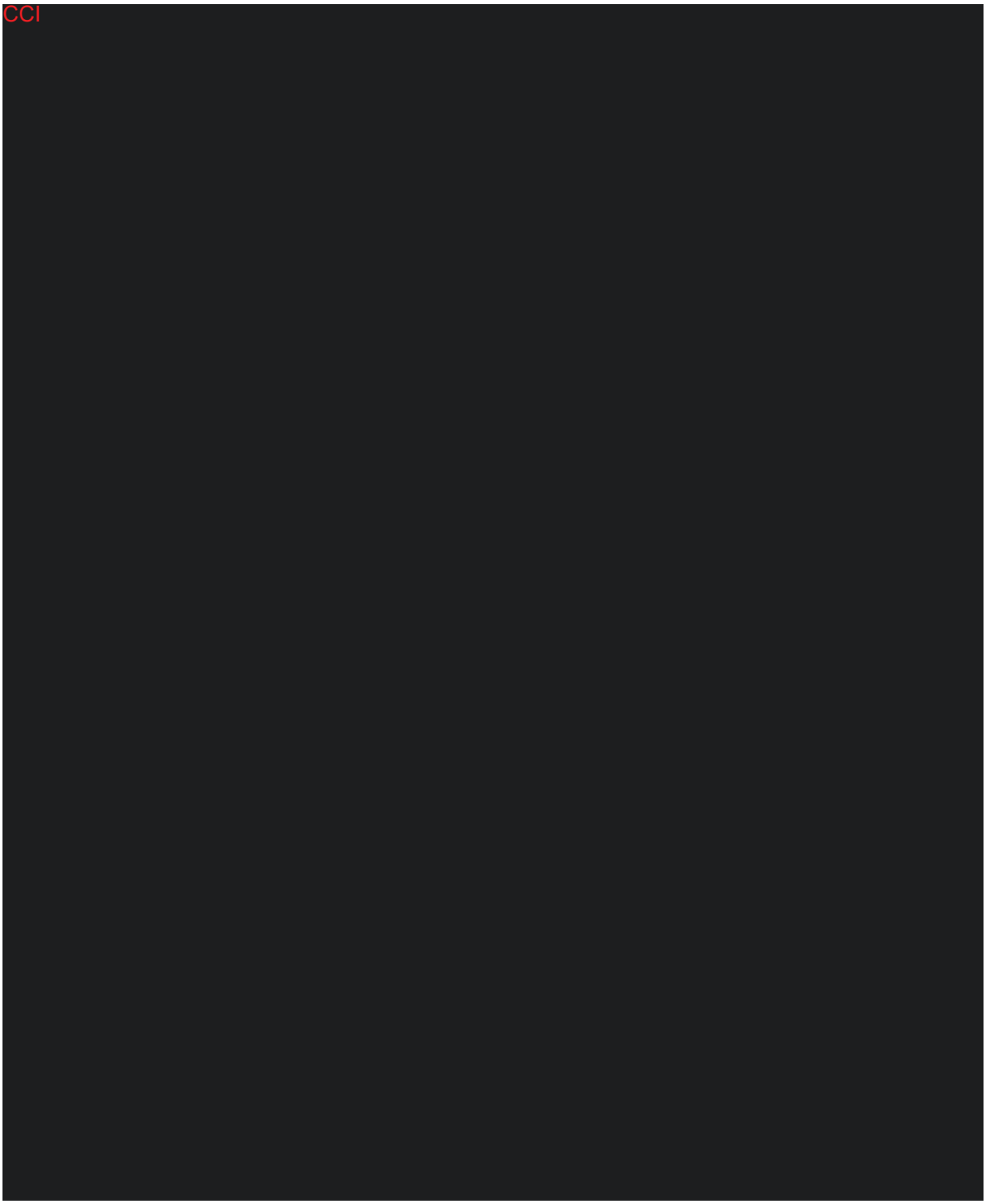
APPENDIX I NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (NCI-CTCAE) GRADING SCALE

Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI), Version 4.03

Published: 28 May 2009 (v4.03: June 14, 2010)

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

APPENDIX J PATIENT REPORTED OUTCOMES



APPENDIX K COUNTRY SPECIFIC PREGNANCY AND CONTRACEPTIVE SUPPLEMENT

A woman of childbearing potential (WOCBP) is defined as:

Any woman who has experienced menarche and is not postmenopausal or permanently sterilized. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal woman is defined as:

- Age > 55 years with cessation of menses for 12 or more months
- Age < 55 years but no spontaneous menses for at least 2 years
- Age < 55 years and spontaneous menses within the past 1 year, but currently amenorrheic (e.g., spontaneous or secondary to hysterectomy), and with postmenopausal gonadotropin levels (luteinizing hormone and follicle-stimulating hormone levels > 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved.
- Underwent a bilateral oophorectomy

Pregnancy Prevention Information

Female Subjects

Highly effective methods of birth control are defined as methods that achieve a failure rate of less than 1% per year when used consistently and correctly.

WOCBP must use a highly effective method of birth control during treatment and for an additional 30 days after the last dose of protocol-required therapies. Highly effective methods of birth control for female participants or their male partner include:

- Combined (estrogen and progestogen) hormonal methods: pills, vaginal ring, or skin patch.
- Single hormonal methods (progestogen to stop the release of the egg from the ovary): pills, shots/injections, implants (placed under the skin by a healthcare provider)
- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system (IUS) surgery to tie both fallopian tubes (bilateral tubal ligation/occlusion)

- Vasectomised partner: Provided the partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.
- Sexual abstinence: Refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and with the preferred and usual lifestyle of the subject.

Male Subjects

If the male subjects sole female partner has received medical confirmation that she is postmenopausal or she has had a permanent sterilization method (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or the male subject has had a vasectomy with medical confirmation of surgical success, or his sole female partner has had a bilateral tubal ligation/occlusion, additional contraceptive methods are not required during this study. Otherwise, if the male subject's female partner could become pregnant, the male must:

- Practice true sexual abstinence. (Refraining from heterosexual intercourse during treatment and for an additional 90 days following the last dose of study drug administration. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and be the preferred and usual lifestyle of the subject.)

  Or

- Use a condom with spermicide during treatment and for an additional 90 days following the last dose of study drug administration. (Note a condom without spermicide is acceptable in countries where spermicide is not commercially available.)

The female partner should also consider using an acceptable method of effective contraception such as:

- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system (IUS)
- Hormonal birth control method: pill, shots/injections, implants (placed under the skin by a healthcare provider), skin patches, or a vaginal ring
- Female barrier method: diaphragm, cervical cap, or contraceptive sponge (a female condom is not an option because there is a risk of tearing when both partners use a condom)

Male subjects must not donate sperm during treatment and for an additional 90 days following the last dose of study drug administration.

Males with pregnant partners must practice true sexual abstinence or wear a condom during vaginal sex to prevent exposure to the embryo/fetus through semen.

APPENDIX L SAMPLE SERIOUS ADVERSE EVENT REPORT FORM

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to IP)**

1. **Site Information**

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. **Subject Information**

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the serious adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

   Serious Adverse Event Diagnosis or Syndrome* –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria)rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

   Is event serious?* – Indicate Yes or No. This is a mandatory field.

   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   Relationship to IP – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

   Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

   If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**

   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

FORM-056006 *Instructions Page 1 of 2* *Version 7.0 Effective Date: 1 February 2016*

Completion Instructions - Electronic Adverse Event Contingency Report Form
(for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

5. **IP Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.
6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. **Case Description**
    Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

FORM-056006 *Instructions Page 2 of 2* *Version 7.0 Effective Date: 1 February 2016*

AMGEN Study # 20140355 Kyprolis	**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? IP: No / Yes; IP: No / Yes; IP: No / Yes; IP: No / Yes	Outcome of Event 1Resolved 2Not resolved 3Fatal 4Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

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

FORM-056006 *Version 7.0* *Effective Date: 1 February 2016*

Page 1 of 3

AMGEN Study # 20140355 Kyprolis	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

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

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

Date (Day Month Year)	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

FORM-056006 Page 2 of 3 *Version 7.0 Effective Date: 1 February 2016*

AMGEN Study # 20140355 Kyprolis	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee - *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

APPENDIX M PREGANCY NOTIFICATION FORM

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: 20140355

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

APPENDIX N LACTATION NOTIFICATION FORM

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: 20140355

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 O SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 4 AND FOR SUPERSEDING PROTOCOL AMENDMENT 4

Protocol Title: A Randomized, Open-label, Phase 3 Study in Subjects with Relapsed and Refractory Multiple Myeloma Receiving Carfilzomib in Combination with Dexamethasone, Comparing Once-weekly versus Twice-weekly Carfilzomib Dosing

Amgen Protocol Number 20140355 (formerly CFZ014)

Amendment Date: 07 March 2017

Rationale:

In Protocol Amendment 4, the protocol is amended to:

- Switch progression-free survival (PFS) from a key secondary objective/endpoint to the primary objective/endpoint and overall response rate (ORR) from the primary objective/endpoint to a key secondary objective/endpoint

  Rationale: This study was originally designed with ORR as the primary endpoint because response rates, especially high-quality responses of substantial duration, are important indicators of benefit in relapsed and refractory multiple myeloma. However, recent advances in antimyeloma therapy have altered the landscape such that PFS is now considered to be the more relevant regulatory endpoint in this setting. To support regulatory interactions and protect the integrity of the PFS data, the primary endpoint has been amended to PFS, with ORR as a key secondary endpoint.

- Change the purpose and timing of the interim PFS analysis

  Rationale: The purpose and timing of the interim PFS analysis were amended to monitor efficacy and allow the possibility of stopping the trial early for efficacy.

- Revise statistical language to align with changes in objectives/endpoints and purpose and timing of the interim PFS analysis
- Update Table 12 (Stopping Boundaries for Progression-free Survival)
- Allow the possibility for long-term follow-up for overall survival
- Add Section 4.4.1 (End of Study)
- Add Section 8.4 (Product Complaints)
- Update Table 5 (Carfilzomib Dose Modifications for Nonhematologic Toxicity)

- Add Section 9.4.2.5 (Thromboprophylaxis)
- Add the following forms in the Appendices
    - Sample Serious Adverse Event Report Form
    - Pregnancy Notification Form
    - Lactation Notification Form
- Update Section 2 (Background Information)
- Correct an error in the study schema inserted into Protocol Amendment 4 (thereby creating a Superseding Amendment 4)
- Make minor text clarifications, additions, corrections, and edits throughout the protocol

In Superseding Protocol Amendment 4, the protocol is amended to:

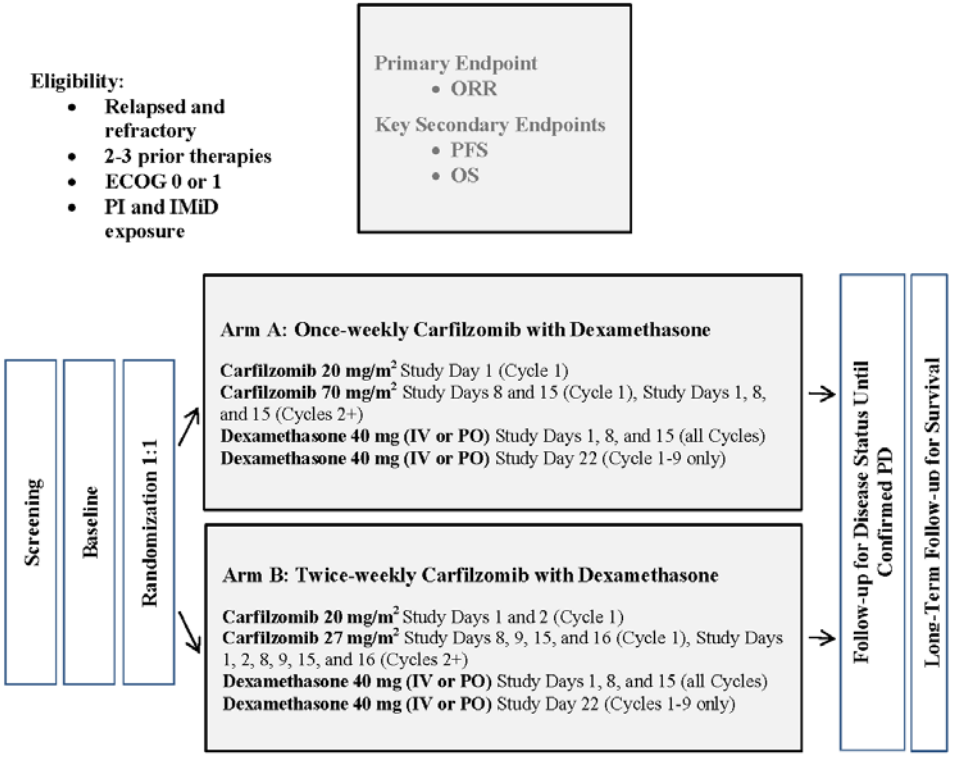
- Correct an error in the dexamethasone dosing in the study schema inserted into Protocol Amendment 4
- Make minor edits throughout the protocol

Table 1. Summary of Amendment Changes

Section	Text in Protocol	Amended Text	Rationale for Change
Section: Global, Footer	**Replace:** Amendment 3: 22 April 2016	**With:** **Superseding** Amendment **4**: **07 March 2017**	Administrative change
Section: Title Page		**Add:** **Date of Protocol Amendment 4.0: 08 February 2017**	Administrative change
Section: Title Page		**Add:** **Date of Superseding Protocol Amendment 4.0: 07 March 2017**	Administrative change
Section: Protocol Acceptance Page, Issue/Date	**Replace:** 20140355 (Protocol Amendment 3.0)/22 April 2016	**With:** 20140355 (**Superseding** Protocol Amendment **4**.0)/**07 March 2017**	Administrative change
Section: Synopsis, Study objective(s), Primary Objective	**Replace:** To compare the overall response rate (ORR) of once-weekly carfilzomib dosing in combination with dexamethasone to the ORR of twice- weekly carfilzomib dosing in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma who have received prior treatment with a proteasome inhibitor and an IMiD (immunomodulatory agent).	**With:** To compare the **progression-free survival** (**PFS**) of once-weekly carfilzomib dosing in combination with dexamethasone to the **PFS** of twice-weekly carfilzomib dosing in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma who have received prior treatment with a proteasome inhibitor and an IMiD (immunomodulatory agent).	Primary/secondary objective switch
Section: Synopsis, Study objective(s), Secondary Objectives, Bullet 1	**Replace:** Progression-free survival (PFS)	**With:** **Overall response rate** (**ORR**)	Primary/secondary objective switch
Section: Synopsis, Study design, Line 5	**Replace:** The primary endpoint is ORR.	**With:** The primary endpoint is **PFS**.	Primary/secondary endpoint switch

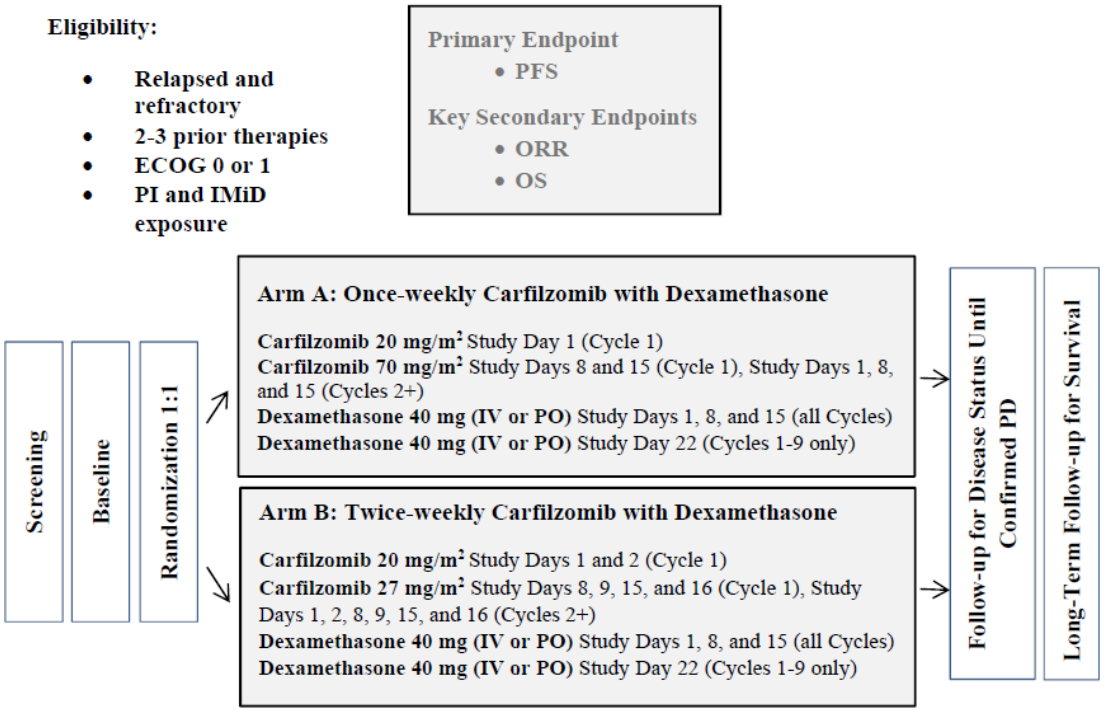
Section	Text in Protocol	Amended Text	Rationale for Change
Section: Synopsis, Study design, Study Schema	**Replace:** Original Study 20140355 Schema below	**With:** Revised Study 20140355 Schema below	Alignment with Primary/secondary objective switch

Original Study 20140355 Schema:



ECOG = Eastern Cooperative Oncology Group; IMiD = immunomodulatory agents; IV = intravenous(ly); ORR = overall response rate; OS = overall survival; PD = disease progression; PFS = progression-free survival; PI = proteasome inhibitor; PO = orally.

Revised Study 20140355 Schema:



ECOG = Eastern Cooperative Oncology Group; IMiD = immunomodulatory agents; IV = intravenous(ly); ORR = overall response rate; OS = overall survival; PD = **progressive disease**; PFS = progression-free survival; PI = proteasome inhibitor; PO = orally.

Section	Text in Protocol	Amended Text	Rationale for Change
Section: Synopsis, Sample size justification	**Replace:** CCI	**With:** CCI	Statistical revision to align with primary objective/endpoint change
Section: Synopsis, Efficacy variables, Paragraph 1	**Replace:** The primary endpoint it is overall response rate (ORR).	**With:** The primary endpoint is **PFS**.	Primary/secondary endpoint switch
Section: Synopsis, Efficacy variables, Paragraph 2	**Replace:** Secondary endpoints are: progression-free survival (PFS), overall survival (OS), safety and tolerability, and pharmacokinetics (sparse sampling) (PK).	**With:** Secondary endpoints are: **ORR**, overall survival (OS), safety and tolerability, and pharmacokinetics (sparse sampling) (PK).	Primary/secondary endpoint switch

Section	Text in Protocol	Amended Text	Rationale for Change
Section: Synopsis, Statistical methods and analyses, Paragraph 2	**Replace:** The primary endpoint, ORR, is defined as the proportion of subjects achieving a best overall response of partial response (PR), very good partial response (VGPR), complete response (CR) or stringent complete response (sCR) based on the IMWG-URC.	**With:** The primary endpoint, **PFS, will be calculated from the time of randomization until PD or death due to any cause, whichever occurs first. If a subject is alive or lost to follow-up without experiencing documented disease progression by the data cutoff date, the PFS data for the subject will be censored at the date of last valid disease and response assessment. The distribution of PFS will be estimated using the Kaplan-Meier method. The inferential comparison between treatment groups will be made using the log-rank test stratified by the randomization stratification factors. The HR and its 95% CI will be estimated using a Cox proportional hazards model stratified by the same randomization stratification factors.**	Statistical revision to align with primary objective/endpoint change
Section: Synopsis, Statistical methods and analyses, Paragraph 3	**Delete:** ~~The inferential comparison of ORR between treatment groups will be conducted using a logistic regression model-based test against the null hypothesis that the odds ratio is ≤ 1 at a 1-sided significance level of 0.025.~~		Statistical revision to align with primary objective/endpoint change
Section: Synopsis, Statistical methods and analyses, Paragraph 4, Line 1	**Replace:** The randomization stratification factors will be included ~~as covariates~~ in the model:	**With:** The **following** randomization stratification factors will be included as covariates in the model:	Statistical revision to align with primary objective/endpoint change

Section	Text in Protocol	Amended Text	Rationale for Change
Section: Synopsis, Statistical methods and analyses, after Paragraph 4		**Add:** **Response and disease progression will be determined using a validated computer algorithm (Onyx Response Computational Assessment [ORCA]), as well as by local investigators and by an Independent Review Committee (IRC). The primary analysis of PFS will be based on ORCA-assessed outcomes. The PFS outcomes assessed by the investigator will serve as a supportive analysis of PFS, as will IRC-assessed outcomes.**	Statistical revision to align with primary objective/endpoint change
Section: Synopsis, Statistical methods and analyses, Paragraph 5	**Replace:** The ORR will be calculated by treatment group and the associated 95% confidence interval [CI] will be estimated using the Clopper-Pearson method. The odds ratio (and its 95% CI) will be estimated using the logistic regression model.	**With:** **The secondary endpoint ORR is defined as the proportion of subjects achieving a best overall response of PR, very good partial response (VGPR), complete response (CR), or stringent complete response (sCR), based on the IMWG-URC.** The ORR will be calculated by treatment group**,** and the associated 95% confidence interval [CI] will be estimated using the Clopper-Pearson method. The odds ratio (and its 95% CI) will be estimated using the logistic regression model.	Clarification

Section	Text in Protocol	Amended Text	Rationale for Change
Section: Synopsis, Statistical methods and analyses, Paragraph 6	**Delete:** ~~Response and disease progression will be determined using a validated computer algorithm (Onyx Response Computational Assessment [ORCA]) as well as by local investigators. The primary analysis of ORR will be based on the ORCA-assessed responses. Investigator-assessed responses will be analyzed as part of a supportive ORR analysis, as will IRC-assessed responses, if an Independent Review Committee (IRC) is convened.~~		Statistical revision to align with primary objective/endpoint change
Section: Synopsis, Statistical methods and analyses, Paragraph 8	**Delete:** The secondary endpoint~~s~~ of ~~PFS and~~ OS will be analyzed using the log-rank test stratified by the randomization stratification factors. The corresponding ~~hazard ratios (~~HRs~~)~~ will be estimated using a stratified Cox proportional hazards model. The distribution of ~~PFS and~~ OS including medians will be summarized using the Kaplan-Meier method.		Statistical revision to align with secondary objective/endpoint change

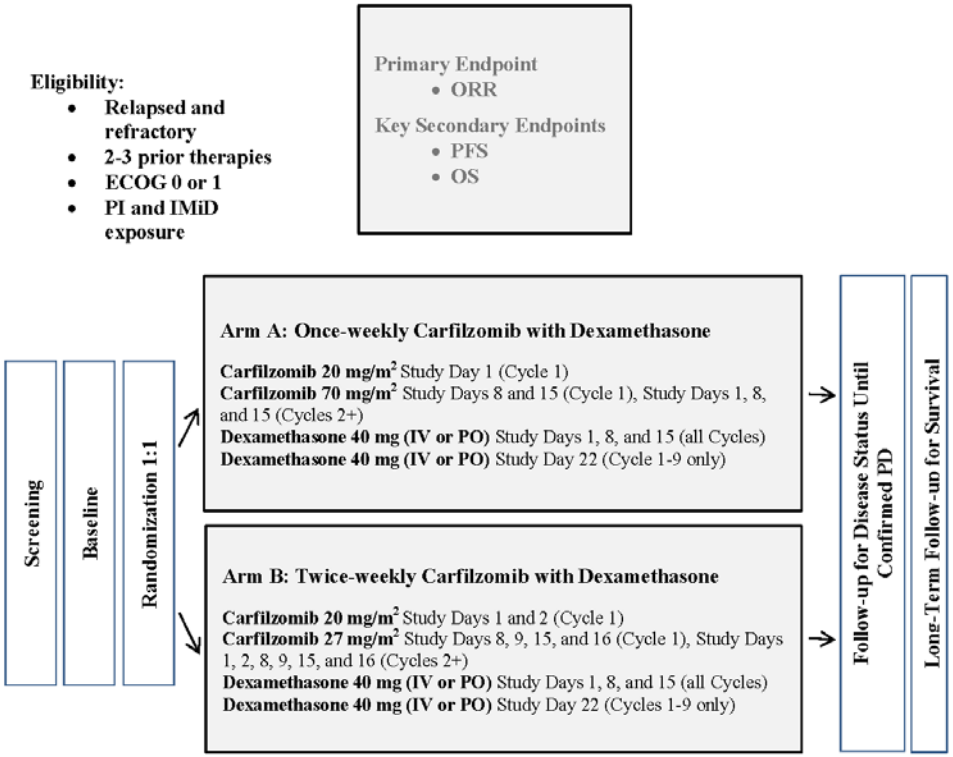
Section	Text in Protocol	Amended Text	Rationale for Change
Section: Synopsis, Statistical methods and analyses, Paragraph 9	**Replace:** The hypotheses for the primary efficacy endpoint, ORR, and secondary efficacy endpoints (PFS and OS) will be tested using a fixed sequence hierarchical testing procedure to control the family-wise Type I error rate below 1-sided 0.025 level. The family of hypotheses is ordered as follows: ORR, PFS, and OS. Starting with the hypothesis of ORR, if any hypothesis in the sequence is rejected at a 1-sided significance level of 0.025, then the subsequent hypothesis will be tested; if any hypothesis is accepted, then the subsequent hypotheses will not be tested.	**With:** The hypotheses for the primary efficacy endpoint, **PFS**, and secondary efficacy endpoints (**ORR** and OS) will be tested using a fixed sequence hierarchical testing procedure to control the family-wise Type I error rate below 1-sided 0.025 level. The family of hypotheses is ordered as follows: **PFS**, **ORR**, and OS. Starting with the hypothesis of **PFS**, if any hypothesis in the sequence is rejected at a 1-sided significance level of 0.025, then the subsequent hypothesis will be tested; if any hypothesis is accepted, then the subsequent hypotheses will not be tested.	Statistical revision to align with primary/secondary objective/endpoint switch

