CLINICAL STUDY PROTOCOL

Protocol Title:	An Open-label, Single-arm, Phase 3 Study of Carfilzomib in Combination With Dexamethasone in Subjects With Relapsed and Refractory Multiple Myeloma in China
Protocol Number: **NCT Number**	20140242 (CFZ005) **NCT03029234**
Name of Investigational Product:	Carfilzomib for Injection
Sponsor:	Onyx Therapeutics, Inc., an Amgen subsidiary One Amgen Center Drive Thousand Oaks, CA 91320 USA
Study Medical Monitors:	PPD [redacted], **MD PhD** One Amgen Center Drive Thousand Oaks, CA 91320 USA PPD [redacted]
Date of Original Protocol:	22 March 2013
Date of Protocol Amendment 1.0	10 May 2016
Date of Protocol Amendment 2.0	09 November 2016
Date of Protocol Amendment 3.0	**23 March 2018**
Date of Superseding Amendment 1.0	**12 April 2018**
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 Amgen, Inc.
Compliance Statement:	This study will be conducted in accordance with Protocol 20140242 (CFZ005), the relevant Onyx Therapeutics, Inc., an Amgen Inc. subsidiary, policies and procedures, the International Conference on Harmonisation (ICH), Good Clinical Practice (GCP) guidelines, and the applicable country and regional (local) regulatory requirements.

PROTOCOL ACCEPTANCE PAGE

Issue/Date: 20140242 (CFZ005)/Protocol Amendment 3.0/23 March 2018

Superseding Amendment 1.0 12/April 2018

I have read this protocol for Study 20140242 (CFZ005) entitled:

Title: An Open-label, Single-arm, Phase 3 Study of Carfilzomib in Combination with Dexamethasone in Subjects with Relapsed and Refractory Multiple Myeloma in China

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) while conducting this clinical investigation. Once signed, the original of this form should be detached from the protocol and returned to Onyx Therapeutics, Inc. or its designee (please retain a copy for your files).

SYNOPSIS

Name of sponsor/company:	**Onyx Therapeutics**, Inc. **(Subsidiary of Amgen, Inc.)**
Name of product:	Carfilzomib for Injection
Title of study and protocol number and phase:	An Open-label, Single-arm, Phase 3 Study of Carfilzomib in Combination with Dexamethasone in Subjects with Relapsed and Refractory Multiple Myeloma in China Protocol Number 20140242 (CFZ005)
Study objective(s):	**Primary Objective:** To evaluate the overall response rate (ORR) after at least 6 cycles of carfilzomib in combination with dexamethasone (Kd) in subjects with multiple myeloma who have previously received an alkylating agent or anthracycline, bortezomib and an immunomodulatory drug (IMiD), have relapsed after 2 or more lines of therapy, and are refractory to the most recently received therapy. Overall response rate (ORR) is defined as the proportion of subjects with the best response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR). The ORR will be determined using best overall response as assessed by the Independent Review Committee (IRC) per IMWG-URC (Durie, 2006; Rajkumar, 2011; **Kumar, 2016**). Secondary Objectives: • To evaluate ORR after at least 6 cycles of Kd using investigator assessment of response • To evaluate ORR after at least 12 cycles of Kd • To estimate clinical benefit rate (CBR) (the proportion of subjects with best response of minimal response, MR, or better) after at least 6 cycles and after at least 12 cycles • To estimate duration of response (DOR) • To estimate duration of clinical benefit (DCB) • To estimate progression-free survival (PFS) • To estimate overall survival (OS) • To estimate time to response (TTR) • To characterize pharmacokinetics (PK) in a subset of subjects ***Exploratory Endpoints:*** **Efficacy endpoints related to response and disease progression will be determined based on a validated computer algorithm (Onyx Response Computational Assessment; [ORCA]) are:** • **ORR after at least 6 cycles of Kd and after at least 12 cycles** • **CBR after at least 6 cycles and after at least 12 cycles** • **Duration of response** • **Duration of clinical benefit** • **Progression-free survival** • **Time to response**
Study design:	This Phase 3 study will be conducted as a multicenter, open-label, single-arm study in China. The study is designed to evaluate the efficacy and safety of carfilzomib at a dose of 20 mg/m^2, with step up to 27 mg/m^2 on Day 8 of Cycle 1, given in combination with low dose dexamethasone in