Section	Text in Protocol	Amended Text	Rationale for Change
Section: Synopsis, Statistical methods and analyses, Paragraph 12	**Replace:** The total study accrual period is expected to be approximately 15 months. The data cutoff date for the primary analysis of ORR will be approximately 4 months after the last patient is randomized. At the time of the final analysis of ORR, interim analysis of PFS and OS will be conducted. The primary objective of this interim analysis is to provide necessary data to help assess the ORR result. Therefore, a 1-sided error level of 0.0001 will be assigned for this interim analysis. Approximately 262 (75%) of PFS events are expected to be included in the interim analysis. Subjects will continue to be followed for disease and survival status until 350 PFS events are observed, which is expected to occur approximately 25 months after the first patient is randomized. These durations are estimated based upon the assumptions of median PFS of 8.2 months in the once-weekly dosing group and 6 months in the twice-weekly dosing group with an underlying hazard ratio (HR) of 0.73. The final analysis of OS will occur at the time of the final analysis of PFS.	**With:** **The final PFS analysis will be conducted when approximately 350 PFS events have occurred or by end of year 2018, whichever is earlier. A total of 350 PFS events will provide 83% power to detect a significant difference in PFS between the 2 treatment groups with 1 interim analysis** [redacted]**. The interim analysis will be performed when approximately 75% of the total PFS events (i.e., 263 events) have occurred. The ORR and OS analyses will be performed at the same time as the PFS analysis (interim or final).**	Statistical revision to align with primary objective/endpoint change
Section: 2.4 STUDY RATIONALE, Paragraph 2, Line 1	The rationale for this study is to compare carfilzomib administered once weekly in combination with dexamethasone, based on the CHAMPION 1 results, to twice-weekly carfilzomib in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma, previously treated with bortezomib and an IMiD.	The rationale for this study is to compare carfilzomib administered once weekly in combination with dexamethasone, based on the CHAMPION 1 results, to twice-weekly carfilzomib in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma, previously treated with **a proteasome inhibitor** and an IMiD.	Correction

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 2.4 STUDY RATIONALE, Paragraph 3	**Replace:** The primary endpoint in this study is ORR. Response rates, especially high-quality responses of substantial duration**,** are important indicators of benefit in relapsed and refractory multiple myeloma (Anderson 2008). A number of studies have shown an association between deeper responses and improved survival in patients with multiple myeloma (Lonial 2014)	**With:** The primary endpoint in this study is **PFS**. Response rates, especially high-quality responses of substantial duration**,** are important indicators of benefit in relapsed and refractory multiple myeloma (Anderson 2008). A number of studies have shown an association between deeper responses and improved survival in patients with multiple myeloma (Lonial 2014). **For these reasons, this study was originally designed with ORR as the primary endpoint and PFS as a key secondary endpoint. Although ORR remains a meaningful clinical endpoint, recent advances in antimyeloma therapy have altered the landscape such that PFS is now considered to be the more relevant regulatory endpoint in this setting. To support regulatory interactions and protect the integrity of the PFS data, the primary endpoint has been amended to PFS, with ORR as a key secondary endpoint.**	Addition of rationale for primary/secondary endpoint switch
Section: 3.1 PRIMARY OBJECTIVE	**Replace:** The primary objective of this study is to compare the ORR of once-weekly carfilzomib dosing in combination with dexamethasone to the ORR of twice-weekly carfilzomib dosing in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma who have received prior treatment with a proteasome inhibitor and an IMiD.	**With:** The primary objective of this study is to compare the **PFS** of once-weekly carfilzomib dosing in combination with dexamethasone to the **PFS** of twice-weekly carfilzomib dosing in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma who have received prior treatment with a proteasome inhibitor and an IMiD.	Primary/secondary objective switch

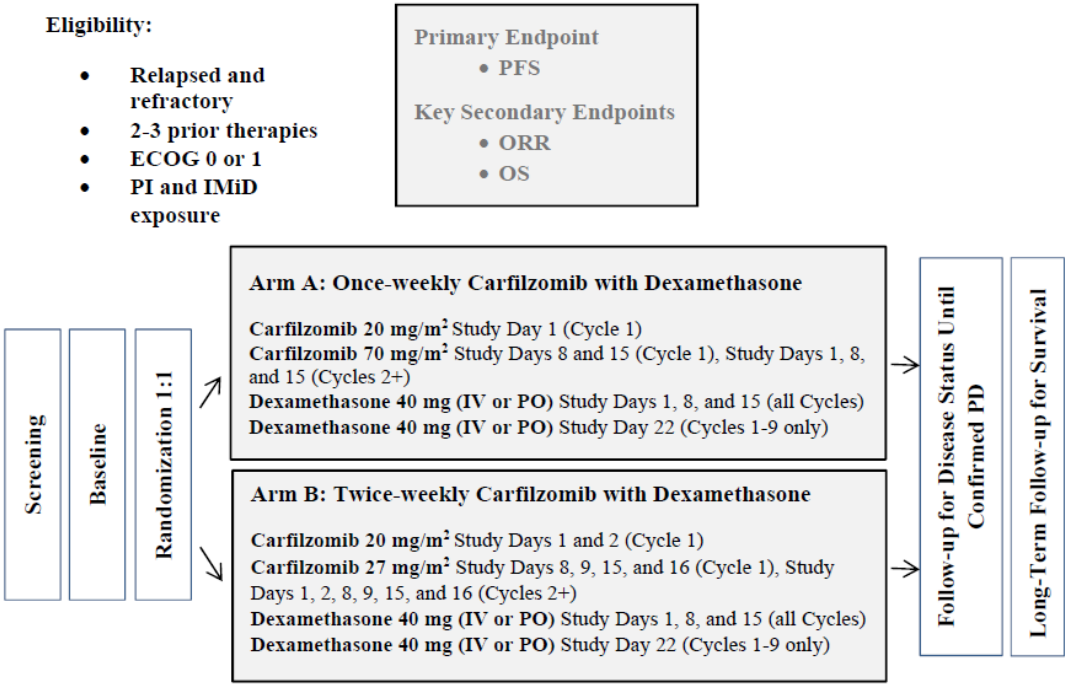
Section	Text in Protocol	Amended Text	Rationale for Change
Section: 3.2 SECONDARY OBJECTIVES, Bullet 1	**Replace:** Progression-free survival (PFS)	**With:** **ORR**	Primary/secondary objective switch
Section: 4.1 STUDY DESIGN, Figure 2 Study 20140355 Schema	**Replace:** Original Study 20140355 Schema below	**With:** Revised Study 20140355 Schema below	Alignment with Primary/secondary objective switch

Original Study 20140355 Schema:



ECOG = Eastern Cooperative Oncology Group; IMiD = immunomodulatory agents; IV = intravenous(ly); ORR = overall response rate; OS = overall survival; PD = disease progression; PFS = progression-free survival; PI = proteasome inhibitor; PO = orally.

Revised Study 20140355 Schema:



ECOG = Eastern Cooperative Oncology Group; IMiD = immunomodulatory agents; IV = intravenous(ly); ORR = overall response rate; OS = overall survival; PD = **progressive disease**; PFS = progression-free survival; PI = proteasome inhibitor; PO = orally.

Section	Text in Protocol	Amended Text	Rationale for Change
Section: STUDY DESIGN, Paragraph 4	**Replace:** The primary endpoint is ORR.	**With:** The primary endpoint is **PFS.**	Primary/secondary endpoint switch
Section: 4.4 ESTIMATED STUDY DURATION AND CLOSURE	**Replace:** The total study accrual period is expected to be approximately 15 months. The data cut off date for the primary analysis of ORR will be approximately 4 months after the last subject is randomized. Subjects will be followed for disease and survival status until approximately 350 PFS events are observed, which is expected to occur approximately 25 months after the first subject is randomized. These durations are estimated based upon the assumptions of median PFS of 8.2 months in the once-weekly dosing arm and 6 months in the twice-weekly dosing arm with an underlying hazard ratio (HR) of 0.73.	**With:** The total study accrual period is expected to be approximately 15 months. **The interim analysis of PFS will occur when approximately 263 PFS events are observed. If the interim analysis crosses the boundary, the trial may stop early for efficacy; otherwise s**ubjects will be followed for disease and survival status until approximately 350 PFS events are observed **or by end of year 2018, whichever is earlier**.	Statistical revision to align with change in primary objective/endpoint and purpose and timing of the interim PFS analysis.

Section	Text in Protocol	Amended Text	Rationale for Change
Section: after Section 4.4 ESTMATED STUDY DURATION AND CLOSURE		**Add:** 4.4.1 **END OF STUDY** **Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.** **The primary completion is anticipated to occur when approximately 350 PFS events occur or end of year 2018, whichever is earlier. The primary completion date is the date when data for the primary endpoint are last collected for the purposes of conducting the primary analysis or the end of year 2018, whichever is earlier.** **If the study concludes prior to the primary completion date originally planned in the protocol (i.e., early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (i.e., last subject last visit).** **End of Study: The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (i.e., last subject last visit), following any additional parts in the study (e.g., long-term follow-up), as applicable.**	Addition of section for end of study definition

Section	Text in Protocol	Amended Text	Rationale for Change
Section: after 8.3 STUDY DRUG ACCOUNTABILITY		**Add:** 8.4 **PRODUCT COMPLAINTS** **A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.** **This includes any drug(s), device(s) or combination product(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product.** **Any product complaint(s) associated with an investigational product(s) or non-investigational product(s) or device(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.**	Addition of instructions for reporting product complaints
Section: 9.3.1.2 Nonhematologic Toxicity, Table 5 Carfilzomib Dose Modifications for Nonhematologic Toxicity	Replace: Original Table 5 below	**With:** Revised Table 5 below	Update of guidelines

Original Table 5:

Nonhematologic Toxicity	Required Action[a]
Renal Dysfunction	
• Serum creatinine ≥ 2 × baseline, OR • CrCl < 15 mL/min, OR • CrCl decr*eases to ≤ 50%* of baseline, OR • Requirement for dialysis	• Withhold doses while the cause of renal dysfunction is being assessed • If attributable to carfilzomib, resume at 1 dose decrement when CrCl has recovered to within 25% of baseline • If not attributable to carfilzomib, resume the same dose or reduce by 1 dose decrement, at the investigator's discretion, when CrCl has recovered to within 25% of baseline • For patients on dialysis receiving carfilzomib, the dose is to be administered after the dialysis procedure
Hepatic Dysfunction	
• ≥ Grade 3 Elevations of AST, ALT, or total bilirubin	• Withhold doses. • Resume at 1 dose decrement when the grade has returned to baseline
Infection	
• ≥ Grade 3 Infection	• Withhold doses • Resume at the same dose level, when the infection is controlled
Cardiovascular Dysfunction	
• Congestive Heart Failure	• Withhold doses for any subject with symptomatic heart failure, whether or not it is attributed to carfilzomib • Resume at 1 dose decrement, when symptoms have resolved or returned to baseline
• LVEF < 40%, OR • LVEF < 55%, if decreased > 20% from baseline	• Withhold doses • Resume at 1 dose decrement, when LVEF returns to ≥ 40%, or to within 15% of baseline, if carfilzomib was held due to a drop to < 55%
• Pulmonary Hypertension	• Withhold doses ~~and assess the benefit: risk of resuming carfilzomib~~ • If the assessment favors benefit, carfilzomib may be resumed at the same dose level or at 1 dose decrement, at the investigator's discretion

Nonhematologic Toxicity	Required Action[a]
Thrombotic Microangiopathy	
• Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS)	• Withhold doses when TTP/HUS is suspected • If the diagnosis is excluded, resume at the same dose level • If the diagnosis is confirmed, the decision to resume or not resume carfilzomib is at the investigator's discretion. The safeness of resuming carfilzomib following TTP/HUS is unknown. • Manage symptoms per standard of care including, plasma exchange as clinically indicated [b]
Encephalopathy	
• Posterior reversible encephalopathy syndrome (PRES)	• Withhold doses ~~and assess the benefit:risk of resuming carfilzomib~~ • Consider evaluation with neuroradiological imaging for onset of visual or neurological symptoms suggestive of PRES • If the diagnosis is excluded, resume at the same dose level • If the diagnosis is confirmed, the decision to resume or not resume carfilzomib is at the investigator's discretion. The safeness of resuming carfilzomib following PRES is unknown.
Other Nonhematologic Toxicity	
• ≥ Grade 3 and attributed to carfilzomib	• Withhold doses • Resume at 1 dose decrement, when toxicity has resolved to Grade ≤ 2 or to baseline

Revised Table 5:

Nonhematologic Toxicity	Required Action[a]
Renal Dysfunction	
• Serum creatinine ≥ 2 × baseline, OR • CrCl < 15 mL/min, OR • CrCl decr*eases to ≤ 50%* of baseline, OR • Requirement for dialysis	• Withhold doses while the cause of renal dysfunction is being assessed • If attributable to carfilzomib, resume at 1 dose decrement when CrCl has recovered to within 25% of baseline • If not attributable to carfilzomib, resume the same dose or reduce by 1 dose decrement, at the investigator's discretion, when CrCl has recovered to within 25% of baseline • For patients on dialysis receiving carfilzomib, the dose is to be administered after the dialysis procedure
Hepatic Dysfunction	
• **Mild to moderate liver dysfunction: defined as 2 consecutive values, at least 28 days apart, of:** **(3) Total bilirubmin (> 33% direct) > 1 x ULN to < 3 x ULN** **OR** **(4) An elevation of AST and/or ALT with normal bilirubin**	• **25% dose reduction.** • **Dose may be re-escalated if liver function tests return to normal and drug-induced hepatotoxicity is excluded.**
• Grade 3 **elevation in ALT and/or AST (> 5 x ULN)**	• **Hold carfilzomib until resolution to baseline.** • **Monitor any abnormality weekly. Resume carfilzomib with a 25% dose reduction if drug-induced hepatoxicity is excluded.**
• **Grade 3 elevation in total bilirubin**	• **Hold carfilzomib until resolution to baseline. Monitor total bilirubin and direct bilirubin weekly.** • **Upon resolution of total bilirubin to normal, resume carfilzomib dosing with at 25% dose reduction if drug-induced hepatotoxicity is excluded.**
• **Drug-induced hepatoxicity attributable to carfilzomib**	• **Discontinue carfilzomib.**
Infection	
• ≥ Grade 3 Infection	• Withhold doses • Resume at the same dose level, when the infection is controlled
Cardiovascular Dysfunction	
• Congestive Heart Failure	• Withhold doses for any subject with symptomatic heart failure, whether or not it is attributed to carfilzomib • Resume at 1 dose decrement, when symptoms have resolved or returned to baseline
• LVEF < 40%, OR • LVEF < 55%, if decreased > 20% from baseline	• Withhold doses • Resume at 1 dose decrement, when LVEF returns to ≥ 40%, or to within 15% of baseline, if carfilzomib was held due to a drop to

Nonhematologic Toxicity	Required Action[a]
	< 55%
• **≥ Grade 2** Pulmonary Hypertension	• Withhold doses • **Carfilzomib** may be resumed at 1 dose decrement **when pulmonary hypertension resolves to grade ≤ 1**
Thrombotic Microangiopathy	
• Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS)	• Withhold doses when TTP/HUS is suspected • If the diagnosis is excluded, resume at the same dose level • If the diagnosis is confirmed, **discontinue carfilzomib. Subjects should not be rechallenged.** • Manage symptoms per standard of care including, plasma exchange as clinically indicated [b]
Venous Thrombosis	
• **≥ Grade 3**	• **Hold carfilzomib and adjust anticoagulation regimen.** • **Resume at full dose once anticoagulation has been optimized per treating investigator's discretion.**
Encephalopathy	
• Posterior reversible encephalopathy syndrome (PRES)	• Withhold doses • Consider evaluation with neuroradiological imaging for onset of visual or neurological symptoms suggestive of PRES • If the diagnosis is excluded, resume at the same dose level • If the diagnosis is confirmed, **discontinue carfilzomib. Subjects should not be rechallenged.**
Other Nonhematologic Toxicity	
• ≥ Grade 3 and attributed to carfilzomib	• Withhold doses • Resume at 1 dose decrement, when toxicity has resolved to Grade ≤ 2 or to baseline

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 9.4.1.2 Pregnancy and Contraception, Line 1	**Replace:** Contraception must continue during study drug dose interruption intervals until 30 days (females) or 90 days (males) after the last study drug administration.	**With:** Contraception must continue during study**,** **during** drug dose interruption intervals**, and** until 30 days (females) or 90 days (males) after the last study drug administration.	Edit
Section: after Section 9.4.2.4		**Add:** **9.4.2.5 Thromboprophylaxis** **Venous thromboembolism has been observed in patients receiving carfilzomib. Thromboprophylaxis may be considered on the basis of a benefit-risk assessment.**	Addition of language for thromboprophylaxis
Section: 12.4 SERIOUS ADVERSE EVENT REPORTING AND DOCUMENTATION REQUIREMENTS, Paragraph 1, Line 2	**Replace:** The SAE will be reported by completing and submitting the SAE report form through the EDC system. In the event that the EDC system is not available, paper SAE report forms may be used to report the SAE to Amgen Global Patient Safety.	**With:** The SAE will be reported by completing and submitting the SAE report form through the EDC system. In the event that the EDC system is not available, paper SAE report forms may be used to report the SAE to Amgen Global Patient Safety **(Appendix L).**	Administrative addtion
Section: 12.5 PREGNANCY AND LACTATION EXPOSURE REPORTING, Paragraph 1, Line 4	**Replace:** The pregnancy will be reported on a Pregnancy Notification Worksheet.	**With:** The pregnancy will be reported on a Pregnancy Notification Worksheet **(Appendix M)**.	Administrative addition
Section: 12.5 PREGNANCY AND LACTATION EXPOSURE REPORTING, Paragraph 6, Line 6	**Replace:** The investigator will complete a Lactation Notification Worksheet.	**With:** The investigator will complete a Lactation Notification Worksheet **(Appendix N)**.	Administrative addition

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 13.1.1 PRIMARY ENDPOINTS	**Replace:** The primary endpoint is ORR, which is defined as the proportion of subjects who achieved a confirmed PR, VGPR, CR, or sCR according to the IMWG URC.	**With:** The primary endpoint is **PFS**, which is defined as **the time in months from randomization to the earlier of disease progression or death due to any cause**.	Primary/secondary endpoint switch
Section: 13.1.2 SECONDARY ENDPOINTS, Bullet 1	**Replace:** • PFS, defined as the time in months from randomization to the earlier of disease progression or death due to any cause.	**With:** • **ORR**, defined as the **proportion of subjects who achieved a confirmed PR, VGPR, CR, or sCR, according to the IMWG-URC**.	Primary/secondary endpoint switch

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 13.3.2.1 Primary Efficacy Endpoint, Paragraphs 1-2	**Replace:** The primary efficacy endpoint is ORR. The data cutoff date for the analysis of ORR is about 4 months after the last subject is randomized (approximately 19 month after the first subject was randomized). The inferential comparison of ORR between treatment groups will be made using a logistic regression model-based test against the null hypothesis that the odds ratio is ≤ 1 at a 1-sided significance level of 0.025. The regression model will include the randomization stratification factors as covariates: • ISS stage at study entry (Stage 1 versus Stage 2 and 3) • Refractory to bortezomib treatment (Yes versus No) • Age (< 65 versus ≥ 65 years) The ORR will be calculated by treatment group and the associated 95% CI will be estimated using the Clopper Pearson method. The odds ratio (and its 95% CI) will be estimated using the logistic regression model.	**With:** **The primary efficacy endpoint is PFS. Progression-free survival will be calculated from the time of randomization until disease progression or death due to any cause, whichever occurs first. If a subject is alive or lost to follow-up without experiencing documented disease progression by the data cutoff date, the PFS data for the subject will be censored at the date of last valid disease and response assessment. Detailed PFS data censoring rules will be described in the SAP.** **The distribution of PFS, including median, will be estimated using the Kaplan-Meier method. Progression-free survival rates at selected time points will be reported by treatment group. The 95% CI for the median and other percentiles of PFS will be constructed using the method of Klein and Moeschberger (1997) with log-log transformation. The 95% CIs for PFS rates were estimated using the method by Kalbfleisch and Prentice (1980) with log-log transformation. The inferential comparison between treatment groups will be made using the log-rank test stratified by the randomization stratification factors specified in Section 7. The hazard ratio (HR) and its 95% CI will be estimated using a Cox proportional hazards model stratified by the same randomization stratification factors. Duration of follow up for PFS will be estimated using the reverse Kaplan-Meier method (Schemper 1996; Smith 2006).**	Statistical revision to align with primary objective/endpoint change

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 13.3.2.1 Primary Efficacy Endpoint, Paragraph 3	**Replace:** Response and disease progression will be determined using a validated computer algorithm (Onyx Response Computational Assessment; [ORCA]) as well as by local investigators. The primary analysis of ORR will be based on the ORCA-assessed responses. Investigator-assessed responses will be analyzed as a supportive analysis of ORR, as will IRC-assessed responses, if an Independent Review Committee (IRC) is convened.	**With:** Response and disease progression will be determined using a validated computer algorithm (Onyx Response Computational Assessment; [ORCA])**,** as well as by local investigators **and by an Independent Review Committee (IRC)**. **The primary analysis of PFS will be based on ORCA-assessed outcomes. The PFS outcomes assessed by the investigator will serve as a supportive analysis of PFS, as will IRC-assessed outcomes.** **The final PFS analysis will be conducted when approximately 350 PFS events have occurred or by end of year 2018, whichever is earlier. A total of 350 PFS events will provide 83% power to detect a significant difference in PFS between the 2 treatment groups with 1 interim analysis** CCI [redacted] **The interim analysis will be performed when approximately 75% of the total PFS events (i.e., 263 events) have occurred. See also Section 13.8 for the interim analysis plan for PFS.**	Statistical revision to align with primary objective/endpoint change

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 13.3.2.1 Primary Efficacy Endpoint, Paragraph 4	**Delete:** ~~The duration of response (DOR), defined as time in months from the start date of the response to the earlier date of documented PD or death, will be calculated for subjects who achieve sCR, CR, VGPR, or PR. The DOR will be censored at date of the last valid assessment for responders who have not experienced PD or death. The distribution of DOR, including the median will be estimated using the Kaplan-Meier method based on the subjects who achieve overall response.~~		Statistical revision to align with primary objective/endpoint change

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 13.3.2.2.1 Progression-Free Survival	**Replace:** Progression-Free Survival The distribution of PFS, including median, will be estimated using the Kaplan-Meier method. Progression-free survival rates at selected time points will be reported by treatment group. The 95% CI for the median and other percentiles of PFS will be constructed using the method of Klein and Moeschberger (1997) with log-log transformation. The 95% CIs for PFS rates were estimated using the method by Kalbfleisch and Prentice (1980) with log-log transformation. The inferential comparison between treatment groups will be made using the log-rank test stratified by the randomization stratification factors specified in Section 7. The HR and its 95% CI will be estimated using a Cox proportional hazards model stratified by the same randomization stratification factors. Duration of follow-up for PFS will be estimated using the reverse Kaplan-Meier method (Schemper 1996; Smith 2006). The primary analysis of PFS will be based on ORCA-assessed outcomes. The PFS outcomes assessed by the investigator serve as a supportive analysis of PFS, as will IRC-assessed outcomes, if an IRC is convened.	**With:** **Overall Response Rate** **The ORR will be analyzed at the time of the PFS analysis (interim or final), only if the PFS analysis crosses the boundary. The inferential comparison of ORR between treatment groups will be made using a logistic regression model-based test against the null hypothesis that the odds ratio is ≤ 1 at a 1-sided significance level of 0.025. The regression model will include the randomization stratification factors as covariates. The ORR will be calculated by treatment group and the associated 95% CI will be estimated using the Clopper-Pearson method. The odds ratio (and its 95% CI) will be estimated using the logistic regression model.** **The primary analysis of ORR will be based on the ORCA-assessed responses. Investigator assessed responses will be analyzed as a supportive analysis of ORR, as will IRC-assessed responses.**	Statistical revision to align with primary and secondary objective/endpoint switch

Section: 13.3.2.2.1 Progression-Free Survival (cont'd.)	If a subject is alive or lost to follow up without experiencing documented disease progression by the data cutoff date, the PFS data for the subject will be censored at the date of last valid disease and response assessment. Detailed PFS data censoring rules will be described in the SAP. A total of 350 PFS events will be needed for the final PFS analysis in order to have 83% power to detect a significant difference in PFS between the two treatment groups, CCI [redacted] Under the assumptions that the accrual will take about 15 months and the median PFS is 6 months in the twice-weekly dosing group and 8.2 months in the once-weekly dosing group, 350 PFS events are expected to occur approximately 25 months after the first subject is randomized. See also Section 13.8 for the interim analysis plan for PFS.	**The duration of response (DOR), defined as time in months from the start date of the response to the earlier date of documented disease progression or death, will be calculated for subjects who achieve sCR, CR, VGPR, or PR. The DOR will be censored at date of the last valid assessment for responders who have not experienced disease progression or death. The distribution of DOR, including the median, will be estimated using the Kaplan-Meier method on the basis of subjects who achieve overall response.**	

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 13.3.2.2.2 Overall Survival, Paragraph 3	**Replace:** Final analysis of OS will occur at the time of final PFS analysis. Under the assumptions that the accrual will take about 15 months and the median OS is 14 months in the twice weekly dosing group and 17 months in the once-weekly dosing group (HR = 0.82), it is estimated that approximately 245 deaths will be observed at the time of the final PFS analysis (approximately 25 months after the first subject randomized). An interim analysis of OS will occur at the time of ORR analysis. The details of OS interim analysis are in Section 13.8.	**Add:** **The** analysis of OS will **be conducted at the time of the PFS analysis (interim or final), only if both PFS and ORR analyses are positive, per hierarchical testing procedures. There will be no interim analysis for OS. Additional follow-up for OS may be performed.**	Statistical revision to align with primary objective/endpoint change and addition of language to allow for possible long-term follow-up for OS.
Section: 13.3.2.3 Control of Family-wise Type I Error Rate	**Replace:** The hypotheses for the primary efficacy endpoint, ORR, and secondary efficacy endpoints (PFS and OS) will be tested using a fixed sequence hierarchical testing procedure to control the family-wise Type I Error rate below 1-sided 0.025 level. The family of hypotheses is ordered as follows: 1) ORR, 2) PFS, and 3) OS. Starting with the hypothesis of ORR, if any hypothesis in the sequence is rejected at a 1-sided significance level of 0.025, then the subsequent hypothesis will be tested; if any hypothesis is accepted, then the subsequent hypotheses will not be tested.	**Add:** The **null** hypotheses for the primary efficacy endpoint, **PFS**, and secondary efficacy endpoints (**ORR** and OS) will be tested using a fixed sequence hierarchical testing procedure to control the family-wise Type I Error rate below 1-sided 0.025 level. The family of hypotheses is ordered as follows: 1) **PFS**, 2) **ORR**, and 3) OS. Starting with the hypothesis of **PFS**, if any hypothesis in the sequence is rejected at a 1-sided significance level of 0.025, then the subsequent hypothesis will be tested; if any hypothesis is accepted, then the subsequent hypotheses will not be tested.	Statistical revision to align with primary and secondary objective/endpoint switch

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 13.5 DETERMINATION OF SAMPLE SIZE	**Replace:** CCI [redacted]	**With:** CCI [redacted] **the sample size of 460 subjects (230 in each arm) was calculated** CCI [redacted] **a total of 350 PFS events for the final PFS analysis will provide 83% power to detect a significant difference in PFS between the 2 treatment groups with 1-sided overall Type-I error of 0.025 when 1 interim analysis is performed at approximately 75% information time (i.e., 263 events) using the O'Brien-Fleming type alpha spending function,** CCI [redacted]	Statistical revision to align with primary and secondary objective/endpoint switch

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 13.6 INDEPENDENT REVIEW COMMITTEE	**Replace:** An IRC may be convened for this study, if required to support the ORCA-determined results.	**With:** An IRC **will** be convened for this study to support the ORCA-determined results. **The IRC will centrally review the disease-related tests and assessments (Section 10.2) to evaluate disease progression and responses without knowledge of the randomization assignments. The details of the IRC, including the roles and responsibilities of the involved parties, will be described in the IRC Charter.**	Clarification
Section: 13.7 DATA MONITORING COMMITTEE, Paragraph 4	**Replace:** The DMC will meet to review safety data on a periodic basis, including after approximately 40 subjects have completed ≥ 1 cycle and no less frequently than approximately every 6 months thereafter. Unplanned safety review meetings of the DMC may be called at any time**,** if warranted, for an earlier review of safety data.	**With:** The DMC will meet to review safety data on a periodic basis, including after approximately 40 subjects have completed ≥ 1 cycle and no less frequently than approximately every 6 months thereafter. Unplanned safety review meetings of the DMC may be called at any time, if warranted, for an earlier review of safety data. **The DMC will also review the interim PFS analysis results and recommend whether the study should stop early for efficacy.**	Revision to align with primary objective/endpoint change

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 13.8 INTERIM ANALYSIS, Paragraphs 2-3	**Replace:** One interim analysis will be conducted for PFS and OS at the time of the analysis of ORR, which is expected to occur approximately 19 months after the first subject is randomized. It is estimated that approximately 262 (75% of total 350) PFS events and 171 OS events will be observed at the interim analysis. The primary objective of the interim analysis of PFS and OS is to provide necessary data to help assess the results from the analysis of the primary endpoint ORR, and it is intended that all subjects will continue to be followed for disease assessment and survival status until 350 PFS events are observed, given a positive result of the ORR analysis. To ensure proper control of type I error rate, the interim and final analysis of PFS and OS will be analyzed under a group sequential design framework with the stopping boundaries constructed using the alpha-spending function approach. Based on the objective of the interim analysis and the considerations above, a 1-sided error level of 0.0001 is assigned to the interim analysis and the remaining 1-side error level of 0.0249 is reserved for the final analysis. The stopping boundaries are calculated using East 5.4 and presented in Table 12.	**With:** One interim analysis will be conducted for PFS **when** approximately 26**3** (75% of total 350) PFS events **are** observed. The objective of the interim analysis is to **monitor for differences between treatment arms for evidence of a substantial benefit in the carfilzomib once-weekly with dexamethasone arm.** To ensure proper control of type I error rate, the interim and final analysis of PFS will be analyzed under a group sequential design framework with the stopping boundaries constructed using the **O'Brien-Fleming type** alpha-spending function approach. The stopping boundaries **in an example scenario** are calculated using East **6**.4 and presented in Table 12. **Actual boundaries will be calculated on the basis of observed PFS events up to the data cut-off date for the interim analysis. If the DMC recommends to stop the study for efficacy after reviewing the interim analysis results, the sponsor will consider stopping the trial and conclude that the carfilzomib once-weekly with dexamethasone arm prolongs PFS compared to the carfilzomib twice-weekly with dexamethasone arm.**	Clarification and statistical revision to align with primary objective/endpoint change

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 13.8 INTERIM ANALYSIS, Table 12	**Replace:** Original Table 12 below	**With:** Revised Table 12 below	Statistical revision to align with primary and secondary objective/endpoint switch

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Section	Text in Protocol	Amended Text	Rationale for Change
Section: 16 REFERENCES, Reference 19	**Move order to after Reference 20**		Minor edit
Section: APPENDIX L SUMMARY OF CHANGES FOR AMENDMENT 3	**Delete Appendix L**		Administrative
Section: after APPENDIX K COUNTRY-SPECIFIC PREGNANCY AND CONTRACEPTIVE SUPPLEMENT		**Add:** **APPENDIX L SAMPLE SERIOUS ADVERSE EVENT REPORT FORM** (shown below)	Addition of Sample Serious Adverse Event Report Form

APPENDIX L SAMPLE SERIOUS ADVERSE EVENT REPORT FORM

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to IP)**

1. **Site Information**

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. **Subject Information**

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the serious adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

   Serious Adverse Event Diagnosis or Syndrome* –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria)rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

   Is event serious?* – Indicate Yes or No. This is a mandatory field.

   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   Relationship to IP – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

   Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

   If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**

   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

FORM-056006 *Instructions Page 1 of 2* *Version 7.0 Effective Date: 1 February 2016*

Completion Instructions - Electronic Adverse Event Contingency Report Form
(for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

5. **IP Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.
6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. **Case Description**
    Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

FORM-056006 *Instructions Page 2 of 2* *Version 7.0 Effective Date: 1 February 2016*

AMGEN Study # 20140355 Kyprolis	**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?								Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
						IP1 No	IP1 Yes	IP2 No	IP2 Yes	IP3 No	IP3 Yes	IP4 No	IP4 Yes		
				☐ Yes ☐ No											
				☐ Yes ☐ No											
				☐ Yes ☐ No											

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

IP:		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 #
<<IP>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

FORM-056006 *Version 7.0* *Effective Date: 1 February 2016*

Page 1 of 3

AMGEN Study # 20140355 Kyprolis	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

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

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

Date (Day Month Year) / Test / Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20140355 Kyprolis	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

FORM-056006

Page 3 of 3

Version 7.0 Effective Date: 1 February 2016

Section	Text in Protocol	Amended Text	Rationale for Change
Section: after APPENDIX K COUNTRY-SPECIFIC PREGNANCY AND CONTRACEPTIVE SUPPLEMENT		**Add:** **APPENDIX M PREGNANCY NOTIFICATION FORM** (shown below)	Addition of Pregnancy Notification Form

APPENDIX M PREGANCY NOTIFICATION FORM

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: 20140355

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

Section	Text in Protocol	Amended Text	Rationale for Change
Section: after APPENDIX K COUNTRY-SPECIFIC PREGNANCY AND CONTRACEPTIVE SUPPLEMENT		**Add:** **APPENDIX N LACTATION NOTIFICATION FORM** (shown below)	Addition of Lactation Notification Form

APPENDIX N LACTATION NOTIFICATION FORM

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: 20140355

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

Section	Text in Protocol	Amended Text	Rationale for Change
Section: after APPENDIX K COUNTRY-SPECIFIC PREGNANCY AND CONTRACEPTIVE SUPPLEMENT		**Add:** **APPENDIX O SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 4 AND SUPSERSEDING PROTOCOL AMENDMENT 4**	Addition of Summary of Changes for Protocol Amendment 4 and Superseding Protocol Amendment 4

APPENDIX O SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 4

Protocol Title: A Randomized, Open-label, Phase 3 Study in Subjects with Relapsed and Refractory Multiple Myeloma Receiving Carfilzomib in Combination with Dexamethasone, Comparing Once-weekly versus Twice-weekly Carfilzomib Dosing

Amgen Protocol Number 20140355 (formerly CFZ014)

Amendment Date: 08 February 2017

Rationale:

The protocol is amended to:

- Switch progression-free survival (PFS) from a key secondary objective/endpoint to the primary objective/endpoint and overall response rate (ORR) from the primary objective/endpoint to a key secondary objective/endpoint

  Rationale: This study was originally designed with ORR as the primary endpoint because response rates, especially high-quality responses of substantial duration, are important indicators of benefit in relapsed and refractory multiple myeloma. However, recent advances in antimyeloma therapy have altered the landscape such that PFS is now considered to be the more relevant regulatory endpoint in this setting. To support regulatory interactions and protect the integrity of the PFS data, the primary endpoint has been amended to PFS, with ORR as a key secondary endpoint.

- Change the purpose and timing of the interim PFS analysis

  Rationale: The purpose and timing of the interim PFS analysis were amended to monitor efficacy and allow the possibility of stopping the trial early for efficacy.

- Revise statistical language to align with changes in objectives/endpoints and purpose and timing of the interim PFS analysis
- Update Table 12 (Stopping Boundaries for Progression-free Survival)
- Allow the possibility for long-term follow-up for overall survival
- Add Section 4.4.1 (End of Study)
- Add Section 8.4 (Product Complaints)
- Update Table 5 (Carfilzomib Dose Modifications for Nonhematologic Toxicity)
- Add Section 9.4.2.5 (Thromboprophylaxis)
- Add the following forms in the Appendices

- Sample Serious Adverse Event Report Form
- Pregnancy Notification Form
- Lactation Notification Form

- Update Section 2 (Background Information)
- Make minor text clarifications, additions, corrections, and edits throughout the protocol

SUMMARY OF CHANGES

Deletions of text are presented in strikethrough format. Added text is presented in bold format.

Section	**Text in Protocol**	**Amended Text**	**Rationale for Change**
Section: Global	**Replace:** CFZ014	**With:** **20140355 (Formerly CFZ014)**	Administrative change
Section: Title Page, Sponsor	**Replace:** Onyx Therapeutics, Inc. 249 East Grand Avenue South San Francisco, CA 94080	**With:** Onyx Therapeutics, Inc., **an Amgen Inc. subsidiary** **One Amgen Center Drive** **Thousand Oaks,** CA **91320 USA**	Updated Sponsor contact information
Section: Title Page, Study Medical Monitor	**Replace:** PPD , MD 249 East Grand Avenue South San Francisco, CA 94080 PPD	**With:** PPD , MD, **MS** **One Amgen Center Drive, M/S 27-4-A** **Thousand Oaks, CA 91320 USA** PPD	Updated study medical monitor information
Section: Title Page, Clinical Study Protocol Approval Signature Page		**Add:** **Date of Protocol Amendment 3.0**	Administrative change
Section: Confidentiality Statement	**Replace:** Onyx Therapeutics, Inc., a wholly owned subsidiary of Onyx Pharmaceuticals, Inc.	**With:** Onyx Therapeutics, Inc., a wholly owned subsidiary of Onyx Pharmaceuticals, Inc., **an Amgen Inc. subsidiary**	Administrative change
Clinical Study Protocol Approval Signature Page	**Replace:** Onyx Therapeutics, Inc. 249 East Grand Avenue South San Francisco, CA 94080	**With:** **Amgen Inc.** **One Amgen Center Drive** **Thousand Oaks, CA 91320, USA** **Phone: + 1 805 447-1000**	Updated Sponsor contact information

Section	Text in Protocol	Amended Text	Rationale for Change
Section: Protocol Acceptance Page	**Replace:** Protocol Amendment 2.0	**With:** Protocol Amendment **3**.0	Administrative change
Section: Protocol Acceptance Page	**Replace:** 28 April 2015	**With:** **22 April 2016**	Administrative change
Section: Synopsis, Study Objectives, primary objective	**Replace:** To compare the overall response rate (ORR) between once-weekly carfilzomib dosing in combination with dexamethasone to twice-weekly carfilzomib dosing in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma who have received prior treatment with bortezomib and an IMiD (immunomodulatory agent).	**With:** To compare the overall response rate (ORR) **of** once-weekly carfilzomib dosing in combination with dexamethasone to **the ORR of** twice-weekly carfilzomib dosing in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma who have received prior treatment with **a proteasome inhibitor** and an IMiD (immunomodulatory agent).	Revised text for consistency within overall protocol
Section: Synopsis, Study Design, paragraph 1, sentence 1	**Replace:** This is an open-label, multicenter, randomized Phase 3 study comparing carfilzomib dosing in combination with dexamethasone administered once-weekly to twice-weekly carfilzomib dosing in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma, previously treated with bortezomib and an (IMiD).	**With:** This is an open-label, multicenter, randomized Phase 3 study comparing carfilzomib dosing in combination with dexamethasone administered once-weekly to twice-weekly carfilzomib dosing in subjects with relapsed and refractory multiple myeloma, previously treated with **a proteasome inhibitor** and an (IMiD).	Revised text for consistency within overall protocol
Section: Synopsis, Study Design, paragraph 2, bullet 1	**Replace:** • The International Staging	**With:** • The International Staging System (ISS)	Revised text for clarification

Section	Text in Protocol	Amended Text	Rationale for Change
	System (ISS) at study entry (Stage 1 versus Stage 2 or 3)	at study entry (Stage 1 versus Stage 2 or 3) **per International Myeloma Working Group (Greipp 2005). See Appendix H**	
Section: Synopsis, Study Design, paragraph 6, sentences 1 and 2	**Replace:** Subjects will be assessed for response using central laboratory results on Day 1 of each cycle.	**With:** Subjects will be assessed for response using central laboratory results **every 28 days (± 4 days)**.	Updated text for disease assessment timepoints to align with other sections in protocol
Section: Synopsis, Study Design, paragraph 6, sentence 3	**Replace:** For subjects who discontinue treatment before disease progression occurred (such as for an adverse event, noncompliance, etc.), disease response assessments will be performed using central laboratory response every 4 weeks until disease progression.	**With:** For subjects who discontinue treatment before disease progression occurred (such as for an adverse event, noncompliance, etc.), disease response assessments will be performed using central laboratory response every **28 days** until disease progression.	Updated text for disease assessment timepoints to align with other sections in protocol
Section: Synopsis, Study Design, paragraph 6, sentences 1 and 2	**Replace:** Follow-up for survival will continue approximately every 3 months, or as needed, for all surviving subjects until study closure.	**With:** Follow-up for survival will continue approximately every **12 weeks ±28 days**, or as needed, for all surviving subjects until study closure.	Updated text for disease assessment timepoints to align with other sections in protocol
Section: Synopsis, Number of investigational sites, 4.2 Number of Centers	**Replace:** Approximately 120 sites worldwide	**With:** Approximately 1**5**0 sites worldwide	Updated number of sites to include potential New Zealand and Australian sites
Section: Synopsis, Treatment Regimen, paragraph 1, sentence 2	**Replace:** Carfilzomib and dexamethasone will be administered in 28-day cycles in 1 of 2 treatment	**With:** Carfilzomib and dexamethasone will be administered in 28-day cycles in 1 of 2 treatment regimens. All cycles will start	Revised text for consistency within overall protocol

Section	Text in Protocol	Amended Text	Rationale for Change
	regimens. All cycles will start 28 days (± 2) after the start of the prior cycle.	28 days (± 2 **days**) after the start of the prior cycle.	
Section: Synopsis, Subject Selection, sentence 1, 5. Subject Selection, sentence 1	**Replace:** Approximately 460 subjects will be enrolled in this study.	**With:** Approximately 460 subjects will be **randomized** in this study.	Administrative change
Section: Synopsis, Inclusion and Exclusion Criteria, 5.1 Inclusion Criteria, 5.2 Exclusion Criteria	**Replace:** Criteria Numbers 1 ,2 ,3……	**With:** **Criteria Numbers 101, 102, 103…….**	Administrative change
Section: Synopsis, Inclusion Criteria, criterion 104 a, 5.1 Inclusion Criteria, criterion 104 a	**Replace:** a. Nonresponsive to most recent therapy (stable disease ~~only or~~ progressive disease [PD] while on treatment), or	**With:** a. Nonresponsive to most recent therapy (stable disease or progressive disease [PD] while on treatment), or	Administrative change
Section: Synopsis, Inclusion Criteria, criterion 105, 5.1 Inclusion Criteria, criterion 105	**Replace:** 105. At least 2 but no more than 3 prior therapies for multiple myeloma	**With:** 105. At least 2**,** but no more than 3**,** prior **lines of** therapy for multiple myeloma	Revised text for clarification
Section: Synopsis, Inclusion Criteria, criterion 108, 5.1 Inclusion Criteria, criterion 108	**Replace:** 108. Documented response of at least partial response (PR) to 1 line of prior therapy	**With:** 108. Documented response of at least partial response (PR) to **at least** 1 prior line of therapy	Revised text for clarification
Section: Synopsis, Inclusion Criteria, criterion 109, 5.1 Inclusion Criteria, criterion 109	**Replace:** 109. Measureable disease with at least 1 of the following assessed within 21 days prior to randomization:	**With:** 109. Measurable disease**,** with at least 1 of the following assessed **at a central laboratory** within the 21 days prior to randomization:	Revised text for consistency within overall protocol
Section: Synopsis, Inclusion Criteria, criterion 109 c, 5.1 Inclusion Criteria,	**Replace:** c. In subjects without detectable	**With:** c. In subjects without **measurable** serum or	Revised text for clarification

Section	Text in Protocol	Amended Text	Rationale for Change
criterion 109 c	serum or urine M-protein, serum free light chain (SFLC) ≥ 100 mg/L (involved light chain) and an abnormal serum kappa lambda ratio	urine M-protein, serum free light chain (SFLC) ≥ 100 mg/L (involved light chain) and an abnormal serum kappa lambda ratio	
Section: Synopsis, Inclusion Criteria, criterion 112, 5.1 Inclusion Criteria, criterion 112	**Replace:** 112. Adequate organ and bone marrow function within the 21 days prior to randomization defined by:	**With:** 112. Adequate organ and bone marrow function **performed at a central laboratory** within the 21 days prior to randomization defined by:	Revised text for consistency within overall protocol
Section: Synopsis, Inclusion Criteria, criterion 112 c, 5.1 Inclusion Criteria, criterion 112 c	**Replace:** c. Absolute neutrophil count (ANC) ≥ 1000/mm^3 (screening ANC should be independent of growth factor support for ≥ 1 week)	**With:** c. Absolute neutrophil count (ANC) ≥ 1 × **10^9/L** (screening ANC **must** be independent of growth factor support for ≥ **7 days**)	Revised text for consistency within overall protocol
Section: Synopsis, Inclusion Criteria, criterion 112 d, 5.1 Inclusion Criteria, criterion 112 d	**Replace:** d. Hemoglobin ≥ 8.0 g/dL (Use of erythropoietic stimulating factors and red blood cell [RBC] transfusion per institutional guidelines is allowed, however the most recent RBC transfusion may not have been done within 7 days prior to obtaining screening hemoglobin.)	**With:** d. Hemoglobin ≥ 8 g/dL (Use of erythropoietic stimulating factors and red blood cell [RBC] transfusion**s** per institutional guidelines **are** allowed, however the most recent RBC transfusion may not have been done within 7 days prior to obtaining **the** screening hemoglobin.)	Administrative change
Section: Synopsis, Inclusion Criteria, criterion 112 e, 5.1 Inclusion Criteria, criterion 112 e	**Replace:** e. Platelet count ≥ 50,000/mm^3 (≥ 30,000/mm^3 if myeloma involvement in the bone marrow is > 50%. Subjects should not have	**With:** e. Platelet count ≥ 50,000/mm^3 (≥ 30,000/mm^3 if myeloma involvement in the bone marrow is > 50%. Subjects **must** not have received platelet transfusions for at	Revised text for consistency within overall protocol

Section	Text in Protocol	Amended Text	Rationale for Change
	received platelet transfusions for at least 1 week prior to obtaining the screening platelet count.)	least **7 days** prior to obtaining the screening platelet count.)	
Section: Synopsis, Inclusion Criteria, criterion 112 f, 5.1 Inclusion Criteria, criterion 112 f	**Replace:** f. Calculated or measured creatinine clearance (CrCl) of ≥ 30 mL/min. Calculation should be based on the Cockcroft and Gault formula: [(140 – Age) × Mass (kg) / (72 × Creatinine mg/dL)]; multiply result by 0.85 if female	**With:** f. Calculated or measured creatinine clearance (CrCl) of ≥ 30 mL/min. Calculation **must** be based on the Cockcroft and Gault formula: [(140 – Age) × Mass (kg) / (72 × Creatinine mg/dL)]; multiply result by 0.85 if female	Revised text for clarification
Synopsis: Synopsis, Inclusion Criteria, criterion 113, 5.1 Inclusion Criteria, criterion 113	**Replace:** 113. Females of childbearing potential (FCBP) must have a confirmed negative serum pregnancy test within the 21 days prior to randomization (performed at a central laboratory)	**With:** **1**13. Females of childbearing potential (FCBP) must have a confirmed negative serum pregnancy test performed at a central laboratory, within the 21 days prior to randomization, **and must not be breastfeeding**.	Revised text for consistency within overall protocol
Synopsis: Synopsis, Inclusion Criteria, criterion 114, 5.1 Inclusion Criteria, criterion 114	**Replace:** 14. Females of childbearing potential and male subjects who are sexually active with FCBP must agree to use effective concomitant method(s) of contraception during the study and for 30 days following the last study drug treatment administration.	**With:** **1**14. Females of childbearing potential must agree to use **highly** effective concomitant method(s) of contraception during the study and for 30 days following the last study drug treatment administration. **(Refer to Appendix K for specific contraception requirements.)**	Revised to distinguish female and male contraceptive guidance
Synopsis: Synopsis, Inclusion Criteria, criterion 115, 5.1 Inclusion Criteria,		**Add:** **115. Male subjects who are sexually active**	Updated text to align with current carfilzomib core safety language