	subjects with relapsed and refractory multiple myeloma. Subjects must have received at least two prior regimens and are required to have previous treatment with an alkylating agent or anthracycline, bortezomib, and an IMiD. Subjects will receive a 30 minute infusion of intravenous (IV) carfilzomib on Days 1, 2, 8, 9, 15 and 16, and 20 mg oral dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, and 23 in 28-day Cycles. On Cycle 1, Days 1 and 2, subjects will receive carfilzomib 20 mg/m^2. If tolerated (defined as absence of any treatment-related adverse event [AE] requiring dose reduction, delay, or the dose to be held), the dose will be escalated to 27 mg/m^2 on Cycle 1 Day 8 and all subsequent doses. Study treatments will be administered until disease progression, unacceptable toxicity, or discontinuation of study treatment for any other reason, whichever occurs first. Dose reductions of carfilzomib and dexamethasone will be permitted per protocol guidelines. The enrollment period is anticipated to be approximately 16 months. Upon discontinuation of study treatment for reasons other than disease progression, subjects will be followed every 4 weeks until disease progression, or withdrawal of consent. After disease progression, each subject will be followed every 3 months (± 2 weeks) for OS for up to 3 years from the start of their study treatment, or until the subject has withdrawn from further participation, is lost to follow-up, has died, or the sponsor makes a decision to close the study. Pharmacokinetic analyses will be characterized in a subset of 15 subjects at selected sites. Subjects who do not complete all PK assessments will be replaced.
Number of investigational sites:	Approximately 15 sites in China will participate in this study
Planned number of subjects:	Approximately 120 subjects with relapsed and refractory multiple myeloma are planned for enrollment in this study
Sample size justification:	This study will enroll approximately 120 subjects with relapsed and refractory multiple myeloma to evaluate both efficacy and safety of carfilzomib (K) in combination with dexamethasone (d). CCI [redacted] CCI
Study population:	Subjects with relapsed and refractory multiple myeloma with disease that is measurable by serum and/or urine protein electrophoresis, and/or serum free-light chain (SFLC) assay may participate in this study.
Test product, dose, and mode of administration:	Subjects will receive IV carfilzomib on Days 1, 2, 8, 9, 15 and 16, and dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, and 23 in 28-day cycles. On Cycle 1, Days 1 and 2, subjects will receive carfilzomib 20 mg/m^2. If Cycle 1, Day 1 and 2 doses are administered and well tolerated (defined as absence of any treatment-related AE requiring dose reduction, delay, or the dose to be held), the dose will be escalated to 27 mg/m^2 for all subsequent doses, beginning with Cycle 1 Day 8. Dexamethasone will be given at 20 mg on all dosing days in each cycle.

Reference therapy, dose, and mode of administration:	Not applicable
Treatment regimen(s):	Carfilzomib and dexamethasone treatments will be administered in 28-day cycles until disease progression, unacceptable toxicity, or discontinuation from study treatment for any other reason, whichever occurs first.
Inclusion criteria:	Inclusion Criteria: 1. Multiple myeloma 2. Subjects must have measurable disease, defined as one or more of the following: a. Serum M-protein ≥ 1 g/dL b. Urine M-protein ≥ 200 mg/24 hours c. In subjects without measurable serum or urine M-protein, SFLC > 100 mg/L (involved light chain) and an abnormal κ/λ ratio 3. Subjects must have been responsive (i.e., achieved a minimal response [MR] or better) to at least one of their prior treatment regimens 4. Refractory to the most recently received therapy. Refractory disease defined as ≤ 25% response to, or progressing during therapy or within 60 days after last therapy 5. Subjects must have received ≥ 2 prior regimens. Induction therapy and stem cell transplant (± maintenance) will be considered as 1 regimen as described in Section 9.1.2 6. Subjects must have received prior treatment with bortezomib and an IMiD 7. Subjects must have received an alkylating agent or anthracycline alone or in combination with other myeloma treatments (this may include high-dose melphalan as part of the conditioning regimen prior to a stem cell transplant) 8. Males and females ≥ 18 years of age 9. Life expectancy of more than 3 months 10. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0–2 11. Adequate hepatic function, with bilirubin < 2.0 times the upper limit of normal (ULN), and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3.0 times the ULN 12. Absolute neutrophil count (ANC) ≥ 1,000/mm3, hemoglobin ≥ 8.0 g/dL, and platelet count ≥ 50,000/mm3 • Subjects should not have received platelet transfusions for at least 1 week prior to obtaining the screening platelet count • Screening ANC should be independent of granulocyte colony stimulating factor (G-CSF) or granulocyte macrophage colony stimulating factor (GM-CSF) support for ≥ 1 week and pegylated G-CSF for ≥ 2 weeks • Use of erythropoietic stimulating factors and red blood cell (RBC) transfusions per institutional guidelines is allowed; however, most recent RBC transfusion may not have been done within 7 days prior to obtaining screening hemoglobin