Section	Text in Protocol	Amended Text	Rationale for Change
criterion 115		**with a FCBP must agree to use condoms (unless they have had a vasectomy with medical confirmation of surgical success), during treatment and for an additional 90 days following the last study drug administration.**	
Synopsis: Synopsis, Inclusion Criteria, criterion 116, 5.1 Inclusion Criteria, criterion 116		**Add:** **116. Male subjects must agree to not donate sperm during treatment and for an additional 90 days following the last study drug administration.**	Updated text to align with current carfilzomib core safety language
Synopsis: Synopsis, Exclusion Criteria, criterion 208, 5.2 Exclusion Criteria, criterion 208	**Replace:** 08. Cytotoxic chemotherapy within the 28 days prior to randomization	**With:** **2**08. Cytotoxic chemotherapy **or other antineoplastic therapy, aside from immunotherapy or proteasome inhibitors**, within the 28 days prior to randomization	Revised text for clarification
Synopsis: Synopsis, Exclusion Criteria, criterion 209, 5.2 Exclusion Criteria, criterion 209	**Replace:** 09. Immunotherapy within the 21 days prior to randomization	**With:** **2**09. Immunotherapy, **such as an IMiD or a proteasome inhibitor** within the 21 days prior to randomization	Revised text for clarification
Synopsis: Synopsis, Exclusion Criteria, criterion 210, 5.2 Exclusion Criteria, criterion 210	**Replace:** 10. Glucocorticoid therapy within the 14 days prior to randomization that exceeds a cumulative dose of 160 mg dexamethasone or 1000 mg prednisone	**With:** **2**10. Glucocorticoid therapy exceed**ing** a cumulative dose of 160 mg dexamethasone or **equivalent**, within the 14 days prior to randomization	Revised text for clarification
Synopsis: Synopsis, Exclusion Criteria, criterion 214, 5.2 Exclusion Criteria, criterion 214	**Replace:** 14. Contraindication to dexamethasone or any of the required concomitant drugs or	**With:** **2**14. Contraindication to dexamethasone or any of the required concomitant **medications** or supportive treatments	Revised text for clarification

Section	Text in Protocol	Amended Text	Rationale for Change
	supportive treatments, including hypersensitivity to antiviral drugs, or intolerance to hydration due to pre-existing pulmonary or cardiac impairment		
Synopsis: Synopsis, Exclusion Criteria, criterion 215, 5.2 Exclusion Criteria, criterion 215	**Replace:** Active congestive heart failure (New York Heart Association [NYHA] Class III or IV, refer to Appendix F), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, acute diffuse infiltrative pulmonary disease, pericardial disease, or myocardial infarction within 6 months prior to enrollment	**With:** Active congestive heart failure (New York Heart Association [NYHA] Class III or IV, refer to Appendix F), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, acute diffuse infiltrative pulmonary disease, pericardial disease, or myocardial infarction within 6 months prior to **randomization**	Revised text for clarification
Synopsis: Synopsis, Exclusion Criteria, criterion 216, 5.2 Exclusion Criteria, criterion 216	**Replace:** 16. Active infection within the 14 days prior to randomization requiring systemic antibiotics	**With:** 216. Active infection requiring systemic **treatment** within the 14 days prior to randomization	Revised text for clarification
Synopsis: Synopsis, Exclusion Criteria, criterion 220, 5.2 Exclusion Criteria, criterion 220	**Replace:** 20. Uncontrolled hypertension or uncontrolled diabetes despite medication	**With:** 220. Uncontrolled hypertension or diabetes **mellitus**	Revised text for clarification
Synopsis: Synopsis, Exclusion Criteria, criterion 223, 5.2 Exclusion Criteria, criterion 223	**Replace:** 23. Known human immunodeficiency virus (HIV) seropositivity, hepatitis C infection, or hepatitis B infection (subjects with past hepatitis B	**With:** 223. Known human immunodeficiency virus (HIV) seropositivity, hepatitis C infection, or hepatitis B infection. Subjects with past hepatitis B virus infection, defined as having a negative HBsAg test and a positive	Administrative change

Section	Text in Protocol	Amended Text	Rationale for Change
	virus (HBV) infection or resolved HBV infection defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti HBc] antibody test are eligible; subjects positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.)	antibody to hepatitis B core antigen (anti HBc) antibody test, are eligible. Subjects positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.	
Synopsis: Synopsis, Exclusion Criteria, criterion 226, 5.2 Exclusion Criteria, criterion 226		**Delete:** ~~226. Female subjects who are pregnant or lactating~~	Removed text to avoid duplication with the inclusion criteria
Section: Synopsis, Efficacy Variable, paragraph 3	**Replace:** Disease assessments according to the International Myeloma Working Group-Uniform Response Criteria (IMWG-URC) will be conducted at baseline and then at Cycle 2 Day 1 (C2D1) and on Day 1 of every cycle thereafter until progression.	**With:** Disease assessments according to the International Myeloma Working Group-Uniform Response Criteria (IMWG-URC) will be conducted at baseline and then **every 28 days (± 4 days)** thereafter until progression.	Updated text for disease assessment timepoints to align with other sections in protocol
Section: Synopsis, Intensive PK and PDn Substudy	**Replace:** Intensive pharmacokinetic (PK) and pharmacodynamic (PDn) samples will be obtained as a substudy (approximately n = 15 in each arm) from subjects who consent to the additional testing at selected sites. Pharmacokinetic samples will be collected on Day 15 of Cycle 1 and PDn	**With:** Intensive pharmacokinetic (PK) and pharmacodynamic (PDn) samples will be obtained as a substudy (approximately n = 15 **evaluable subjects** in each arm) from subjects who consent to the additional testing at selected sites. Pharmacokinetic samples will be collected on Day 15 of Cycle 1 and PDn samples will be collected	Revised text for consistency within overall protocol

Section	Text in Protocol	Amended Text	Rationale for Change
	samples will be collected on Days 1, 15, 16, 17, and 22 of Cycle 1.	on Days 1, 15, 16, 17, and 22 of Cycle 1.	
Section: Synopsis, Health related Quality of Life (HRQL), paragraph2, sentence 1	**Replace:** All questionnaires should be administered prior to study treatment on Day 1 of Cycle 1, then every other cycle during treatment and every 12 weeks (every 84 days ± 4 days) until progression, or withdrawal of consent during LTFU.	**With:** **QLQ-C30, QLQ-MY20 and EQ-5D-5L** questionnaires should be administered prior to study treatment on Day 1 of Cycle 1, then every **second** cycle **(Cycle 1, 3, 5, etc)** during treatment and every 12 weeks (every 84 days ± 4 days) until progression, or withdrawal of consent during LTFU.	Revised text for clarification
Section: Synopsis, Health related Quality of Life (HRQL), paragraph 2, sentence 2		**Add:** **Patient convenience and satisfaction questionnaire will be collected at Cycle 2 and EOT only.**	Revised text for consistency within overall protocol
Section: Synopsis, Health related Quality of Life (HRQL), paragraph 2, sentence 3	**Replace:** Healthcare resource utilization data related to AEs will be collected for all subjects during the study.	**With:** Healthcare resource utilization will be collected for all subjects during the study.	Updated text for collection of healthcare resource utilization as collection will not just be for AE related healthcare resource utilization
Section: Synopsis, Health related Quality of Life (HRQL), paragraph 2, sentence 4		**Add:** **Details on hospitalizations (not related to adverse events) will also be collected.**	Added text for collection of hospitalizations not related to AEs to align to with later section
Section: Synopsis, Safety variables, sentence 3	**Replace:** All subjects will be monitored for adverse events for 30 days after the past administration of study treatment.	**With:** All subjects will be monitored for adverse events for **at least** 30 days after the past administration of study treatment.	Revised text for consistency within overall protocol

Section	Text in Protocol	Amended Text	Rationale for Change
Section: Synopsis, Statistical methods and analyses, paragraph 4, bullet 2	**Replace:** • Refractory to proteasome inhibitor ([PI] bortezomib) treatment (Yes versus No)	**With:** • Refractory to bortezomib) treatment (Yes versus No)	Revised text for consistency within overall protocol
Section: Synopsis, Statistical methods and analyses, paragraph 6, sentence 3	**Replace:** Investigator-assessed responses will be analyzed as part of a supportive ORR analysis	**With:** Investigator-assessed responses will be analyzed as part of a supportive ORR analysis**, as will IRC-assessed responses, if an Independent Review Committee (IRC) is convened**.	Added text regarding potential use of an IRC.
Section: 1 List of abbreviations and definitions of terms		**Delete:** ~~CRO contract research organization~~	Administrative change
Section: 1 List of abbreviations and definitions of terms		**Add:** **FISH fluorescence in situ hybridization**	Administrative change
Section: 1 List of abbreviations and definitions of terms		**Add:** **IPIM Investigational Product Instruction Manual**	Administrative change
Section: 1 List of abbreviations and definitions of terms	**Replace:** IWRS Interactive Web Response System	**With:** **IVR/**IWR Interactive **Voice (IVR) and** Web Response **(IWR)**	Administrative change
Section: 2.1 Introduction, paragraph 2	**Replace:** Per the approved label, carfilzomib is administered intravenously (IV) over 2 to 10 minutes, on 2 consecutive days each week for 3 weeks (Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle). The recommended Cycle 1 dose is	**With:** Per the **2012** approved label, carfilzomib is administered intravenously (IV) over 10 minutes, on 2 consecutive days each week for 3 weeks (Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle). The recommended Cycle 1 dose is 20 mg/m^2/day with an increase to 27 mg/m^2 on Cycle 2 Day 1	Updated text to reflect new IB version

Section	Text in Protocol	Amended Text	Rationale for Change
	20 mg/m^2/day with an increase to 27 mg/m^2 on Cycle 2 Day 1 onwards (Carfilzomib Investigator's Brochure [IB] Version 15, 26 February 2015).	onwards (Carfilzomib Investigator's Brochure [IB]).	
Section: 2.3.1 Carfilzomib Background (Nonclinical), paragraph 1, sentence 1	**Replace:** Carfilzomib (formerly known as PR-171) is a tetrapeptide epoxyketone-based inhibitor of the ~~of the~~ 20S proteasome, primarily of the CT-L activity, and at higher concentrations, of multiple 20S proteolytic activities.	**With:** Carfilzomib (formerly known as PR-171) is a tetrapeptide epoxyketone-based inhibitor 0S proteasome, primarily of the CT-L activity, and at higher concentrations, of multiple 20S proteolytic activities.	Updated text to reflect new IB version
Section: 2.3.1 Carfilzomib Background (Nonclinical), paragraph 1, sentences 2 and 3		**Add:** **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 C40H57N5O7 and the molecular weight is 719.91.**	Updated text to reflect new IB version
Section: 2.3.1 Carfilzomib Background (Nonclinical), paragraph 1, sentences 4	**Replace:** This selectivity may be responsible for the reductions in myelosuppression and neuropathy observed in nonclinical studies comparing carfilzomib with bortezomib.	**With:** This selectivity may be responsible for the reductions in myelosuppression and neuropathy observed in **clinical and** nonclinical studies comparing carfilzomib with bortezomib.	Updated text to reflect new IB version

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 2.3.2 Carfilzomib Background (Clinical), paragraph 1	**Replace:** As of 12 January 2015, approximately 2949 **i**ndividual subjects have been treated with carfilzomib as participants in Onyx-sponsored clinical studies. Approximately 1975 subjects have been treated with carfilzomib through the 69 completed or actively enrolling investigator-sponsored trials (ISTs) (Carfilzomib IB). There are five Phase 3 studies in multiple myeloma: PX-171-009 (ASPIRE), PX-171-011 (FOCUS), 2011-003 (ENDEAVOR), 2012-005 (CLARION), and this study, CFZ014 (A.R.R.O.W.). In addition, 137 subjects with solid tumors have been treated with carfilzomib in completed Onyx-sponsored clinical studies.	**With:** As of **10 July** 2015, approximately 29**21** individual subjects have been treated with carfilzomib as participants in Onyx-sponsored clinical studies **and 89 subjects have been enrolled in studies in Japan sponsored by Ono Pharmaceutical Company**. Approximately **3549** subjects have been treated with carfilzomib through the **76** completed or actively enrolling investigator-sponsored trials (ISTs) (Carfilzomib IB). There are five Phase 3 studies in multiple myeloma: PX-171-009 (ASPIRE), PX-171-011 (FOCUS), 2011-003 (ENDEAVOR), 2012-005 (CLARION), and this study, CFZ014 (A.R.R.O.W.). Addition**ally**, 137 subjects with solid tumors have been treated with carfilzomib in completed Onyx-sponsored clinical studies.	Updated date to reflect most recent statistics on study drug.
Section: 2.3.2 Carfilzomib Background (Clinical), paragraph 5, sentence 5	**Replace:** The Phase 2 PX-171-003 – Part 2 (A1) study with single agent carfilzomib at 20/27 mg/m^2 in a similar population, which is the basis for the current label, had an ORR of 23.7%.	**With:** The Phase 2 PX-171-003 – Part 2 (A1) study with single agent carfilzomib at 20/27 mg/m^2 in a similar population had an ORR of **22.9% in the Safety population**.	Updated text to reflect new IB version
Section: 2.4 Study Rationale, paragraph 1, sentence 3	**Replace:** Preliminary results from the ongoing Phase 2 portion of this	**With:** Preliminary results from the ongoing Phase 2 portion of this multicenter, single-	Administrative change

Section	Text in Protocol	Amended Text	Rationale for Change
	multicenter, single-arm study suggested that the dose and regimen of 70 mg/m^2 once-weekly appears to be well tolerated, highly active and could offer a more convenient treatment regimen for subjects as discussed in Section 2.5.	arm study suggested that the dose and regimen of 70 mg/m^2 once-weekly appear**ed** to be well tolerated, highly active**,** and **able to** offer a more convenient treatment regimen for subjects as discussed in Section 2.5.	
Section: 2.4 Study Rationale, paragraph 2	**Replace:** The rationale for this study is to compare carfilzomib dosing in combination with dexamethasone administered once-weekly, infused over 30 minutes based on the CHAMPION 1 results to twice-weekly carfilzomib dosing in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma, previously treated with bortezomib and an IMiD. The hypothesis is that this regimen will have superior efficacy with an acceptable safety profile and a more convenient dosing regimen when compared with the US approved dose and schedule.	**With:** The rationale for this study is to compare carfilzomib **administered once weekly** in combination with dexamethasone**,** based on the CHAMPION 1 results**,** to twice-weekly carfilzomib in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma, previously treated with bortezomib and an IMiD. The hypothesis is that this regimen will have superior efficacy with an acceptable safety profile and a more convenient dosing regimen when compared with the US approved dose and schedule **of carfilzomib administered at 20/27 mg/m^2 twice weekly**.	Revised text for consistency within overall protocol
Section: 2.5 Dose Rationale, paragraph 1	**Replace:** Carfilzomib 20/27 mg/m^2 twice-weekly is the approved monotherapy dose and 20/70 mg/m^2 once-weekly is	**With:** Carfilzomib 20/27 mg/m^2 twice-weekly is **an** approved monotherapy dose and 20/70 mg/m^2 once-weekly is the MTD that was determined in the CHAMPION 1	Administrative change

Section	Text in Protocol	Amended Text	Rationale for Change
	the MTD that was determined in the CHAMPION 1 study described in Section 2.5.1.	study described in Section 2.5.1.	
Section: 2.5 Dose Rationale, paragraph 3	**Replace:** Carfilzomib study treatment administration will use a step-up approach in which the first dose level for all subjects will be 20 mg/m^2 (Cycle 1 Day 1 for the once-weekly regimen and Cycle 1 Days 1 and 2 for the twice-weekly regimen) and increased to 70 mg/m^2 or 27 mg/m^2 respectively, beginning on Day 8 of Cycle 1.	**With:** Carfilzomib study treatment administration will use a step-up approach in which the first dose level for all subjects will be 20 mg/m^2 (Cycle 1 Day 1 for the once-weekly regimen and Cycle 1 Days 1 and 2 for the twice-weekly regimen) and **the dose level will then** increase to 70 mg/m^2 or 27 mg/m^2 respectively, beginning on Day 8 of Cycle 1.	Administrative change
Section: 2.5.1 Rationale for Once-weekly Dosing, paragraph 1, sentence 1	**Replace:** CHAMPION 1, a Phase 1b/2 study in subjects with relapsed multiple myeloma who had received 1 to 3 prior therapies was initiated to investigate higher doses of carfilzomib given once-weekly in combination with dexamethasone, and results indicate that these modifications were well tolerated and active.	**With:** CHAMPION 1, a Phase 1b/2 study in subjects with relapsed multiple myeloma who had received 1 to 3 prior therapies was initiated to investigate higher doses of carfilzomib given once-weekly in combination with dexamethasone, and **preliminary** results indicate**d** that these modifications were well tolerated and active.	Updated text to reflect new IB version statistics
Section: 2.5.1 Rationale for Once-weekly Dosing, paragraphs 8, 9, and 10	**Replace:** As of 07 January 2015, 104 subjects (Phase 1 n = 15, Phase 2 n = 89) have received at least 1 dose of carfilzomib at the MTD. The majority of subjects	**With:** As of 0**1 May** 2015, 104 subjects (Phase 1 n = 15, Phase 2 n = 89) have received at least 1 dose of carfilzomib at the MTD. The majority of subjects (82%) had received prior bortezomib. A total of 48% of subjects	Updated text to reflect new IB version statistics

Section	Text in Protocol	Amended Text	Rationale for Change
	(82%) had received prior bortezomib. A total of 48% of subjects were bortezomib-refractory, 28% were lenalidomide-refractory, and 16% were refractory to both. The ORR to date was 72% (95% CI: 63% to 81%) with a CBR of 80% (95% CI: 71% to 87%). Median PFS was 10.6 months (95% CI: 7.2 to not estimable). Preliminary median carfilzomib treatment duration in the ongoing study is 5.3 months (range: 0.03 to 18.8) (Berenson 2015). All 104 subjects experienced at least 1 AE. The most common AEs (≥ 15% of subjects) were fatigue (48%), nausea (32%), insomnia (30%), anemia, headache, diarrhea (each 24%), dyspnea (23%), upper respiratory tract infection (22%), cough (21%), pyrexia (19%), thrombocytopenia (18%), constipation (16%), back pain, peripheral edema, and dizziness (each 15%). A total of 57 subjects (55%) experienced at least 1 Grade 3 or higher AE. The most common (≥ 5% of subjects) Grade 3 or higher AEs were fatigue (9%), thrombocytopenia, dyspnea, back pain (each 6%), anemia, and	were bortezomib-refractory, 28% were lenalidomide-refractory, and 16% were refractory to both. The ORR to date was 7**7**% (95% CI: 6**8**% to 8**5**%) with a CBR of 8**4**% (95% CI: 7**5**% to **90**%). Median PFS was 10.6 months (95% CI: **9.0** to **16.1**). Preliminary median carfilzomib treatment duration in the ongoing study is **8**.3 months (range: **> 1** to **20**) **for the Phase 1 portion of the study and 7.2 months**. (range: 0.03 **to 22.6) for the Phase 2 portion of the study** (Berenson 2015). All 104 subjects experienced at least 1 AE. The most common AEs (≥ 15% of subjects) were fatigue (**52**%), nausea (3**5**%), headache, diarrhea (**each 31**%), insomnia, upper respiratory tract infection (**each 30%**), cough (2**6**%), dyspnea (2**5**%), anemia (24%), thrombocytopenia, pyrexia (**each 22**%), peripheral edema (**20**%), and back pain (1**7**%). A total of **64** subjects (**62**%) experienced at least 1 Grade 3 or higher AE. The most common (≥ 5% of subjects) Grade 3 or higher AEs were fatigue (**11**%), **pneumonia (7%)**, thrombocytopenia, **hypertension**, acute renal failure (each 6%), dyspnea, anemia, back pain, **asthenia**, and **chronic obstructive pulmonary disease** (each 5%) (Carfilzomib IB). The preliminary results from CHAMPION 1 demonstrated that once-weekly carfilzomib at 70 mg/m^2 administered as a 30-minute infusion in combination with dexamethasone	

Section	Text in Protocol	Amended Text	Rationale for Change
	acute renal failure (each 5%) (Carfilzomib IB). The preliminary results from CHAMPION 1 demonstrated that once-weekly carfilzomib at 70 mg/m^2 administered as a 30-minute infusion in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma had an acceptable safety and tolerability profile and promising efficacy. Ninety subjects are planned for the Phase 2 portion of the study.	in subjects with relapsed and refractory multiple myeloma had an acceptable safety and tolerability profile and promising efficacy. **Eighty-nine** subjects **were enrolled into** the Phase 2 portion of the study.	
Section: 2.5.2 Pharmacokinetics and Pharmacodynamics Data for Once-weekly Dosing, paragraph 2, sentence 4	**Replace:** The mean C_{max} following the 70 mg/m^2 dose administered as a 30-minute infusion is 2640 ng/mL, which is lower than the mean C_{max} of 4232 ng/mL in Study PX-71-003 – Part 2 (A1) following the IV infusion of 27 mg/m^2 over 2 to 10 minutes (Carfilzomib IB).	**With:** The mean C_{max} following the 70 mg/m^2 dose administered as a 30-minute infusion is 2640 ng/mL, which is lower than the mean C_{max} of 4232 ng/mL in Study PX-**1**71-003- Part 2 (A1)**,** following the IV infusion of 27 mg/m^2 over 2 to 10 minutes (Carfilzomib IB).	Administrative change
Section: 2.5.2 Pharmacokinetics and Pharmacodynamics Data for Once-weekly Dosing, paragraph 3, sentence 2	**Replace:** No statistically significant relationships between C_{max} and efficacy and safety endpoints were found.	**With:** No statistically significant relationships between C_{max} and efficacy **or** safety endpoints were found.	Administrative change
Section: 3.1 Primary Objective	**Replace:** The primary objective of this	**With:** The primary objective of this study is to	Revised text for consistency within overall protocol

Section	Text in Protocol	Amended Text	Rationale for Change
	study is to compare the ORR between once-weekly carfilzomib dosing in combination with dexamethasone to twice-weekly carfilzomib dosing in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma who have received prior treatment with bortezomib and an IMiD.	compare the ORR **of** once-weekly carfilzomib dosing in combination with dexamethasone to **the ORR of** twice-weekly carfilzomib dosing in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma who have received prior treatment with **a proteasome inhibitor** and an IMiD.	
Section: 4.1 Study Design, paragraph 2, sentence 2	**Replace:** Subjects must have had 2 or 3 prior therapies for multiple myeloma and received treatment with bortezomib and an IMiD.	**With:** Subjects must have had 2 or 3 prior therapies for multiple myeloma and received treatment with **a proteasome inhibitor** and an IMiD.	Revised text for consistency within overall protocol
Section: 4.1 Study Design, paragraph 3, bullet 1	**Replace:** • International Staging System (ISS) Stage at study entry (Stage 1 versus Stage 2 or 3)	**With:** • International Staging System (ISS) Stage at study entry (Stage 1 versus Stage 2 or 3) **per International Myeloma Working Group (Greipp 2005). See Appendix H**	Revised text for clarification
Section: 4.1 Study Design, paragraph 5, sentence 1	**Replace:** Disease assessments will be conducted at Screening (within 21 days before dosing on Cycle 1 Day 1) and then on Day 1 of every cycle beginning with Cycle 2 and each cycle thereafter, End of Treatment (EOT) and during LTFU every 4 weeks (every 28 days ± 4 days), until PD and/or	**With:** Disease assessments will be conducted at Screening (within 21 days before **randomization**) and then every 28 days ± 4 days **after** Cycle 1 Day 1, End of Treatment (EOT) and during LTFU every 28 days ± 4 days, until PD and/or administration of subsequent antimyeloma therapy.	Updated text for disease assessment timepoints to align with other sections in protocol

Section	Text in Protocol	Amended Text	Rationale for Change
	administration of subsequent antimyeloma therapy.		
Section: 4.2 Number of Centers	**Replace:** Approximately 120 sites worldwide will participate.	**With:** Approximately 1**5**0 sites worldwide will participate.	Updated number of sites to include potential New Zealand and Australian sites
Section: 5 Subject Eligibility	**Replace:** 5 Subject Selection Approximately 460 subjects will be enrolled in this study. Subjects will be evaluated for study eligibility within the 21 days prior to randomization.	**With:** 5 Subject **Eligibility**	Removed text to avoid duplication in protocol
Section: 6 Subject Screening, paragraph 1, sentence 2	**Replace:** Evaluations obtained as part of routine medical care that do not require central lab testing and are performed during the Screening period may be used as the study-specific protocol required evaluations.	**With:** Evaluations obtained as part of routine medical care **prior to signing of the ICF may be used to satisfy the screening requirements, provided that these evaluations were obtained within the required screening period and do not require analysis at a central laboratory.**	Revised text for clarification
Section: 6 Subject Screening, paragraph 3	**Replace:** The Screening period for a particular subject commences at the point at which the subject signs the ICF, and must be completed within the 21 days prior to randomization.	**With:** The Screening period commences **when** the subject **or a legally-authorized representative** signs the ICF. **Screening** must be completed within the 21 days prior to randomization.	Revised text for clarification
Section: 7 Subject Randomization, title	**Replace:** Subject Enrollment And	**With:** Subject Randomization	Administrative change

Section	Text in Protocol	Amended Text	Rationale for Change
	Randomization		
Section: 7 Subject Randomization, paragraph 1	**Replace:** Eligibility information for each subject must be provided to the study medical monitor or designee and reviewed and approved prior to randomization (refer to separate study reference manual). The Randomization will be carried out centrally through an Interactive Web Response System (IWRS).	**With:** **The primary investigator will determine the subject's eligibility, ensuring that the results of the required screening procedures are consistent with all of the eligibility criteria presented in Section 5. No eligibility waivers will be permitted.** Randomization will be carried out centrally through an interactive **voice and** web response (**IVR/IWR) system. Please refer to the separate study reference manual.**	Updated text to align with the administrative processes followed by Amgen
Section: 7 Subject Randomization, paragraph 5	**Replace:** After Screening, eligibility determination, and randomization, study treatment will ideally commence on the day of randomization but at least within 5 calendar days of randomization according to treatment group assignment. Initiation of study treatment (Cycle 1 Day 1) delay > 5 days after randomization must be approved by the study medical monitor.	**With:** Study treatment will ideally commence on the day of randomization**,** but at least within 5 calendar days of randomization. Initiation of study treatment (Cycle 1 Day 1) > 5 **calendar** days after randomization must be approved by the study medical monitor.	Clarified the timing of initiation of study treatment
Section: 8 Study Drugs, title	**Replace:** Study Treatment	**With:** Study **Drugs**	Revised text for consistency within overall protocol
Section: 8.1.1 Physical Description		**Delete:** ~~8.1.1 Physical Description~~ ~~Carfilzomib is a synthetic small molecule~~	Removed section to avoid duplication of IPIM

Section	Text in Protocol	Amended Text	Rationale for Change
		~~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 C40H57N5O7 and the molecular weight is 719.91. It specifically functions as an inhibitor of the CT L activity of the 20S proteasome which leads to the accumulation of protein substrates within the cell and induction of apoptosis.~~	
Section: 8.1.2 Formulation		**Delete:** ~~8.1.2 Formulation~~ ~~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 C mM sodium citrate buffer (pH C) containing C % (w/v) sulfobutylether beta cyclodextrin (SBE CD, Captisol).~~	Removed section to avoid duplication of IPIM
Section: 8.1.1 (newly renumbered) Packaging and Labeling, sentence 3	**Replace:** Additional details are provided in the pharmacy manual.	**With:** Additional details are provided in the **Investigational Product Instruction Manual (IPIM)**.	Revised text to correct name of IPIM
Section: 8.1.2 (newly renumbered) Storage, paragraph 1, sentence 3		**Delete:** ~~Carfilzomib vials must be kept in cartons in order to protect from light until ready for reconstitution.~~	Removed sentence to avoid duplication of IPIM
Section: 8.1.2 (newly renumbered)		**Delete:**	Removed paragraph to avoid

Section	Text in Protocol	Amended Text	Rationale for Change
Storage, paragraph 2		~~Once carfilzomib is reconstituted and inspected, the clear solution may 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 must be used within 4 hours if not refrigerated and within 24 hours if it has been stored in a light-tight refrigerator (refer to Table 3).~~	duplication of IPIM
Section: 8.1.2 (newly renumbered) Storage, Table 3 Stability of Reconstituted Carfilzomib for Injection (60 mg/vial)		**Delete:** **Table 3**	Removed table to avoid duplication of IPIM
Section: 8.1.2 (newly renumbered) Storage, paragraph 2		**Add:** **Please refer to the IPIM for further storage information.**	Added cross reference to IPIM to avoid text duplication
Section: 8.2 Dexamethasone, paragraph 1, sentence 2	**Replace:** Onyx (and/or designee) may provide dexamethasone, if the investigational site is unable to obtain adequate supply.	**With:** **Sponsor** (and/or designee) may provide dexamethasone, if the investigational site is unable to obtain adequate supply.	Administrative change
Section: 8.3 Study Drug Accountability	**Replace:** Onyx (or designee), and the investigator must maintain records of each shipment of investigational product (IP). Upon receipt of IP, the designated recipient at the investigational site will inspect the shipment, verify the number and condition of the vials, and prepare an inventory or	**With:** **Please refer to the IPIM for details on study drug accountability.**	Added cross reference to IPIM to avoid text duplication

Section	Text in Protocol	Amended Text	Rationale for Change
	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. Responsibility for drug accountability at the study site rests with the investigator; however, the investigator may assign drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be readily available for inspection by the study monitor and are open to inspection at any time by the sponsor/representative and any applicable regulatory authorities. The investigator must ensure that the IPs are used in accordance with the protocol. The investigator will also maintain records adequately documenting that the subjects were provided the treatment specified and reconciling all IPs. Remaining supplies will be retained by the pharmacy at the end of the study, and any unused medication will be discarded or		

Section	Text in Protocol	Amended Text	Rationale for Change
	destroyed according to institutional Standard Operating Procedures (SOPs). Documentation of destruction of unused study medication will be maintained by the site. For each subject, the site pharmacy personnel will be required to record and document proper per protocol dispensing of carfilzomib and dexamethasone. Additional details are provided in the pharmacy manual.		
Section: 9.1 Treatment Regimen, paragraph 1	**Replace:** Carfilzomib and dexamethasone will be administered in 28-day cycles. All cycles will start 28 days (± 2) after the start of the prior cycle.	**With:** Carfilzomib and dexamethasone will be administered in 28-day cycles. All cycles will start 28 days (± 2 **days**) after the start of the prior cycle.	Revised text for consistency within overall protocol
Section: 9.1 Treatment Regimen, paragraph 2, sentences 1 and 2	**Replace:** Once-weekly carfilzomib must never be administered within the 5 days following a previous carfilzomib infusion.	**With:** **In the** once-weekly carfilzomib **arm, intra-cycle doses of carfilzomib and dexamethasone may be administered within ± 2 days of the scheduled dose. However, carfilzomib** must **not** be administered within the 5 days following a previous carfilzomib infusion. **Dose delays > 2 days are only permitted during the start of a new cycle.**	Revised text for clarification.
Section: 9.1 Treatment Regimen, paragraph 3	**Replace:** In the twice-weekly carfilzomib	**With:** In the twice-weekly carfilzomib arm, every	Revised text for clarification

Section	Text in Protocol	Amended Text	Rationale for Change
	arm, every effort should be made to maintain the Days 1, 2, 8, 9, 15, and 16, every 28-day schedule. If this is not possible due to extenuating circumstances, then priority should be to maintain consecutive dosing days. For example, if Day 1 of a new cycle is started 2 days later than originally scheduled, the entire cycle should shift by 2 days, such that the new Days 1, 2, 8, 9, 15, and 16 of the next cycle schedule is maintained. If a mid-cycle dose is missed, that dosing day should be skipped and not made up. Dose delays > 2 days are only permitted during the start of a new cycle.	effort should be made to maintain the Days 1, 2, 8, 9, 15, and 16, every 28-day schedule. If this is not possible, then priority should be to maintain consecutive dosing days. For example, if Day 1 of a new cycle is started 2 days later than originally scheduled, the entire cycle should shift by 2 days, such that the new Days 1, 2, 8, 9, 15, and 16 of the next cycle **are** maintained. **Dosing on nonconsecutive days should only occur under exceptional circumstances, such as interruptions due to national holidays. There must always be at least 5 days between the second dose of one week and the first dose of the following week (i.e., between Days 2 and 8, and Days 9 and 15). Mid-cycle doses that are missed should not be made up, unless these parameters are maintained.**	
Section: 9.1 Treatment Regimen, paragraph 4	**Replace:** The reason for all cycle delays, missed doses, and dose interruptions will be reported.	**With:** The reason**s** for all cycle delays, **schedule changes,** missed doses, and dose interruptions will be reported.	Revised text for clarification
Section: 9.2 Intravenous Hydration	**Replace:** 9.2 Intravenous Hydration Subjects will receive IV prehydration prior to each carfilzomib infusion during Cycle 1. Prehydration will consist of 250 to 500 mL normal saline or other appropriate IV fluid. Thereafter, carfilzomib	**With:** 9.2 Intravenous **Pre**hydration Subjects will receive IV prehydration prior to each carfilzomib infusion during Cycle 1. Prehydration will consist of 250 to 500 mL normal saline or other appropriate IV fluid. Thereafter, carfilzomib prehydration should only be administered if the subject's condition and/or risk factors require **it**. The	Revised text for clarification

Section	Text in Protocol	Amended Text	Rationale for Change
	prehydration should only be administered if the subject's condition and/or risk factors require hydration. The total amount of prehydration will be reported and the reason for hydration after Cycle 1 will be reported.	total **volume** of prehydration and the reason for **pre**hydration after Cycle 1 will be **recorded**.	
Section: 9.2.1 Study Treatment Administration, Figure 3, footnote c	**Replace:** [C] Dexamethasone on Day 22 in both treatment arms will be administered only during Cycles 1 to 9 and should be given PO; dexamethasone will not be administered on Day 22 after Cycle 9.	**With:** [C] Dexamethasone on Day 22 in both treatment arms will be administered only during Cycles 1 to 9 and should be given PO**, whenever possible**	Revised text for clarification
Section: 9.2.1.1 Carfilzomib, paragraph 2, sentence 2	**Replace:** 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.	**With:** 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.	Revised text for clarifcation
Section: 9.2.1.1 Carfilzomib, paragraph 2, sentences 3, 4 and 5		**Delete:** ~~The dose can be calculated using the subject's actual body surface area (BSA) at Baseline; however, dosing adjustments for subsequent actual BSA determinations are 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~~	Revised text for clarification

Section	Text in Protocol	Amended Text	Rationale for Change
		~~gains/losses of ≥ 20% of baseline body weight.~~	
Section: 9.2.1.1 Carfilzomib, paragraph 3, sentences 4 and 5	**Replace:** Carfilzomib should be administered via a dedicated IV line. If an existing IV line or permanent infusion device (e.g., porta-cath) is used for carfilzomib administration, the line must be flushed with a minimum of 20 mL of 5% Dextrose Injection (D5W), prior to and following carfilzomib infusion.	**With:** Carfilzomib should be administered via a dedicated IV line**, whenever possible. Refer to the IPIM for detailed information regarding equipment and flush requirements**.	Added cross reference to IPIM to avoid text duplication
Section: 9.2.1.2 Dexamethasone, sentence 2	**Replace:** Dexamethasone will be administered at least 30 minutes (but no more than 4 hours) prior to carfilzomib infusion on Days 1, 8, and 15 in both arms.	**With:** Dexamethasone will be administered at least 30 minutes (but no more than 4 hours) prior to carfilzomib infusion on Days 1, 8, and 15 in both **treatment** arms.	Revised text for clarification
Section: 9.2.1.2 Dexamethasone, sentence 3	**Replace:** Dexamethasone on Day 22 should be taken PO.	**With:** Dexamethasone on Day 22 should be taken PO**, whenever possible**.	Revised text for clarification
Section: 9.2.1.2 Dexamethasone, sentence 4	**Replace:** Note: Dexamethasone on Day 22 in both treatment arms will only be administered during Cycles 1 to 9; dexamethasone will not be administered on Day 22 after Cycle 9.	**With:** Note: Dexamethasone on Day 22 in both treatment arms will only be administered during Cycles 1 to 9.	Revised text for clarification
Section: 9.3 Dose Modification Rules	**Replace:**	**With:**	Clarified procedures for dose

Section	Text in Protocol	Amended Text	Rationale for Change
	9.3 Dose Modification Guidelines In the event of a possible study treatment-related AE, the clinical investigator should assess to the best of his/her ability its relationship to carfilzomib and/or dexamethasone. Dose reduction guidelines for carfilzomib include guidelines where the dose of carfilzomib is decreased based on the observed toxicity. • If a subject requires an interruption of carfilzomib of more than 4 weeks, the subject should be removed from study treatment. Exceptions to this must be discussed with the study medical monitor. • If the carfilzomib dose is reduced, the reduced dose level will be continued for at least 1 complete cycle. If the reduced dose level is well tolerated for at least one complete cycle, the dose level prior to the reduction may be resumed at the investigator's discretion. If carfilzomib is permanently stopped due to toxicity per below dose modification guidelines (Table 5 and Table 6), dexamethasone dosing should also be stopped and the subject	9.3 Dose Modification **Rules** In the event of a possible study treatment-related AE, the clinical investigator should assess, to the best of his/her ability, its relationship to carfilzomib and/or dexamethasone. Dose reduction **rules** for carfilzomib **are presented in Tables 4 and 5 and are often event-specific**. • If a subject requires interruption of carfilzomib **for** more than **28 day**s, the subject should be removed from study treatment. Exceptions must **first** be **approved by** the study medical monitor. • If **a subject requires** carfilzomib dose reduc**tion**, the reduced dose level will be continued for at least 1 complete cycle. **After that,** if the reduced dose level **ha**s **been** well tolerated, the **previous** dose level may be resumed at the investigator's discretion. • **If carfilzomib is temporarily held due to an AE, dexamethasone should be continued, unless the investigator determines that criteria for interrupting dexamethasone have also been met.** • If carfilzomib is permanently **discontinued** due to toxicity, dexamethasone **must** also be **discontinued** and the subject **will be followed for disease progression per the guidelines in Section 10.10.1**.	interruption for a carfilzomib AE.

Section	Text in Protocol	Amended Text	Rationale for Change
	followed for disease progression per protocol-specified disease response criteria prior to initiating new antimyeloma therapies. • If dexamethasone is permanently withdrawn due to toxicity, the subject may continue to receive carfilzomib at the clinical investigator's discretion and must follow protocol required procedures and assessments.	• If dexamethasone is permanently **discontinued** due to toxicity, the subject may continue to receive **study treatment with** carfilzomib at the investigator's discretion.	
Section: 9.3.1 Carfilzomib: Rules for Dose Modification, heading	**Replace:** 9.3.1 Carfilzomib: Guidelines for Dose Modification	**With:** 9.3.1 Carfilzomib: **Rules** for Dose Modification	Administrative change
Section: 9.3.1 Carfilzomib: Rules for Dose Modification, paragraph 1	**Replace:** Dose reduction levels of carfilzomib for toxicity management of individual subjects are provided in Table 4.	**With:** Dose **decrements for** carfilzomib are provided in Table **3**.	Revised text for clarification
Section: 9.3.1 Carfilzomib: Rules for Toxicities and Dose Modification, Table 3, footnote 1		**Add:** **Added footnote to dose column.** **[a] Note: If dose reduction of carfilzomib is required on C1D1 (Arm A) or C1D1 or D2 (Arm B), the investigator should contact the medical monitor to discuss the situation, before any additional doses of carfilzomib are administered.**	Revised text for clarification
Section: 9.3.1 Carfilzomib: Guidelines for Toxicities and Dose Modification,	**Replace:** Treatment guidelines for specific	**With:** **The requirements for carfilzomib dose**	Revised text for clarification

Section	Text in Protocol	Amended Text	Rationale for Change
paragraph 2	hematologic toxicities are outlined in Section 9.3.1.1 and nonhematologic toxicities in Section 9.3.1.2.	**modification** for specific hematologic **and nonhematologic** toxicities are outlined in Section**s** 9.3.1.1 and 9.3.1.2**, respectively**.	
Section: 9.3.1.1 Hematologic Toxicity, paragraph 1	**Replace:** Guidelines for dose modification in the event of thrombocytopenia and neutropenia are summarized in Table 5.	**With:** **Requirements** for dose modification **of carfilzomib** in the event**s** of thrombocytopenia, neutropenia**, or neutropenic fever** are summarized in Table **4**.	Revised text for clarification
Section: 9.3.1.1 Hematologic Toxicity, Table 4, title	**Replace:** Carfilzomib Dosing Guidelines for Treatment-emergent Hematologic Toxicity	**With:** Carfilzomib Dose **Modification Rules** for Treatment-emergent Hematologic Toxicity	Revised text for clarification
Section: 9.3.1.1 Hematologic Toxicity, Table 4	**Replace:** Original Table 5 below	**With:** Revised Table 4 below	Revised for clarity and for consistency with current carfilzomib safety guidance

Original Table 5:

Hematologic Toxicity	Recommended Action[a]	
Thrombocytopenia		
When platelets fall to $\leq 30 \times 10^9$/L	If platelets 10–30 $\times 10^9$/L without evidence of bleeding	Continue at same dose.
	If evidence of bleeding or platelets $< 10 \times 10^9$/L	Withhold dose until platelets return to $\geq 10 \times 10^9$/L and/or bleeding is controlled, then resume at same dose.
For each subsequent drop to $\leq 30 \times 10^9$/L	If platelets 10–30 $\times 10^9$/L without evidence of bleeding	Continue at same dose.
	If evidence of bleeding or platelets $< 10 \times 10^9$/L	Withhold dose until platelets return to $\geq 10 \times 10^9$/L and/or bleeding is controlled, then resume at 1 dose decrement.
Neutropenia		
When ANC falls to $\leq 0.75 \times 10^9$/L	If ANC 0.5–0.75 $\times 10^9$/L	Continue at same dose.
	If ANC $< 0.5 \times 10^9$/L	Withhold dose until ANC returns to $\geq 0.5 \times 10^9$/L, then resume at same dose.
For each subsequent drop to $\leq 0.75 \times 10^9$/L	If ANC 0.5–0.75 $\times 10^9$/L	Continue at same dose.
	If ANC $< 0.5 \times 10^9$/L	Withhold dose until ANC returns to $\geq 0.5 \times 10^9$/L, then resume at 1 dose decrement.
Neutropenic fever	1) If $< 1000/mm^3$ and single temperature > 38.3°C *OR* 2) temperature > 38.0°C for more than 1 hour	Withhold dose until ANC returns to baseline grade, then resume at same dose.

ANC = absolute neutrophil count; NA = not applicable.

[a] The maximum allowed dose interruption is 4 weeks.

Revised Table 4:

Hematologic Toxicity	**Required** Action	
Thrombocytopenia		
• **Platelets ≤10 × 10^9/L, OR** • **Platelets ≤30 × 10^9/L with evidence of bleeding/bruising**	**1st episode**	• Withhold doses. • **Resume at the same dose level when** platelets ≥ 10 × 10^9/L and bleeding is controlled.
	Subsequent episodes	• **Withhold doses.** • **Resume at 1 dose decrement when platelets ≥ 10 × 10^9/L and bleeding is controlled.**
Neutropenia		•
• **ANC < 0.5 × 10^9/L**	**1st episode**	• Withhold doses. • **Resume at the same dose level when** ANC ≥ 0.5 × 10^9/L
	Subsequent episodes	• **Withhold doses.** • **Resume at 1 dose decrement when ANC ≥ 0.5 × 10^9/L**
Febrile neutropenia		
• **ANC < 0.5 x 10^9/L and oral temperature either:** o **> 38.5°C, OR** o **> 38.0°C on 2 consecutive measurements over 2 hours**	**1st and subsequent episodes**	• Withhold doses. • **Resume at the same dose level when** ANC returns to baseline grade and fever resolves.

ANC = absolute neutrophil count; NA = not applicable.

9.3.1.2 Nonhematologic Toxicity, paragraph 1	**Replace:** Guidelines for dose modification in the event of nonhematologic toxicities are summarized in Table 6.	**With:** **Requirements** for dose modification **of carfilzomib** in the event of nonhematologic toxicities are summarized in Table 5.	Revised text for clarification
9.3.1.2 Nonhematologic Toxicity, Table 5, Title	**Replace:** Carfilzomib Dosing Guidelines for Nonhematologic Toxicity	**With:** Carfilzomib Dose **Modifications** for Nonhematologic Toxicity	Revised text for clarification
Section: 9.3.1.2 Nonhematologic Toxicity, Table 5	**Replace:** Original Table 6 below	**With:** Revised Table 5 below	Revised text for clarification

Original Table 6:

Nonhematologic Toxicity	Recommended Action[a]
Renal Dysfunction	
Serum creatinine equal to or greater than 2 × Baseline, or CrCl < 15 mL/min (or CrCl decreases to ≤ 50% of baseline), or need for dialysis	Withhold dose and continue monitoring renal function (serum creatinine or creatinine clearance). If attributable to carfilzomib, resume when renal function has recovered to within 25% of Baseline; start at 1 dose level reduction. If not attributable to carfilzomib, dosing may be resumed at the discretion of the physician. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician. For patients on dialysis receiving carfilzomib, the dose is to be administered after the dialysis procedure.
≥ Grade 3 Elevation in LFTs (AST, ALT, or total bilirubin)[b]	Withhold dose. Resume at 1 dose decrement when toxicity has resolved to Baseline.[c]
Grade 3 Infection	• Withhold carfilzomib until infection resolves. Resume carfilzomib at same dose.
Congestive heart failure	• 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.
LVEF Reductions	
For resting LVEF < 40% or reduction of LVEF to < 55% if the drop is greater than 20% from Baseline	Withhold until LVEF returns to > 40% or, if held due to a drop to < 55%, to within 15% of Baseline. Resume at 1 dose decrement.[c]
Micro-Angiopathy	

Nonhematologic Toxicity	Recommended Action[a]
Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS)	If suspected TTP/HUS, withhold carfilzomib. Manage symptoms per standard of care including plasma exchange as clinically indicated. If the diagnosis of TTP/HUS is excluded, carfilzomib administration may resume if clinically appropriate.
Any Other Drug-Related Non-Hematologic Toxicity ≥ Grade 3	For carfilzomib attribution, withhold dose. Resume at 1 dose decrement when toxicity has resolved to Grade 2 or less or to Baseline grade. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician. Additional dose modification guidance for adverse drug reactions are per the Carfilzomib IB.
Pulmonary Hypertension	Withhold until resolved or returned to baseline. Restart at the dose used prior to the event or reduce dose by 1 dose level (i.e., 27 mg/m^2 to 20 mg/m^2 for the twice weekly schedule or 70 mg/m^2 to 56 mg/m^2 for the once weekly schedule), at the discretion of the physician. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.
Posterior reversible encephalopathy syndrome (PRES; with symptoms including headaches, altered mental status, seizures, visual loss, and hypertension)	If suspected PRES, withhold carfilzomib. Consider evaluation with neuroradiological imaging for onset of visual or neurological symptoms suggestive of PRES. If the diagnosis of PRES is excluded, carfilzomib administration may resume if clinically appropriate.

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CrCl = creatinine clearance; eCRF = electronic Case Report Form; IB = Investigator's Brochure;
LFTs = liver function tests; LVEF = left ventricular ejection fraction; mL = milliliter(s); ULN = upper limit of normal.
Note: Carfilzomib dose schedule does not need to be adjusted for baseline renal dysfunction.

[a] The maximum allowed dose interruption is 4 weeks.
[b] If AST or ALT is ≥ 3 × ULN, the "evaluation of treatment-emergent liver abnormalities" eCRF should be completed.
[c] Dose reduction should be attempted first to manage treatment-emergent toxicities.

Revised Table 5:

Nonhematologic Toxicity	**Required** Action[a]
Renal Dysfunction	
• Serum creatinine ≥ 2 × baseline**, OR** • CrCl < 15 mL/min**, OR** • rCl decr*eases to ≤ 50%* **of baseline, OR** • **Requirement** for dialysis	• Withhold dose**s while the cause of renal dysfunction is being assessed.** • If attributable to carfilzomib, resume **at 1 dose decrement** when CrCl has recovered to within 25% of baseline • If not attributable to carfilzomib, resume the same dose **or** reduce **by** 1 dose **decrement**, at the i**nvestigator's** discretion**, when CrCl has recovered to within 25% of baseline** • For patients on dialysis receiving carfilzomib, the dose is to be administered after the dialysis procedure.
Hepatic Dysfunction	
• ≥ Grade 3 Elevations of AST, ALT, or total bilirubin	• Withhold dose**s**. • Resume at 1 dose decrement when **the grade** has **returned** to baseline.[c]
Infection	
• ≥ Grade 3 Infection	• Withhold **doses**. • Resume at the same **dose level**, **when the infection is controlled**.
Cardiovascular Dysfunction	
• Congestive Heart Failure	• **Withhold doses for any subject with symptomatic heart failure, whether or not it is attributed to carfilzomib** • **Resume at 1 dose decrement, when symptoms have resolved or returned to baseline**
• LVEF < 40%, OR • **LVEF < 55%, if decreased** > 20% from Baseline	• Withhold **doses** • **Resume at 1 dose decrement, when** LVEF returns to ≥ 40%**, or to within 15% of baseline,** if **carfilzomib was** held due to a drop to <55**%**
• Pulmonary Hypertension	• **Withhold doses and assess the benefit: risk of resuming carfilzomib.** • **If the assessment favors benefit, carfilzomib may be resumed at the same dose level or at 1 dose decrement, at the investigator's discretion**.
Thrombotic Microangiopathy	
• Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome	• **Withhold doses when TTP/HUS is suspected.**

Nonhematologic Toxicity	**Required** Action[a]
(TTP/HUS)	• If the **diagnosis is excluded, resume at the same dose level.** • If **the diagnosis is confirmed, the decision to resume or not resume carfilzomib is at the investigator's discretion. The safeness of resuming carfilzomib following TTP/HUS is unknown.** • Manage symptoms per standard of care including, plasma exchange as clinically indicated[b]**.**
Encephalopathy	
• Posterior reversible encephalopathy syndrome (PRES)	• **Withhold doses and assess the benefit:risk of resuming carfilzomib.** • Consider evaluation with neuroradiological imaging for onset of visual or neurological symptoms suggestive of PRES. • **If the diagnosis is excluded, resume at the same dose level.** • **If the diagnosis is confirmed, the decision to resume or not resume carfilzomib is at the investigator's discretion. The safeness of resuming carfilzomib following PRES is unknown.**
Other Nonhematologic Toxicity	
• **≥ Grade 3 and attributed to carfilzomib**	• **Withhold doses.** • **Resume at 1 dose decrement,, when toxicity has resolved to Grade ≤ 2 or to Baseline.**

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CrCl = creatinine clearance; eCRF = electronic Case Report Form; IB = Investigator's Brochure;
LFTs = liver function tests; LVEF = left ventricular ejection fraction; mL = milliliter(s); ULN = upper limit of normal.

Note: Carfilzomib dose schedule does not need to be adjusted for baseline renal dysfunction.

[a] The maximum allowed dose interruption is 4 weeks**, except with approval by the medical monitor.**

[b] **Subjects requiring plasma exchange must be withdrawn from study treatment. Every effort should be made to assess disease status in accordance with IMWG criteria, before plasma exchange is initiated**.

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 9.3.2 Dexamethasone: Guidelines for Toxicities and Dose Modification, paragraph 1	**Replace:** Dose reduction levels of dexamethasone for toxicity management of individual subjects are provided in Table 7.	**With:** Dose **decrements for** dexamethasone are provided in Table 6.	Revised text for clarification
Section: 9.3.2 Dexamethasone: Guidelines for Toxicities and Dose Modification, paragraph 2	**Replace:** Dexamethasone will be permanently discontinued after 2-dose level 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. Guidelines for dexamethasone-related toxicities are summarized in Table 8	**With:** Dexamethasone will be permanently discontinued**, if toxicity persists following 2 dose level reductions.** At the investigator's discretion, dexamethasone may be tapered, prior to complete discontinuation, according to institutional practice. **The requirements** for **dose modification due to** dexamethasone-related toxicities are summarized in Table 7	Revised text for clarification
Section: 9.3.2 Dexamethasone: Guidelines for Toxicities and Dose Modification, Table 7, title	**Replace:** Treatment Guidelines for Dexamethasone-related Toxicities	**With:** Treatment **Rules** for Dexamethasone-related Toxicities	Revised text to emphasize requirement
Section: 9.3.2 Dexamethasone: Guidelines for Toxicities and Dose Modification,, Table 7	**Replace:** Original Table 8 below	**With:** Revised Table 7 below	Revised text for clarification

Original Table 8:

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)	Withhold 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)	Withhold 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)	Withhold 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.

Revised Table 7:

Toxicity	**Required** Action
Edema	
≥ Grade 3: • **Limb Edema** • **Truncal Edema**	• Withhold **doses and diurese as needed.** • **Resume at 1 dose decrement when Grade ≤ 1 or baseline**.
Gastrointestinal Distress	
Grade 1 or 2: • Dyspepsia**, OR** • Gastri**tis, OR** • Gastric or Duodenal Ulcer	• **Continue doses while attempting medical management.** • **If symptoms persist, reduce by 1 dose decrement**
≥ Grade 3: • Dyspepsia, **OR** • Gastritis, **OR** • Gastric or Duodenal Ulcer	• Withhold **doses**. • Resume at 1 dose decrement, **when symptoms return to baseline**. • If symptoms **recur** despite **appropriate medical management** discontinue dexamethasone permanently.
• Acute pancreatitis	• Discontinue dexamethasone permanently.
Psychiatric Disorders	
≥ Grade 2: • **Confusion, OR** • **mood alteration**	• Withhold **doses**. • **Resume** at 1 dose decrement**, when symptoms return to baseline**.
Other Toxicities	
• ≥ Grade **3 and attributed to dexamethasone**	• Withhold d**oses**. • **Resume** at 1 dose decrement, **when toxicity has resolved to ≤ Grade 2**.

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 9.3.3 Conditions not Requiring Dose Reduction, paragraph 1	**Replace:** The following conditions are exceptions to the above guidelines. Carfilzomib and dexamethasone do not need to be held in the following cases:	**With:** The following conditions are exceptions to the **requirements presented** above. Carfilzomib and dexamethasone do not **require dose modification** in the following cases:	Revised text for consistency within overall protocol
Section: 9.3.3 Conditions not Requiring Dose Reduction, paragraph 1, bullet 1	**Replace:** Grade 3 nausea, vomiting, or diarrhea (unless persisting more than 3 days with adequate treatment of antiemetics or antidiarrheal agents)	**With:** Grade 3 nausea, vomiting, or diarrhea (unless persisting more than 3 days **despite appropriate use** of antiemetics or antidiarrheal agents)	Revised text for clarification
Section: 9.3.3 Conditions not Requiring Dose Reduction, paragraph 1, bullet 2	**Replace:** • Grade 3 dexamethasone-related hyperglycemia	**With:** • Grade 3 hyperglycemia	Removed requirement for hyperglycemia to be dexamethasone-related
Section: 9.4 Concomitant Medications and Therapies, heading	**Replace:** Concomitant Medications and Concomitant Therapies	**With:** Concomitant Medications and Therapies	Administrative change
Section: 9.4 Concomitant Medications and Therapies, paragraph 1, sentence 2	**Replace:** For all randomized subjects, all administered concomitant medications and therapies, from signing of the informed consent until 30 days after the subject's last dose of study treatment, must be recorded in the designated electronic Case Report Form (eCRF).	**With:** For all randomized subjects, all administered concomitant medications and therapies, from signing of the informed consent until 30 days after the last dose of study treatment, must be recorded in the designated electronic Case Report Form (eCRF).	Administrative change
Section: 9.4 Concomitant Medications and Therapies, paragraph 2	**Replace:** Concomitant medications required for the study or used prophylactically should be described as such in the designated CRF. Concomitant medications prescribed for "prn (as needed) use" on an "as needed" basis should not be reported	**With:** Concomitant medications required for the study or used prophylactically should be described as such in the designated **e**CRF. Concomitant medications prescribed for "prn**" or "**as needed**"** use should not be reported, unless actually	Administrative change

Section	Text in Protocol	Amended Text	Rationale for Change
	unless actually administered.	administered.	
Section: 9.4 Concomitant Medications and Therapies, paragraph 3	**Replace:** Blood or blood products are not considered concomitant medications and must be recorded on the appropriate eCRF.	**With:** Blood **and** blood products are not considered concomitant medications and must be recorded on the appropriate eCRF.	Administrative change
Section: 9.4.1 Required Concomitant Medications	**Replace:** Required prophylactic medications should be initiated at least 24 hours prior to the first administration of carfilzomib.	**With:** Required prophylactic medications should be initiated at least **1 day** prior to the first administration of carfilzomib.	Revised text for clarification
Section: 9.4.1.1 (old) Antiviral Prophylaxis		**Section moved to section 9.4.2.1**	Revised for consistency with the current label
Section: 9.4.1.1 (newly renumbered) Gastrointestinal Prophylaxis	**Replace:** Lansoprazole, 15 mg PO daily, or other oral proton-pump inhibitor according to institutional practice to prevent peptic ulcer disease is a required concomitant medication throughout the duration of study treatment with dexamethasone.	**With:** Lansoprazole or other oral proton-pump inhibitor**, dosed** according to institutional practice**, is required** to prevent peptic ulcer disease throughout the duration of treatment with dexamethasone.	Administrative change
Section: 9.4.1.2 Pregnancy and Contraception, paragraph 1	**Replace:** Contraception must continue during study drug dose interruption intervals until 30 days after the last study drug administration.	**With:** Contraception must continue during study drug dose interruption intervals until 30 days **(females) and 90 days (males)** after the last study drug administration. If applicable, refer to the Country Specific Pregnancy and Contraceptive Supplement (refer to Appendix K).	Updated text to align with current carfilzomib core safety language
Section: 9.4.1.2 Pregnancy and Contraception, paragraph 2	**Replace:** If the subject thinks she may be pregnant (e.g., if a menstrual period in a FCBP does not occur at	**With:** If **a** subject thinks she may be pregnant (e.g., if a menstrual period in a**n** FCBP does not occur at	Revised text for consistency within overall protocol

Section	Text in Protocol	Amended Text	Rationale for Change
	the anticipated time), study drug treatment must be interrupted, and a serum pregnancy test must be performed locally. Study drug administration may resume after documentation of a nonpregnant state.	the anticipated time), study drug treatment must be interrupted, and a **urine or** serum pregnancy test must be performed locally. Study drug administration may resume after documentation of a nonpregnant state.	
Section 9.4.2 Recommended Concomitant Medications, heading	**Replace:** Optional and Allowed Concomitant Medications	**With:** **Recommended** Concomitant Medications	Revised text for clarification
Section 9.4.2 Recommended Concomitant Medications	**Replace:** 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. Subjects should be well hydrated to reduce the risk of TLS and decline in renal function; refer to the current Carfilzomib IB for safety guidance regarding TLS. 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 in accordance with American Society of Clinical Oncology (ASCO) Guidelines (Smith 2006), 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. Subjects may receive bisphosphonates. Palliative radiation for pain management is permitted with the written approval of the study	**With:** **9.4.2.1** Antiviral Prophylaxis Valacyclovir (or an equivalent antiviral **agent**) is recommended for prophylaxis against herpes zoster reactivation. **9.4.2.2 Uric Acid-lowering Agents** Allopurinol or other approved uric acid-lowering agent **are recommended for** subjects at high risk for tumor lysis syndrome (TLS) due to high tumor burden. Refer to the current Carfilzomib IB for safety guidance regarding TLS. **9.4.2.3 Mycostatin or Oral Fluconazole** Mycostatin or oral fluconazole **may be given** to prevent oral thrush **throughout the duration of treatment with dexamethasone.** **9.4.2.4 Antiemetics and Antidiarrheal Agents** Antiemetics and antidiarrheal agents **are recommended for prophylaxis and/or management of treatment-related gastrointestinal symptoms.**	Headings added for ease of use within the protocol

Section	Text in Protocol	Amended Text	Rationale for Change
	medical monitor.		
Section: 9.4.3 Excluded Concomitant Medications and Therapies	**Replace:** The clinical investigator should contact the study medical monitor if concomitant use of excluded medications or therapies is required, to determine the appropriateness of continued study treatment administration. Concurrent therapy with a marketed or investigational anticancer therapeutic or radiation to large marrow reserves for either a palliative or therapeutic intent is prohibited. Additionally, no alternative or investigational anticancer therapy (other than that received in the study) is allowed prior to documentation of PD per protocol-specified disease response criteria. Any new anticancer therapies a subject received during the study (from randomization to study completion or early discontinuation) must be recorded in the designated eCRF. Corticosteroids for nonmalignant conditions (e.g., asthma, inflammatory bowel disease) equivalent to a dexamethasone dose > 4.0 mg/day or prednisone > 20 mg/day are not permitted. Higher steroid doses given short term for exacerbations of nonmalignant conditions (e.g., asthma flare) are permitted with the approval of the study medical monitor. Subjects requiring the use of excluded concomitant medications or procedures will be withdrawn from study treatment. Plasmapheresis is not permitted at any time during the Screening period or while the subject	**With:** **If an investigator deems that use of an excluded concomitant medication or therapy is required, but does not believe that withdrawal from study treatment is indicated, he/she must contact the study medical monitor to determine if continued study treatment is acceptable.** **9.4.3.1 Anticancer Agents** Therapy with a marketed or investigational anticancer **agent that is not required per this protocol is prohibited, while subjects remain on study treatment, and should be avoided prior to documentation of disease progression.** **9.4.3.2 Radiation Therapy** **Radiation to large marrow reserves is prohibited, however, focal palliative radiation is allowed with permission from the study medical monitor.** **9.4.3.3 Myeloid Growth Factors** **Prophylactic use of myeloid growth factors is prohibited, but they may be used for management of neutropenia, in accordance with American Society of Clinical Oncology (ASCO) Guidelines (Smith 2006).** **9.4.3.4 Corticosteroids** **Corticosteroids should not be used to treat concurrent medical** conditions**, unless the dose remains less than the** equivalent **of 4 mg/day**	Reorganized section and added headings for ease of use within the protocol and to clarify concomitant medications and therapies that were excluded

Section	Text in Protocol	Amended Text	Rationale for Change
	is receiving study treatment. If a subject who has started screening procedures requires plasmapheresis, or is anticipated to require plasmapheresis during or after the Screening period, this subject will be considered ineligible and will not be enrolled. For subjects requiring plasmapheresis while on study treatment every attempt should be made to document disease status by IMWG criteria first, and then discontinue study treatment and enter LTFU for monitoring survival and PFS. Subjects requiring plasmapheresis must have 2 serum samples (for serum protein electrophoresis [SPEP] and immunofixation) and at least one 24-hour urine sample (urine protein electrophoresis [UPEP] and immunofixation) obtained prior to the procedure.	**of** dexamethasone**.** Short term **use of higher doses may be permitted to treat acute** exacerbations of **concurrent medical** conditions**, but this must be discussed** with the study medical monitor **as soon as is possible.** **9.4.3.5 Plasmapheresis** Plasmapheresis is not permitted at any time during the Screening period or while the subject is receiving study treatment. If a subject who has started screening procedures requires plasmapheresis, or is anticipated to require plasmapheresis during or after the Screening period, this subject will be considered ineligible. For subjects requiring plasmapheresis while on study treatment**,** every attempt should be made to document disease status by IMWG criteria first. Study treatment **must be discontinued and the subject will** enter LTFU. **9.4.3.6 Novel Agents for Non-neoplastic Conditions** **The use of novel agents for non-neoplastic conditions is prohibited throughout the duration of treatment and for 30 days following the last dose of study treatment.**	
Section: 10.1.1 Multiple Myeloma History and Prior Lines of Therapy Assessment, paragraph 1, sentence 1		**Delete:** ~~Subjects must have confirmed and verifiable diagnosis of multiple myeloma and documented relapse after at least 2 but no more than 3 therapies for multiple myeloma.~~	Deleted text to remove redundancies
Section: 10.1.1 Multiple Myeloma History and Prior Lines of Therapy	**Replace:** A new therapy is also considered to start when a	**With:** A new therapy is also considered to start when a	Revised text for clarification

Section	Text in Protocol	Amended Text	Rationale for Change
Assessment, paragraph 1, bullet 1, sentence 2	planned period of observation off-therapy is interrupted by a need for additional lines of therapy for the disease.	planned period of observation off-therapy is interrupted by a need for additional lines of therapy.	
Section: 10.1.1 Multiple Myeloma History and Prior Lines of Therapy Assessment, paragraph 1, bullet 2	**Replace:** • An increase in treatment administration, with the intention of recapturing response in a patient with evidence of disease progression on that line of therapy is considered a new therapy.	**With:** • An increase in treatment administration, with the intention of recapturing response in a patient with evidence of disease progression on that line of therapy**,** is considered **to be** a new **line of** therapy.	Revised text for clarification
Section: 10.1.1 Multiple Myeloma History and Prior Lines of Therapy Assessment, paragraph 2, after bullet 2		**Add:** **If available, historical FISH data should be entered into the eCRF. The following results should be captured:** ○ **t(4;14)** ○ **t(6;14)** ○ **t(11;14)** ○ **t(14;16)** ○ **t(14;20)** ○ **Del 17p** ○ **Del 13** ○ **Chromosome 1 abnormalities**	Updated to clarify that cytogenetic abnormalities from prior testing should be reported as part of multiple myeloma history
Section: 10.1.3 Complete Physical Examination	**Replace:** A physical examination will be performed during Screening, prior to dosing on Day 1 of each cycle and at the EOT. For Cycle 1 Day 1, the screening physical examination may be used if within 7 days prior to Cycle 1 Day 1. Physical exam may be completed up to 3 days prior to Day 1 of each cycle. Additional physical	**With:** A physical examination will be performed during Screening, prior to dosing on Day 1 of each cycle**,** and at the EOT. For Cycle 1 Day 1, the screening physical examination may be used if **performed** within 7 days prior to Cycle 1 Day 1. Physical exam may be completed up to 3 days prior to Day 1 of each cycle. **At a**	Clarified required components of complete physical examination

Section	Text in Protocol	Amended Text	Rationale for Change
	examinations may be performed at the discretion of the study investigator to assess potential AEs and for the medical management of the subject. Abnormal findings that should be recorded as an AE and will include but not limited to: • Examination of cardiovascular and respiratory systems • Abdominal examination • Peripheral neuropathy (PN) assessment (including the neurologic physical exam) • Height (at Screening only) • Weight Body surface area determination should occur on Day 1 of each cycle prior to dosing. BSA is determined by a standard formula such as the Mosteller Formula (Mosteller 1987): BSA (m^2) = ([Height (cm) × Weight (kg)]/ 3600)½. Abnormal physical examination findings prior to Screening will be captured as medical history. Abnormal physical examination findings observed after the signing of informed consent will be recorded as AEs.	**minimum, the** physical exam should include **constitutional, abdominal, cardiovascular, and respiratory assessments.** **Clinically significant abnormal findings identified after the signing of informed consent must be reported as AEs and examined more frequently, as clinically indicated. Note: Clinically significant abnormal physical examination findings identified prior to the signing of informed consent should be reported as part of Medical History, not as AEs.** BSA is **to be** determined by a standard formula**,** such as the Mosteller Formula (Mosteller 1987): BSA (m^2) = ([Height (cm) × Weight (kg)]/ 3600)½**. BSA must be recalculated and used for subsequent dose determinations, if the subject experiences a weight change of ≥20%. Recalculations of BSA must be made using the same technique as used at baseline**.	
Section: 10.1.4 Eastern Cooperative Oncology Group Performance Status	**Replace:** Eastern Cooperative Oncology Group Performance Status will be assessed during physical examination at Screening prior to randomization to determine eligibility and at the EOT visit. Eastern Cooperative Oncology Group Performance Status grades and descriptions are tabulated in Appendix E.	**With:** Eastern Cooperative Oncology Group Performance Status will be assessed at Screening and at the EOT visit. Eastern Cooperative Oncology Group Performance Status grades and descriptions are tabulated in Appendix E.	Revised text for clarification
Section: 10.1.5 International Staging	**Replace:**	**With:**	Revised text for

Section	Text in Protocol	Amended Text	Rationale for Change
System Stage Determination	Beta-2 microglobulin and albumin will be assessed at the central laboratory during Screening to determine ISS Stage at study entry (refer to Appendix B and Appendix H). The ISS Stage determined within the 21 days prior to randomization will be used to stratify the subject. These results must be evaluated at the central laboratory and available at the time of randomization.	Beta-2 microglobulin and albumin will be assessed at the central laboratory during Screening, to determine ISS Stage (refer to Appendix B and Appendix H). **These results must be available, prior to randomization.**	consistency within overall protocol
Section: 10.1.6 24-Hour Urine		**Delete:** ~~10.1.6 24 Hour Urine~~ ~~Subjects will be instructed to collect 24 hour urine samples for assessment of UPEP at Screening, and as required during the study. This collection will occur over 2 days and will be assessed at the central laboratory. For further instruction, refer to study laboratory manual.~~	Relocated text for clarity
Section: 10.2 Multiple Myeloma Disease Assessments, paragraph 2 (old)		**Delete:** ~~Results for disease assessments SPEP, UPEP, SFLC, and immunofixation must be available at Screening and before randomization and will be repeated on Cycle 1 Day 1 (unless screening values are within 7 days of Cycle 1 Day 1). Post-Cycle 1 Day 1 UPEP and urine immunofixation will be measured:~~ • ~~Only if Cycle 1 Day 1 UPEP ≥ 200 mg/24 hours~~ • ~~To confirm a disease response (for very good partial response [VGPR] or better) or progression (if applicable)~~	Reorganized section for clarification
Section: 10.2 Multiple Myeloma	**Replace:**	**With:**	Reorganized section

Section	Text in Protocol	Amended Text	Rationale for Change
Disease Assessments, paragraph 3	Cycle 1 Day 1 (screening values may be used if obtained within 7 days prior to Cycle 1 Day 1), Cycle 2 Day 1 and each cycle thereafter, EOT and during LTFU (every 4 weeks, until PD and/or started a subsequent antimyeloma therapy): • SPEP, UPEP (24-hour assessment, no substitute method is acceptable), and immunofixation • SFLC • Quantitative immunoglobulins	Cycle 1 Day 1 **before treatment begins** (screening values may be used if obtained within 7 days prior to Cycle 1 Day 1), and **every 28 days (± 4 days)** thereafter, **at** EOT and during LTFU **if disease progression has not already been documented** (every **28 days ± 4 days**, until PD and/or started a subsequent antimyeloma therapy): • SPEP, **immunofixation** • UPEP (24-hour assessment, no substitute method is acceptable), and immunofixation**: post-Cycle 1 Day 1 measurements required only if Cycle 1 Day 1 UPEP ≥ 200 mg/24 hours or to confirm a disease response (for very good partial response [VGPR] or better) or progression (if applicable)** • SFLC**: post-Cycle 1 Day 1 measurements required only for SFLC measurable disease or to confirm stringent complete response (sCR)**	for clarification
Section: 10.2 Multiple Myeloma Disease Assessments, paragraph 4		**Add:** **Subjects will be instructed to collect 24-hour urine samples for assessment of UPEP at Screening and as required during the study. This collection will occur over 2 days and will be assessed at the central laboratory. For further instructions, refer to the Central Laboratory Services Manual.**	Reorganized section for clarification
Section: 10.2 Multiple Myeloma Disease Assessments, paragraph 5	**Replace:** Disease assessments at baseline are collected	**With:** **Radiological** disease assessments at baseline are	Reorganized section for clarification

Section	Text in Protocol	Amended Text	Rationale for Change
	only after subject eligibility is confirmed by the study medical monitor and may be done after randomization (as long as it is done before the start of treatment and no more than 21 days before Cycle 1 Day 1 dosing) and include: <u>Extramedullary Plasmacytoma Assessment</u> • A plasmacytoma evaluation will be conducted at baseline only if a lesion is suspected clinically. Historical assessment for extramedullary plasmacytoma evaluation done as part of standard of care may be used as baseline as long as it was performed within 30 days prior to Cycle 1 Day 1 dosing. • If an extramedullary plasmacytoma is detected, evaluation will be repeated during treatment only to confirm a response of PR or better, or to confirm PD. • Measurable lesions must have a longest diameter of at least 1 cm and the product of cross diameter is at least 1 cm^2. Plasmacytomas of lesser size are considered unmeasurable. Bidimensional lesion measurements must be performed and recorded in the designated eCRF. The same technique may include: palpation, ultrasound, x-ray, computed tomography (CT) scan, magnetic resonance imaging (MRI), positron emission tomography (PET), or other standard-of-care method must be employed for each measurement <u>Skeletal Survey</u> • Skeletal survey will include lateral	collected after subject eligibility is confirmed and may be done after randomization (as long as **they are** done before the start of treatment). **Radiological disease assessments that were done per standard of care within 30** days before Cycle 1 Day 1 **can be used as study baseline disease assessments. They** include: <u>Extramedullary Plasmacytoma Assessment</u> • A plasmacytoma evaluation will be conducted at baseline, only if a lesion is suspected clinically. • If an extramedullary plasmacytoma is detected, evaluation will be repeated during treatment, to confirm a response of PR or better or to **assess for** PD **based on plasmacytoma**. • **Plasmacytomas are considered measurable if they** have a longest diameter of at least 1 cm and the product of cross diameter **measurements** is at least 1 cm^2. Plasmacytomas of lesser size are considered unmeasurable. Bidimensional measurements must be recorded in the designated eCRF. The same technique **must be used to evaluate plasmacytomas throughout the duration of study participation and** may include: palpation, ultrasound, x-ray, computed tomography (CT) scan, magnetic resonance imaging (MRI), positron emission tomography (PET), or **any** other **technique that is considered to be** standard of care**.** <u>Skeletal Survey</u>	

Section	Text in Protocol	Amended Text	Rationale for Change
	radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. The skeletal survey will be conducted at baseline and will be repeated if worsening clinical symptoms suggest PD, or as clinically indicated. A historical survey may be used if performed within 30 days prior to Cycle 1 Day 1.	• Skeletal survey will include lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. The skeletal survey will be conducted at baseline and will be repeated if worsening clinical symptoms suggest PD, or as clinically indicated. • **Other radiologic modalities for performing skeletal assessment (e.g., low-dose CT scan) are acceptable, in accordance with regional standards.**	
Section: 10.3.1 Disease Response and Progression Assessments	**Replace:** Determination of disease response must be based on the reported values from the central laboratory results not on local laboratory results. Local laboratory results may be used for hypercalcemia (corrected calcium using albumin) but a confirmatory sample should be collected and sent to the central laboratory for documentation. As with all clinically significant or relevant local laboratory results, hypercalcemia values should be entered into the Case Report Form (CRF). Response will be determined by the investigator based on the disease assessments described above and the IMWG-URC (see definitions in Appendix G). Myeloma response will be assessed at each cycle prior to the initiation of subsequent cycles.	**With:** Determination of disease response must be based on the reported values from the central laboratory. Local laboratory results may be used for hypercalcemia (corrected calcium **based on** albumin), but a confirmatory sample should be collected and sent to the central laboratory for documentation. **Investigator-**determined **responses must be** based on **results from the central laboratory** and **must be consistent with** the IMWG-URC (see definitions in Appendix G).	Reworded text for clarification
Section: 10.3.2 Tumor Response Assessment, bullets 1, 2, 3, 4, and 5	**Replace:** • All laboratory-based PD (except bone	**With:** • All laboratory-based PD (except bone	Reworded text for clarification

Section	Text in Protocol	Amended Text	Rationale for Change
	marrow sample) and all response categories require 2 consecutive assessments made at any time before initiation of any new therapy. Confirmatory lab samples should be separated by at least 1 calendar day. • All response categories also require no evidence of progression including new bone lesions if radiographic studies were performed. • The preferred method for a confirmation of CR or sCR is a bone marrow biopsy. However, an aspirate slide is acceptable for confirmation of CR (a confirmatory bone marrow sample is not required). • Extramedullary plasmacytoma evaluation (if present at Screening). It is not required to have 2 consecutive radiographic tests to confirm response or progression of extramedullary plasmacytoma. • In the case where a patient does not have measurable M-protein by UPEP at baseline (i.e., screening UPEP < 200 mg/24 hours), when SPEP is consistent with response (i.e., ≥ PR), 2 consecutive UPEP must be performed to confirm response.	marrow sample) and all response categories require 2 consecutive assessments made at any time before initiation of new therapy. • All response categories require **that there be** no evidence of **disease** progression**,** including **confirmation of no** new bone lesions**,** if radiographic studies were performed. • The preferred method of confirm**ing** CR or sCR is a bone marrow biopsy; however, **a bone marrow** aspirate is **also** acceptable for confirmation of CR. • Extramedullary plasmacytoma evaluation (if present at Screening). **Two** consecutive radiographic tests **are not required** to confirm response or progression of extramedullary plasmacytoma. • In the case where a patient does not have measurable M-protein by UPEP at baseline (i.e., **baseline** UPEP < 200 mg/24 hours), when SPEP is consistent with response (i.e., ≥ PR), 2 consecutive UPEP **measurements** must be performed to confirm response.	
Section: 10.3.3 Disease Progression, paragraph 1, sentence 2	**Replace:** Signs and symptoms related to disease progression (e.g., 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).	**With:** Signs and symptoms related to disease progression (e.g., pathologic fracture in a subject with progressive multiple myeloma) should be reported in the appropriate **e**CRF as an AE or as an SAE (if the event in question meets the criteria for seriousness).	Revised text for consistency within overall protocol

Section	Text in Protocol	Amended Text	Rationale for Change
Section:10.3.3 Disease Progression, paragraph 2	**Replace:** Decisions to discontinue subjects due to PD (including PD due to development of hypercalcemia attributed solely to recurrence/progression of multiple myeloma) must be based on central laboratory evaluation, and must also be verified by the medical monitor. Confirmation of PD will require 2 consecutive central laboratory evaluations that indicate PD. There is no specified time requirement between the 2 central laboratory evaluations. Local laboratory evaluation will not be accepted and change of treatment decisions may only be made based on results of central laboratory evaluation. Progressive disease by non-laboratory based assessment (i.e., plasmacytoma or skeletal lesion) does not require confirmatory report. The assessments outlined in Appendix B are required for PD.	**With:** **Study treatment should not be discontinued on the basis** of **disease** progression**, until PD has been appropriately confirmed per IMWG-URC. Disease progression during LTFU** must also be **confirmed** by **these same criteria.** Confirmation of PD will require 2 consecutive central laboratory evaluations that indicate PD**, except in cases where PD is based on extramedullary lesions or hypercalcemia that is attributed solely to PD. These assessments should be separated in** time **by at least 1 calendar day, but no more than 28 ± 4 calendar days.** Local laboratory **results** may **not be used to determine or confirm disease progression, except when PD is** based on **hypercalcemia.** The assessments outlined in Appendix B are required for PD **determination**.	Clarified requirements discontinuation of subjects for PD
Section: 10.4 Laboratory Tests, paragraphs 1 and 2	**Replace:** Laboratory tests for efficacy and safety during scheduled and unscheduled study visits will be performed at a central laboratory and results recorded in the study database. Additional laboratory samples may be collected and analyzed by local laboratories if immediate results are necessary for management of treatment-emergent adverse events (TEAEs) or dosing determination. Investigator evaluation of disease response should be based solely on the central laboratory results, not on local laboratory.	**With:** Laboratory tests for efficacy and safety during scheduled and unscheduled study visits**, including screening** will be performed at a central laboratory. Additional **safety** laboratory samples **must also** be collected and analyzed by local laboratories if **the** results are necessary **to determine the appropriateness of dose administration. In rare circumstances, when the central laboratory is unable to provide results for tests that are needed to determine eligibility, the study medical monitor may grant permission for local laboratory results to be applied to the screening requirements.**	Clarified because at post Cycle 4 there are no Day 8 lab samples required

Section	Text in Protocol	Amended Text	Rationale for Change
	Clinical laboratory samples may be obtained anytime within the 24 hours prior to the carfilzomib administration and must be reviewed prior to the start of carfilzomib infusion on Days 1, 8, and 15 of all cycles.	**Local labs may also be required** for management of treatment-emergent adverse events (TEAEs)**. Laboratory tests for disease assessment are described in Section 10.2.** **Safety** samples **must** be obtained within the **1 day** prior to carfilzomib administration and **the results** must be reviewed prior to the start of **the** carfilzomib infusion**s** on Days 1, 8, and 15 of **Cycles 1 to 4**. **Beyond Cycle 4, these labs are only required on Days 1 and 15 of each cycle.**	
Section: 10.4.1 Hematology, paragraph 1	**Replace:** Hematology (central laboratory, Table 9) will be performed during Screening, on Days 1, 8, and 15 for Cycles 1 to 4, and EOT. Beyond Cycle 4 labs will be performed on Days 1 and 15 of each cycle. For Cycle 1 Day 1, full hematology from Screening can be used if within 3 days. For subsequent visits, hematology may be completed up to 24 hours prior to scheduled dose.	**With:** Hematology **assessments** (Table 8) will be performed during Screening, on Days 1, 8, and 15 for Cycles 1 to 4, and EOT. Beyond Cycle 4 labs will be performed on Days 1 and 15 of each cycle. For Cycle 1 Day 1, hematology **assessments** from Screening can be used, if **they were obtained** within 3 days **prior to carfilzomib administration**. For subsequent visits, hematology **assessments** may be completed up to **1 day** prior to **the** scheduled dose.	Revised text for consistency within overall protocol
Section: 10.4.1 Hematology, Table 8	**Replace:** WBCs with complete manual or automated differential to include: [a] Total neutrophils Lymphocytes Monocytes Eosinophils Basophils	**With:** WBC **count** with complete differential to include: [a] Neutrophils Lymphocytes Monocytes Eosinophils Basophils	Revised text for consistency within overall protocol

Section	Text in Protocol	Amended Text	Rationale for Change
	RBCs	RBC **count**	
Section: 10.4.1 Hematology, Table 8, footnote a	**Replace:** [a] Absolute or percentage will be acceptable.	**With:** [a] Absolute **counts** or percentage will be acceptable.	Revised text for consistency within overall protocol
Section: 10.4.2 Serum Chemistry, paragraph 1	**Replace:** Full serum chemistry panel (central laboratory, Table 10) will be performed during Screening, on Days 1, 8, and 15 for Cycles 1 to 4, and EOT. Beyond Cycle 4, labs will be performed on Days 1 and 15 of each cycle. For Cycle 1 Day 1, full chemistry from Screening can be used if within 3 days. For subsequent visits, chemistries may be completed up to 24 hours prior to scheduled dose.	**With:** **A** serum chemistry panel (Table 9) will be performed during Screening, on Days 1, 8, and 15 for Cycles 1 to 4, and EOT. Beyond Cycle 4, labs will be performed on Days 1 and 15 of each cycle. For Cycle 1 Day 1, **serum** chemistry **assessments** from Screening can be used**,** if **performed** within 3 days **prior to carfilzomib administration**. For subsequent visits, **serum** chemistries may be completed up to **1 day** prior to **the** scheduled **carfilzomib** dose.	Revised text for consistency within overall protocol
Section: 10.4.2 Serum Chemistry, Table 9, Note at bottom of Table		**Delete:** ~~Note: If AST or ALT is > 3 × ULN, the "evaluation of treatment-emergent liver abnormalities" eCRF should be completed.~~	Removed reference to this eCRF, which is no longer being utilized
Section: 10.5 Electrocardiogram, sentence 2	**Replace:** Electrocardiogram will be required in all subjects at Screening and EOT.	**With:** Electrocardiogram**s** will be required **from** all subjects at Screening and EOT.	Administrative change
Section: 10.6 Echocardiogram, paragraphs 1 and 2	**Replace:** A 2-D transthoracic echocardiogram (ECHO) to assess LVEF for eligibility purposes will be conducted on all potential subjects during Screening and will also serve as the baseline ECHO. If transthoracic ECHO is not available, multigated acquisition (MUGA) will be	**With:** A 2-D transthoracic echocardiogram (ECHO) **is required** to assess LVEF during Screening and will also serve as the baseline ECHO. If transthoracic ECHO is not available, multigated acquisition (MUGA) will be acceptable for	Administrative change

Section	Text in Protocol	Amended Text	Rationale for Change
	acceptable for screening LVEF evaluation. Additionally, any subject with a clinically significant cardiac-related AE should be evaluated by a cardiologist and have a follow-up ECHO if medically indicated.	LVEF evaluation. Any subject with a clinically significant cardiac AE should be evaluated by a cardiologist and **must** have a follow-up ECHO, if medically indicated.	
Section: 10.7 Patient Reported Outcomes, paragraph 2, sentences 1 and 2	**Replace:** All questionnaires should be collected on Day 1 of Cycle 1, then every other cycle during treatment. Questionnaires listed below should be completed by the subject prior to drug administration during treatment cycles:	**With:** All questionnaires should be collected on Day 1 of Cycle 1, then every **second** cycle **(Cycle 1, 3, 5, etc)** during treatment. **The** questionnaires listed below should be completed by the subject prior to drug administration during treatment cycles:	Revised text for consistency within overall protocol
Section: 10.8 Healthcare Resource Utilization	**Replace**: Healthcare resource utilization data related to AEs will be collected for all subjects during the study on the eCRF. These data may include inpatient care, outpatient care, surgery, and use of other medications and therapeutic procedures related to AEs.	**With:** Healthcare resource utilization data related to AEs will be collected **for each subject**. These data may include inpatient care, outpatient care, surgery, and use of other medications and therapeutic procedures related to AEs. **Details on hospitalizations (not related to AEs) will also be collected.**	Added text for collection of hospitalizations not related to AEs to align to with previous section
Section: 10.9 Correlative Studies	**Replace:** Samples for correlative studies will be collected only after Screening laboratories confirm study eligibility for the subject. Intensive PK and PDn will be conducted as a substudy at selected sites. The target number of subjects who participate in the intensive PK/PDn substudy is approximately 15 per arm. Sparse PK samples will only be collected at all other sites from subjects who consent to the additional testing.	**With:** Samples for correlative studies will be collected only after **confirmation of** study eligibility. Intensive PK and PDn will be conducted as a substudy at selected sites. Sparse PK samples will be collected at all other sites, from subjects who consent to the additional testing.	Revised text for consistency within overall protocol

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 10.9.1 Intensive Pharmacokinetics/Pharmacodynamics Substudy, paragraph 1	**Replace:** Approximately 15 subjects in each arm will participate in the intensive PK/PDn substudy at select sites. On both arms, whole blood and PBMCs will be collected from all subjects on Days 1, 15, 16, 17, and 22 of Cycle 1 at the following timepoints summarized in Table 11. Directions for collection, processing, and shipping of PDn blood samples are provided in the laboratory manual. The actual time of when the PDn sample was collected will be recorded.	**With:** Approximately 15 **evaluable** subjects in each arm will participate in the intensive PK/PDn substudy at select sites. On both arms, whole blood and PBMCs will be collected from all subjects on Days 1, 15, 16, 17, and 22 of Cycle 1 at the timepoints (summarized in Table 1**0**). Directions for collection, processing, and shipping of PDn blood samples are provided in the **Central** Laboratory **Services** Manual. The actual time of when the PDn sample was collected will be recorded.	Revised text for consistency within overall protocol
Section: 10.9.1 Intensive Pharmacokinetics/Pharmacodynamics Substudy, Table 10	**Replace:** Timepoints in days.	**With:** **Timepoints in hours.**	Revised text for consistency within overall protocol
Section: 10.9.1 Intensive Pharmacokinetics/Pharmacodynamics Substudy, paragraph 2, sentence 1	**Replace:** For both arms, PK plasma samples will be collected from all subjects for determination of plasma concentrations of carfilzomib on treatment Day 15 of Cycle 1 at the following time points:	**With:** For both **treatment** arms, PK samples will be collected from all subjects for determination of plasma concentrations of carfilzomib on treatment Day 15 of Cycle 1 at the following time points:	Revised text for consistency within overall protocol
Section: 10.9.1 Intensive Pharmacokinetics/Pharmacodynamics Substudy, paragraph 3	**Replace:** The actual time of PK sample collection will be recorded. Samples will be collected within ± 5 minute time window around the nominal time points (except for the time point immediately prior to the end of 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 qualify for protocol deviation. These samples will be	**With:** The actual time of PK sample collection will be recorded. Samples will be collected within ± 5 minute time window**s** around the nominal time points (except for the time point immediately prior to the end of infusion**, for** which the PK collection needs to occur prior to **the** end of infusion). Directions for collection, processing, and shipping of PK samples are provided in the **Central Laboratory Services**	Revised text for clarification

Section	Text in Protocol	Amended Text	Rationale for Change
	assessed at a central laboratory. Directions for collection, processing, and shipping of PK blood samples are provided in the laboratory manual.	Manual.	
Section: 10.9.2 Sparse Pharmacokinetic Sampling, paragraph 1	**Replace:** Sparse PK samples will only be collected at the sites from subjects who do not participate in the intensive PK/PDn substudy and who consent to the additional testing. The actual time of the PK sample collection will be recorded. These samples will be assessed at a central laboratory. Directions for collection, processing, and shipping of PK blood samples are provided in the lab manual.	**With:** Sparse PK samples will be collected from subjects who do not participate in the intensive PK/PDn substudy and who consent to the additional testing. The actual time of the PK sample collection will be recorded. These samples will be assessed at a central laboratory. Directions for collection, processing, and shipping of PK samples are provided in the **Central** Lab**oratory Services** Manua**l**.	Administrative change
Section: 10.10.1 Long-term Follow-up Before Disease Progression, paragraph 1, sentences 1 and 2	**Replace:** For subjects who discontinued treatment before disease progression occurred, disease assessment measurements will be performed (using the central laboratory results) every 4 weeks (every 28 days ± 4 days) until the subject has PD or until withdrawal of consent (Appendix B). Effort should be made to obtain confirmatory PD results (refer to Appendix G) prior to the initiation of new antimyeloma therapy.	**With:** For subjects who discontinue treatment before disease progression occurs, disease assessment**s** will be performed (using the central laboratory results) every 28 days ± 4 days until the subject has PD or until withdrawal of consent (Appendix B). Confirmatory PD results (refer to Appendix G) **must be obtained** prior to the initiation of new antimyeloma therapy.	Aligned with previous section as there will be no anticancer therapy until PD.
Section: 10.10.2 Long-term Follow-up After Disease Progression (For Survival)	**Replace:** After completion of the EOT visit, subjects who have discontinued due to disease progression will be followed for survival status queried by telephone contact or other method approximately every 3 months, or as needed until study closure.	**With:** After completion of the EOT visit, subjects who have discontinued due to disease progression will be followed for survival status**,** queried by telephone contact or other method**,** approximately every **12 weeks ± 28 days**, or as needed until study closure.	Revised text for consistency within overall protocol
Section: 11.1 Withdrawal of Subjects	**Replace:**	**With:**	Administrative change

Section	Text in Protocol	Amended Text	Rationale for Change
from Study Treatment, paragraph 1, bullet 5	• Non-compliance	• Non-compliance **with study requirements**	
Section: 11.1 Withdrawal of Subjects from Study Treatment, paragraph 1, bullet 7	**Replace:** • Study terminated by Onyx	**With:** Study termina**tion** by **Sponsor**	Administrative change
Section: 11.1 Withdrawal of Subjects from Study Treatment, paragraph 1, bullet 8	**Replace:** • Physician decision	**With:** • **Investigator** decision	Administrative change
Section: 11.1 Withdrawal of Subjects from Study Treatment, paragraph 3	**Replace:** If the reason for study 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.	**With:** If the reason for study treatment discontinuation is the occurrence of an AE, the subject will be followed by the investigator until such event(s) resolve**s**, stabilize**s**, **or**, according to the investigator's judgment, no **longer requires** follow-up.	Revised text for clarification
Section: 11.1 Withdrawal of Subjects from Study Treatment, paragraph 4	**Replace:** Study 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 12.3 then it should also be recorded as a SAE in the AE eCRF.	**With:** Study treatment discontinuation due to **PD** should be recorded as "disease progression."	Removed text to avoid duplication
Section: 11.2 Withdrawal of Subjects from Study, paragraph 1, bullet 3	**Replace:** • Onyx decision	**With:** • **Sponsor** decision	Administrative change
Section: 11.3 Study Termination, paragraph 1, sentences 1 and 2	**Replace:** Onyx has the right to terminate this study or to terminate a study site from participating in the study at any time. Reasons for study or site termination may include	**With:** **Sponsor** has the right to terminate this study or to terminate a study site from participating in the study at any time. Reasons for study or site termination may include**, but are not limited to**:	Administrative change

Section	Text in Protocol	Amended Text	Rationale for Change
Section 12 Adverse Events and Serious Adverse Events	**Replace:** An AE is any untoward medical occurrence in a study subject administered an IP regardless of the causal relationship with treatment. An AE, therefore, can be any unfavorable and unintended sign (including laboratory finding), symptom, or disease temporally associated with participation in an investigational study, whether or not considered drug-related. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the subject signs the ICF for participation is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction. All reported AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA).	**With:** An AE is any untoward medical occurrence in a subject administered a **study drug and which is not necessarily caused by** the **study drug**. An AE can therefore be any unfavorable and unintended sign (**e.g. an abnormal** laboratory finding), symptom, or disease temporally associated with **the use of a medicinal product, combination product, or medical device**, whether or not considered related **to the product**. In addition to new events, any **worsening** of a pre-existing condition that occurs after the subject signs the ICF for participation is considered an AE. **Worsening indicates that the pre-existing medical condition or underlying disease 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.** This includes any side effect, injury, toxicity, or sensitivity reaction. All reported AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA).	Revised text for clarification
Section: 12.1.2 Severity, paragraph 1	**Replace:** 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 (NCI 2010).	**With:** 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 **to** assess the severity of AEs (NCI 2010).	Administrative change
Section: 12.1.2 Severity, paragraph 3, sentence 2		**Add:** **Where applicable, clinical sequelae (not the**	Added text to clarify recording of

Section	Text in Protocol	Amended Text	Rationale for Change
		laboratory abnormality) are to be recorded as the AE.	laboratory abnormalities
Section: 12.1.3 Duration, sentence 1	**Replace:** The start and stop date for all AEs will be recorded. The start date is the first date that the subject was aware of the AE and the end date is the date that the event totally resolved or returned to baseline.	**With:** The start and stop date**s** for all AEs will be recorded. The start date is the first date that the subject was aware of the AE and the end date is the date that the event **has changed in grade,** totally resolved, or returned to baseline.	Clarified definition of AE duration for events that change in grade
Section: 12.1.3 Duration, sentence 2		**Add:** **Any changes in grade should be recorded as a separate event.**	Clarified definition of AE duration for events that change in grade
Section: 12.1.4 Causality, paragraph 1	**Replace:** A relationship between carfilzomib and an adverse event is considered causal if there is at least a reasonable possibility the adverse event was caused by carfilzomib administration, i.e., the relationship cannot be ruled out.	**With:** A relationship between **study drug** and an adverse event is considered causal if there is at least a reasonable possibility the adverse event was caused by carfilzomib administration, i.e., the relationship cannot be ruled out.	Administrative change
Section: 12.1.4 Causality, paragraph 4		**Delete:** ~~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 and/or dexamethasone.~~	Removed text that was duplicated
Section: 12.2.1 General, paragraph 3, sentence 3	**Replace:** 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.	**With:** 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 documented in the subject's source file.	Revised to clarify that follow up did not necessarily need to be done by telephone
Section: 12.2.2 Disease Progression		**Delete:**	Removed text to avoid

Section	Text in Protocol	Amended Text	Rationale for Change
		~~12.2.2 Disease Progression~~ ~~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 (e.g., pathologic fracture in a patient with progressive multiple myeloma) should be reported in the appropriate case report form as an AE or as a 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.~~	duplication
Section: 12.3 Serious Adverse Event Definition, bullet 2	**Replace:** • Life-threatening experience defined as any adverse experience that places the subject, in the view of Onyx or investigator, at immediate risk of death at the time of occurrence (i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death).	**With:** • Life threatening experience defined as any adverse experience that places the subject, in the view of **the Sponsor** or investigator, at immediate risk of death at the time of occurrence (i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death).	Administrative change
Section: 12.4 Serious Adverse Event Reporting and Documentation Requirements, paragraph 1	**Replace:** Onyx Drug Safety must be notified of the occurrence of any SAE within 24 hours of the investigator, designee, or site personnel's knowledge of the event. The SAE will be	**With:** **Amgen Global Patient** Safety must be notified of the occurrence of any SAE within 24 hours of the investigator, designee, or site personnel's knowledge of the event. The SAE will be	Administrative change

Section	Text in Protocol	Amended Text	Rationale for Change
	reported by completing and submitting the SAE report form through the EDC system. In the event that the EDC system is not available, paper SAE report forms may be used to report the SAE to Onyx Drug Safety. Please refer to the SAE Reporting Guidelines in the study reference manual.	reported by completing and submitting the SAE report form through the EDC system. In the event that the EDC system is not available, paper SAE report forms may be used to report the SAE to **Amgen Global Patient** Safety. Please refer to the SAE Reporting Guidelines in the study reference manual.	
Section: 12.4 Serious Adverse Event Reporting and Documentation Requirements, paragraph 3, sentence 2	**Replace:** Onyx may request for additional source documentation pertaining to the SAE from the investigational site.	**With:** **The sponsor** may request for additional source documentation pertaining to the SAE from the investigational site.	Administrative change
Section: 12.4 Serious Adverse Event Reporting and Documentation Requirements, paragraph 4	**Replace:** Onyx is responsible for notifying the appropriate global health authorities of SAEs, when required, and in accordance with applicable laws and regulations.	**With:** **The Sponsor** is responsible for notifying the appropriate global health authorities of SAEs, when required, in accordance with applicable laws and regulations.	Administrative change
Section: 12.4 Serious Adverse Event Reporting and Documentation Requirements, paragraph 5	**Replace:** Properly anonymized and de-identified documents (e.g. hospital discharge summaries, autopsy reports, and/or death certificates), as available will be provided to Onyx Drug Safety.	**With:** Properly anonymized and de-identified documents (e.g. hospital discharge summaries, autopsy reports, and/or death certificates), as available will be provided to **Amgen Global Patient** Safety.	Administrative change
Section: 12.5 Pregnancy and Lactation Exposure Reporting, paragraph 1	**Replace:** Pregnancy occurring in a female subject or in a male subject's partner while enrolled in this clinical study through 30 days after the last dose of any study drug was received, although not considered an SAE, must be reported on a Pregnancy Monitoring Form to Onyx Drug Safety and the contract research organization (CRO) within 24 hours of the investigator,	**With:** Pregnancy, although not considered an SAE, must be reported **to Amgen Global Patient** Safety within 24 hours of the **investigator's awareness, if** the pregnancy **has occurred within 30 days of study treatment (for female participants) or within 90 days of study treatment (for female partners of male participants). The pregnancy will be**	Updated the window for breastfeeding following the last dose of drug administration.

Section	Text in Protocol	Amended Text	Rationale for Change
	designee, or site personnel learning of the pregnancy.	**reported on a Pregnancy Notification Worksheet. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.**	
Section: 12.5 Pregnancy and Lactation Exposure Reporting, paragraph 2, sentence 1	**Replace:** If the subject becomes pregnant while taking an Onyx drug, the study treatment will be immediately discontinued.	**With:** If **a** subject becomes pregnant while taking an **Amgen** drug, the study treatment will be immediately discontinued.	Administrative change
Section: 12.5 Pregnancy and Lactation Exposure Reporting, paragraphs 4, 5, and 6	**Replace:** If the outcome of the pregnancy meets a criterion for immediate classification as an SAE (e.g., spontaneous abortion, stillbirth, neonatal death, fetal or neonatal congenital anomaly), the investigator will report the SAE via the EDC system. Newborns should be followed for a minimum of 12 weeks. The investigator is responsible for notifying the Institutional Review Board (IRB) or Independent Ethics Committees (IEC) in accordance with local regulations, of all SAEs. Onyx may request for additional source documentation pertaining to the SAE from the investigational site. If a subject is permanently withdrawn from the study due to a SAE, this information must be included in the initial or follow-up SAE report in the eCRF.	**With:** If the outcome of the pregnancy meets a criterion for immediate classification as an SAE (e.g., spontaneous abortion, stillbirth, neonatal death, fetal or neonatal congenital anomaly), the investigator will report the **event as an** SAE. **With authorization of the subject or female partner, n**ewborns should be followed**-up at 6 and 12 months of age**. If a female subject breastfeeds during treatment with carfilzomib or up to 30 days following the last dose of **study** drug administration, the investigator will notify **Amgen Global Patient Safety** within 24 hours of learning of her breastfeeding. The investigator will discuss the risks and concerns of breastfeeding while taking an IP. The subject will be required to either discontinue breastfeeding or **study treatment**. The investigator **will** complete a **Lactation Notification Worksheet**. **Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested**.	Updated text to align with current carfilzomib core safety language

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 12.5 Pregnancy and Lactation Exposure Reporting, paragraph 7		**Delete:** ~~The investigator will complete a Pregnancy Monitoring Form and report the information regarding the pregnancy, outcome, and status of the newborn, as appropriate~~.	Updated text to align with current carfilzomib core safety language
Section: 12.6 Death Reporting	**Replace:** All deaths that occur from signing of informed consent until 30 days after the last dose of study drug are to be reported as SAEs (other than due to PD - refer to Section 12.4). Deaths occurring after the EOT visit do not need to be reported as SAEs. Additional details of the event (such as the primary and contributory causes of death) should be reported on the death eCRF.	**With:** All deaths that occur from signing of informed consent until 30 days after the last dose of study drug are to be reported as SAEs (**unless** due to PD - refer to Section 12.4). Deaths occurring after the EOT visit do not need to be reported as SAEs. Additional details of the event (such as the primary and contributory causes of death) should be reported on the **end of study** eCRF.	Administrative change
Section: 13 Statistical Considerations, sentence 2	**Replace:** Further details of the analyses will be provided separately in the Statistical Analysis Plan (SAP).	**With:** Further details will be provided separately in the Statistical Analysis Plan (SAP).	Administrative change
Section: 13.1.2 Secondary Endpoints, bullet 4		**Add:** • **Sparse PK**	Revised text for consistency within overall protocol
Section: 13.3.2.1 Primary Efficacy Endpoint, paragraph 1, bullet 2	**Replace:** • Refractory to proteasome inhibitor ([PI] bortezomib) treatment (Yes versus No)	**With:** • Refractory to bortezomib treatment (Yes versus No)	Revised text for consistency within overall protocol
Section: 13.3.2.1 Primary Efficacy Endpoint, paragraph 3, sentence 3	**Replace:** Investigator-assessed responses will be analyzed as a supportive analysis of ORR.	**With:** Investigator-assessed responses will be analyzed as a supportive analysis of ORR, **as will IRC-assessed responses,** if **an IRC is convened**.	Added text regarding potential use for an IRC
Section: 13.3.2.2.1 Progression-Free	**Replace:**	**With:**	Added text regarding

Section	Text in Protocol	Amended Text	Rationale for Change
Survival, paragraph 2	The primary analysis of PFS will be based on ORCA-assessed outcomes. The PFS outcomes assessed by the investigator will serve as a supportive analysis of PFS.	The primary analysis of PFS will be based on ORCA-assessed outcomes. The PFS outcomes assessed by the investigator serve as a supportive analysis of PFS**, as will IRC-assessed outcomes, if an IRC is convened**.	potential use for an IRC
Section: 13.3.3.2 Safety Laboratory Values, paragraph 1	**Replace:** For hematology, chemistry, and other laboratory values, the baseline values and changes from baseline to the minimum, maximum, and last observed values will be summarized descriptively by visit.	**With:** For hematology, chemistry, and other laboratory values, the baseline values, changes from baseline by visit, the minimum, maximum, and last observed values will be summarized descriptively.	Administrative change
Section: 13.3.3.2 Safety Laboratory Values, paragraph 4	**Replace:** Laboratory test results will be graded using the NCI-CTCAE (Version 4.03). Shifts in laboratory toxicity grades to outside the normal range will be evaluated for select laboratory parameters by assessing the maximum increase and/or decrease (as clinically relevant) observed during the course of study treatment relative to the baseline toxicity grade.	**With:** Laboratory test results will be graded using the NCI-CTCAE (Version 4.03). Shifts in laboratory toxicity grades to outside the normal range will be evaluated for select**ed** laboratory parameters by assessing the maximum increase and/or decrease observed during the course of study treatment relative to the baseline toxicity grade.	Administrative change
Section: 13.3.3.2 Safety Laboratory Values, paragraph 5	**Replace:** The subject incidence of Grade 3 and 4 hematological toxicities (including neutropenia, thrombocytopenia, and anemia) will be provided by treatment group. Similar analyses will be done for selected chemistry tests.	**With:** The subject incidence of Grade 3 and 4 hematological **laboratory abnormalities** (including neutropenia, thrombocytopenia, and anemia) will be provided by treatment group**.**	Revised text for consistency within overall protocol
Section: 13.3.3.2 Safety Laboratory Values, paragraph 6	**Replace:** The subject incidence of Grade 3 and 4 nonhematological toxicities (including liver function test [LFT], CrCl) will be provided by treatment group. Similar analyses will be done	**With:** The subject incidence of Grade 3 and 4 nonhematological **laboratory abnormalities** (including liver function test [LFT], CrCl) will be provided by treatment group. Similar	Revised text for consistency within overall protocol

Section	Text in Protocol	Amended Text	Rationale for Change
	for selected chemistry tests.	analyses will be done for selected chemistry tests.	
13.3.3.3 Vital Signs	**Replace:** Vital sign results (systolic and diastolic blood pressure, pulse, and temperature) will be summarized descriptively for baseline values and changes from baseline to the minimum, maximum, and last observed values.	**With:** Vital sign results (systolic and diastolic blood pressure, pulse, **respiratory rate,** and temperature) will be summarized descriptively for baseline values and changes from baseline to the minimum, maximum, and last observed values.	Revised text for consistency within overall protocol
13.3.4 Sparse Pharmacokinetic Analyses, paragraph 1, sentence 3	**Replace:** Concentrations of carfilzomib will be measured in plasma with a validated assay method.	**With:** Concentrations of carfilzomib will be measured in plasma **using** a validated assay method.	Administrative change
13.3.4 Sparse Pharmacokinetic Analyses, paragraph 2, sentence 1	**Replace:** The population pharmacokinetic analysis will be a cumulative analysis that will include population pharmacokinetic data obtained from previous Phase 2 studies that used intensive sampling.	**With:** The population pharmacokinetic analysis will be a cumulative analysis that will include population pharmacokinetic data obtained from previous Phase 2 **and Phase 3** studies that used intensive **or sparse PK** sampling.	Revised text to provided updated information and consistency
Section: 13.6 Independent Review Committee	**Replace:** No Independent Review Committee (IRC) will be used for this study.	**With:** **An** IRC **may** be **convened** for this study**, if required to support the ORCA-determined results**.	Updated text to potentially include an IRC if required
Section: 13.7 Data Monitoring Committee, paragraph 1	**Replace:** An independent Data Monitoring Committee (DMC) will be convened for this study and will act in an advisory capacity to the sponsor with respect to safeguarding the interests of study subjects through periodic safety data reviews, assessing interim safety and efficacy data, and monitoring the overall conduct of the study.	**With:** An independent Data Monitoring Committee (DMC) will be convened for this study and will act in an advisory capacity to the sponsor with respect to safeguarding the interests of study subjects through periodic safety data reviews, assess**ments of** interim safety and efficacy data, and monitoring **of** the overall conduct of the	Administrative change

Section	Text in Protocol	Amended Text	Rationale for Change
		study.	
Section: 13.7 Data Monitoring Committee, paragraph 2	**Replace:** An Independent Statistical Reporting Group (ISRG) will function independently of the Onyx study team in support of the DMC. The ISRG will conduct unblinded analyses, generate the open and closed reports to be reviewed at the DMC meetings, and serve as the liaison between Onyx and the DMC.	**With:** An Independent Statistical Reporting Group (ISRG) will function independently of the **Sponsor** study team in support of the DMC. The ISRG will conduct unblinded analyses, generate the open and closed reports to be reviewed at the DMC meetings, and serve as the liaison between **the Sponsor** and the DMC.	Administrative change
Section: 14.1 Informed Consent, paragraph 2, sentence 1	**Replace:** Onyx or its designated representative will provide the investigator with a sample ICF.	**With:** **The Sponsor** or its designated representative will provide the investigator with a sample ICF.	Administrative change
Section: 14.1 Informed Consent, paragraph 3, sentence 3	**Replace:** The original signed consent must be maintained by the investigator and available for inspection by Onyx its designated representative, or regulatory authority at any time.	**With:** 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.	Administrative change
Section: 14.2 Compliance with Laws and Regulations, paragraph 2, sentence 2	**Replace:** Before the investigational drug is shipped to the investigator, the investigator or designee will provide Onyx with a copy of the IRB/IEC approval letter stating that the study protocol and any subsequent amendments and the ICF have been reviewed and approved.	**With:** Before the investigational drug is shipped to the investigator, the investigator or designee will provide **the Sponsor** with a copy of the IRB/IEC approval letter stating that the study protocol and any subsequent amendments and the ICF have been reviewed and approved.	Administrative change
Section: 14.2 Compliance with Laws and Regulations, paragraph 3, sentence 2	**Replace:** Copies of the investigator's annual report to the IRB/IEC and copies of the IRB/IEC continuance of approval must be submitted to Onyx or designee.	**With:** Copies of the investigator's annual report to the IRB/IEC and copies of the IRB/IEC continuance of approval must be submitted to **the Sponsor** or designee.	Administrative change

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 14.2 Compliance with Laws and Regulations, paragraph 5, sentence 1	**Replace:** Onyx will provide study sites with any Investigational New Drug (IND) safety reports, changes to the IB, and any safety updates.	**With:** **The Sponsor** will provide study sites with any Investigational New Drug (IND) safety reports, changes to the IB, and any safety updates.	Administrative change
Section: 14.3 Subject Confidentiality, paragraph 2, sentence 1	**Replace:** The investigator/institution will permit direct access to source data and documents by Onyx, its designee, the US FDA, and other applicable regulatory authorities.	**With:** The investigator/institution will permit direct access to source data and documents by **the Sponsor**, its designee, the US FDA, and other applicable regulatory authorities.	Administrative change
Section: 15.1 Protocol Amendments, sentence 1	**Replace:** Onyx will implement in writing any substantive changes to this protocol as a protocol amendment.	**With:** **The Sponsor** will implement in writing any substantive changes to this protocol as a protocol amendment.	Administrative change
Section: 15.1 Protocol Amendments, sentence 4	**Replace:** The investigator or designee must send a copy of the approval letter from the IRB/IEC, along with the revised ICF, to Onyx or designee.	**With:** The investigator or designee must send a copy of the approval letter from the IRB/IEC, along with the revised ICF, to **the Sponsor** or designee.	Administrative change
Section: 15.2 Study Termination	**Replace:** Onyx reserves the right to terminate the study at any time. The investigator or designee should notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Onyx or designee.	**With:** **The Sponsor** reserves the right to terminate the study at any time. The investigator or designee should notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to **the Sponsor** or designee.	Administrative change
Section: 15.3.1 Source Documents, sentence 3	**Replace:** These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical study.	**With:** These documents are designed to record all observations and other pertinent data for each subject **randomized** in this clinical study.	Clarified that source document recorded information for subjects who are randomized.

Section	Text in Protocol	Amended Text	Rationale for Change
Section: 15.4.1 Electronic Case Report Forms, paragraph 1, sentence 4	**Replace:** Onyx will supply the eCRF, which must be completed in English.	**With:** **The Sponsor** will supply the eCRF, which must be completed in English.	Administrative change
Section: 15.5 Publication Policy		**Add:** **Publication policy statement**	Added publication policy for consistency with Amgen template
Section: References		**Add:** **Amgen/Onyx. Carfilzomib Investigator's Brochure, version 16. 1. Onyx Therapeutics, Inc. (a wholly owned subsidiary of Onyx Pharmaceuticals, Inc., an Amgen Inc. subsidiary); 16 Jan 2016.**	Administrative change
Section: Appendix A Schedule of Assessments, footnote g, sentence 1	**Replace:** Questionnaires to be collected on Day 1 of Cycle 1, then every other cycle during treatment and every 12 weeks (every 84 days ± 4 days) until progression, or withdrawal of consent during LTFU.	**With:** Questionnaires to be collected on Day 1 of Cycle 1, then every **second** cycle **(Cycle 1, 3, 5, etc)** during treatment and every 12 weeks (every 84 days ± 4 days) until progression, or withdrawal of consent during LTFU.	Revised text for consistency within overall protocol
Section: Appendix B Schedule of Disease Assessments, footnote a	**Replace:** C1D1 (Screening values may be used if obtained within 7 days prior to C1D1). C2D1 and each cycle thereafter, EOT and during LTFU every 4 weeks, (every 28 days ± 4 days) until PD and/or start of a subsequent antimyeloma therapy. Refer to Section 10.2.	**With:** C1D1 **before treatment begins** (Screening values may be used if obtained within 7 days prior to C1D1) and **every 28 days (± 4 days)** thereafter, **at** EOT and during LTFU **if disease progression has not already been documented**, (every 28 days ± 4 days) until PD and/or start of a subsequent antimyeloma therapy. Refer to Section 10.2.	Revised text for consistency within overall protocol
Section: Appendix B Schedule of Disease Assessments, footnote d, sentence 2	**Replace:** All subjects will be followed for survival and disease status (if discontinuation is prior to	**With:** All subjects will be followed for survival and disease status (if discontinuation is prior to	Revised text for consistency within overall protocol

Section	Text in Protocol	Amended Text	Rationale for Change
	progression) by telephone contact or other method every 3 months (± 1 week) for until study closure.	progression) by telephone contact or other method every **12 weeks ± 28 days** for until study closure.	
Section: Appendix B Schedule of Disease Assessments, footnote g, sentence 1	**Replace:** Bone marrow samples: Bone marrow biopsy or aspirate slides will be obtained to confirm sCR or CR, or as clinically indicated.	**With:** Bone marrow samples: Bone marrow biopsy or **bone marrow** aspirate will be obtained to confirm sCR or CR, or as clinically indicated.	Revised text for consistency within overall protocol
Section: Appendix D Schedule of Study Assessments for the Pharmacokinetic Sparse Sampling and Intensive Pharmacokinetic & Pharmacokinetic Pharmacodynamic Sub-Study		**Add:** [a] **24 hours ± 2 hours** after **the end of the** Day 15 **infusion** [b] **48 hours ± 2 hours** after **the end of the** Day 15 **infusion** [c] **168 hours ± 2 hours** after **the end of the** Day 15 **infusion** [d] **24 hours ± 2 hours** after **the end of the** Day 16 **infusion** [e] **144 hours ± 2 hours** after **the end of the** Day 16 **infusion**	Added text to clarify timing of PD sampling
Section: Appendix G Summary of International Myeloma Working Group Uniform Response Criteria (IMWG-URC), sCR, bullet 3	**Replace:** Absence of clonal cells in bone marrow[c] by immunohistochemistry or immunofluorescence[c]	**With:** Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence[c]	Administrative change
Section: Appendix G Summary of International Myeloma Working Group Uniform Response Criteria (IMWG-URC), CR	**Replace:** CR[b]	**Add:** CR[b, h]	Added footnote h to clarify that for patients with sFLC measurable disease only, normal sFLC ratio is also required for CR in addition to the CR criteria listed in the

Section	Text in Protocol	Amended Text	Rationale for Change
			table.
Section: Appendix G Summary of International Myeloma Working Group Uniform Response Criteria (IMWG-URC), CR, bullet 3	**Replace:** • < 5% plasma cells in bone marrow[c]	**With:** • < 5% plasma cells in bone marrow	Footnote c is not applicable to this criterion.
Section: Appendix G Summary of International Myeloma Working Group Uniform Response Criteria (IMWG-URC), Stable disease	**Replace:** • Not meeting criteria for CR, VGPR, PR, or PD	**With:** Not meeting criteria for **sCR**, CR, VGPR, PR, **MR,** or PD	Added sCR and MR for completeness.
Section: Appendix G Summary of International Myeloma Working Group Uniform Response Criteria (IMWG-URC), footnote	Replace: Note: Patients with measurable disease in both serum (SPEP) and urine (UPEP) at study entry are required to meet response criteria in both UPEP and SPEP in order to qualify for a MR or better. Conversely, it should be noted criteria for PD only needs to be met, and confirmed, in 1 parameter. For patients without measurable protein on UPEP at baseline, UPEP will need to be repeated to confirm a response.	**With:** Note: For patients without measurable protein on UPEP at baseline, UPEP will need to be repeated to confirm a response **of VGPR or better**.	Removed the sentences 'Patients with measurable disease in both serum (SPEP) and urine (UPEP) at study entry are required to meet response criteria in both UPEP and SPEP in order to qualify for a MR or better. Conversely, it should be noted criteria for PD only needs to be met, and confirmed, in 1 parameter. ' since they are redundant to footnote a. Added 'of VGPR or better' to clarify UPEP will need to be repeated to confirm VGPR or better (not

Section	Text in Protocol	Amended Text	Rationale for Change
			needed for PR or MR) when UPEP is not measurable at baseline.
Section: Appendix G Summary of International Myeloma Working Group Uniform Response Criteria (IMWG-URC), footnote g	**Replace:** The plasmacytoma specifications for PD are based on Onyx's interpretation of the IMWG-URC and practical considerations for study execution.	**With:** The plasmacytoma specifications for PD are based on **the Sponsor's** interpretation of the IMWG-URC and practical considerations for study execution.	Administrative change
Section: Appendix G Summary of International Myeloma Working Group Uniform Response Criteria (IMWG-URC), footnote h		**Add:** **In patients with sFLC measurable disease only, normal sFLC ratio is required for CR.**	To clarify that for patients with sFLC measurable disease only, normal sFLC ratio is also required for CR in addition to the CR criteria listed in the table.
Section: Appendix J Patient Reported Outcomes, paragraph 1, sentence 1	CCI [redacted]		Revised text for clarification
Section: Appendix K Country Specific Pregnancy And Contraceptive Supplement, pregnancy prevention information, female subjects, paragraph 2	**Replace:** WOCBP must use a highly effective method of birth control during treatment and for an additional 30 days after the last dose of protocol-required therapies. Highly effective methods of birth control include: • Combined (estrogen and progestogen	**With:** WOCBP must use a highly effective method of birth control during treatment and for an additional 30 days after the last dose of protocol-required therapies. Highly effective methods of birth control **for female participants or their male partner** include:	Updated text to align with current carfilzomib core safety language

Section	Text in Protocol	Amended Text	Rationale for Change
	containing) hormonal contraception associated with inhibition of ovulation o Oral o Intravaginal o Transdermal • Progestogen-only hormonal contraception associated with inhibition of ovulation o Oral o Injectable o Implantable • Intrauterine device (IUD) • Intrauterine hormonal-releasing system (IUS) • Bilateral tubal occlusion	• Combined (estrogen and progestogen) hormonal **methods**: **pills, vaginal ring, or skin patch**. • **Single hormonal methods (progestogen to stop the release of the egg from the ovary)**: **pills, shots/injections,** implant**s (placed under the skin by a healthcare provider)** • Intrauterine device (IUD) • Intrauterine hormonal-releasing system (IUS) **surgery to tie both fallopian tubes (**bilateral tubal **ligation**/occlusion**)**	
Section: Appendix K Country Specific Pregnancy And Contraceptive Supplement, Male Subjects, paragraph 1	**Replace:** Male subjects whose partner is a WOCBP potential must use an acceptable method of effective birth control during treatment and for an additional 30 days after the last dose of protocol-required therapies. • Acceptable methods of birth control for male subjects include: • The female partner uses a: o Hormonal birth control method – Oral – Injectable – Transdermal – Implantable – Intravaginal o Intrauterine device (IUD)	**With:** **If the** male subjects **sole female** partner **has received medical confirmation that she is postmenopausal or she has had a permanent sterilization method (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or the male subject has had a vasectomy with medical confirmation of surgical success, or his sole female partner has had a bilateral tubal ligation/occlusion, additional contraceptive** method**s are not required during this study. Otherwise, if the male subject's female partner could become pregnant, the male must:** • Practice **true** sexual abstinence. (Refraining from heterosexual intercourse **during treatment and for an additional 90 days**	Updated the window for breastfeeding following the last dose of drug administration.

Section	Text in Protocol	Amended Text	Rationale for Change
	○ Intrauterine hormonal-releasing system (IUS) ○ The female partner has had a bilateral tubal occlusion • The male subject has had a vasectomy and has received a medical assessment of the surgical success. • Two barrier methods: One by each partner and at least one of the barrier methods must include spermicide ○ Male must use a condom ○ Female partner may use a diaphragm, cervical cap, or contraceptive sponge. (Note: The female condom cannot be used with a male condom). • Sexual abstinence: Refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Unacceptable birth control methods for female and male subjects during treatment with protocol-required therapies include: • Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus) • Spermicides only • Lactational amenorrhoea method (LAM) Female condom and male condom should not be	**following the last dose of study drug administration**. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and be the preferred and usual lifestyle of the subject.) **Or** • **Use a condom with spermicide during treatment and for an additional 90 days following the last dose of study drug administration. (Note a condom without spermicide is acceptable in countries where spermicide is not commercially available.)** **The female partner should also consider using an acceptable method of effective contraception such as:** • Intrauterine device (IUD) • Intrauterine hormonal-releasing system (IUS) • **Hormonal birth control method: pill, shots/injections, implants (placed under the skin by a healthcare provider), skin patches, or a vaginal ring** • Female barrier **method:** diaphragm, cervical cap, or contraceptive sponge (**a** female condom **is not an option because there is a** risk **of tearing when both partners use a** condom) • Male subjects **must not donate sperm** during treatment **and for an additional 90 days following** the **last dose** of study **drug administration.**	

Section	Text in Protocol	Amended Text	Rationale for Change
	used together	**Males** with **pregnant partners must practice true** sexual abstinence **or wear a condom during vaginal sex** to **prevent exposure to the embryo/fetus through semen.**	
Section: Appendix L Summary of Changes		**Add:** Updated Appendix L to include current summary of changes.	Administrative change

APPENDIX L SUMMARY OF CHANGES

Study CFZ014 was amended to include the following:

- Adverse events of pulmonary hypertension and TTP/HUS were added to the dose modification guidelines to be consistent with the guidance provided in the updated Investigator Brochure version 15, dated 26February 2015.
- Updated PK timepoints for intensive and sparse PK sampling as carfilzomib will be administered as an IV infusion over 30 minutes in the once-weekly arm and over 10 minutes in the twice-weekly arm. There is a mid-infusion PK timepoint (15 min after the start of infusion) that is only applicable for the carfilzomib once weekly arm, where carfilzomib is administered over 30 min. The protocol has been amended to state that this PK timepoint, 15 min after the start of infusion, is only required for the carfilzomib once weekly arm.
- Updated clinical information for carfilzomib to be consistent with IB Version 15.0.
- Updated text in the safety section of the protocol to accurately reflect Drug Safety requirements and how and to whom information is provided.
- Updated Medical Monitor information.

In addition, administrative updates have been made to enhance document clarity.

Changes made to this protocol are listed in the table below.

APPENDIX L SUMMARY OF CHANGES

Amendment 1.0:

Study CFZ014 was amended to include the following:

- Clarified that consent is required from subjects if additional blood samples will be collected for PK (sparse sampling) and for the intensive PK and PDn substudy.
- Clarified that dexamethasone should be administrated orally on Day 22 in Cycles 1−9.
- Clarified that dexamethasone will not be administered on Day 22 after Cycle 9.
- Clarified that events occurring prior to consent should be captured as medical history information.
- Clarified the timing of safety labs after Cycle 4.
- Clarified the timing of patient reported outcome questionnaires.

In addition, administrative updates have been made to enhance document clarity. Changes made to this protocol are listed in the table below.

Amendment 1.1:

Two additional administrative updates were made to correct errors found in Protocol CFZ 014 Amendment 1.0:

- The header on pages 100-109, Appendix F, of protocol CFZ014 read "Protocol 2011−003, Amendment 3" instead of reading as "Clinical Study Protocol No. CFZ014".
- Two hyperlinks in the footnote of Appendix A read "Error! Reference source not found" instead of linking to Sections 10.4.1 (Hematology) and 10.4.2 (Serum Chemistry), respectively.