	13. Calculated or measured creatinine clearance (CrCl) of ≥ 30 mL/min. Calculated CrCl should be performed by using a widely accepted equation (e.g., the Cockcroft and Gault equation): ([140 – Age] × Mass [kg] / [72 × Creatinine mg/dL]). Multiply the result by 0.85 if the subject is female. 14. Left ventricular ejection fraction (LVEF) ≥ 40%; 2-dimensional transthoracic echocardiogram (ECHO) is the preferred method of evaluation; multiple gated acquisition scan (MUGA) is acceptable if ECHO is not available 15. Written informed consent in accordance with national, local, and institutional guidelines 16. Female subjects of child-bearing potential (FCBP) must have a negative serum pregnancy test within 7 days prior to first dose of carfilzomib and agree to use an effective method of contraception during and for 30 days following last dose of carfilzomib. This protocol defines a FCBP as a sexually mature woman who: 1) has not undergone a hysterectomy, bilateral oophorectomy, or bilateral salpingectomy, or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months) 17. Male subjects must use an effective barrier method of contraception during the study and for 90 days following the last dose of carfilzomib if sexually active with a FCBP. Male subjects must not donate sperm during treatment and for an additional 90 days after last dose of carfilzomib. Male subjects with pregnant partners must practice sexual abstinence or use a condom during vaginal sex
Exclusion criteria:	**Exclusion Criteria:** 1. Waldenström's macroglobulinemia or immunoglobulin M (IgM) multiple myeloma 2. Subjects who failed to achieve at least a confirmed MR on any of their prior regimens
	3. Subjects with non-secretory multiple myeloma, defined as < 1 g/dL M-protein in serum and < 200 mg/24 hour M-protein in urine, and SFLC ≤ 100 mg/L (involved light chain) 4. Glucocorticoid therapy (prednisone > 10 mg/day or equivalent) within 3 weeks prior to Cycle 1 Day 1 5. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) 6. Plasma cell leukemia (> 2.0×10^9/L circulating plasma cells by standard differential) 7. Chemotherapy with approved or investigative anticancer therapeutics including steroid therapy within the 3 weeks prior to Cycle 1 Day 1 8. Radiation therapy or immunotherapy in the 4 weeks prior to Cycle 1 Day 1; localized radiation therapy within 1 week prior to Cycle 1 Day 1 9. Participation in an investigational therapeutic study within 3 weeks or within 5 drug half-lives ($T_{½}$) prior to Cycle 1 Day 1, whichever time is greater 10. Prior treatment with carfilzomib 11. Major surgery within 3 weeks before Cycle 1 Day 1

	12. Congestive heart failure (New York Heart Association Class III to IV), symptomatic ischemia, conduction abnormalities, uncontrolled by conventional intervention.**Subjects cannot have experienced a** myocardial infarction within 6 months prior to Cycle 1 Day 1 13. Uncontrolled hypertension (a sustained systolic blood pressure > 140 mmHg and/or diastolic BP > 90 mmHg) 14. Acute active infection requiring systemic (**either intravenous or oral**) antibiotics, antivirals, or antifungals; **the** treatment **must be completed at least** 2 weeks prior to Cycle 1 Day 1 15. Known HIV seropositive, hepatitis C infection, and/or hepatitis B (except for patients with hepatitis B surface antigen or core antibody receiving and responding to antiviral therapy directed at hepatitis B: these patients are allowed; **Note: patients who are HepB surface antigen negative at screening, or who are receiving interferon alfa-2a (IFN) or Peginterferon alfa-2a (PEG-IFN) and have Hepatitis B Virus (HBV) DNA < 2000 International Units (IU) at screening, or, are receiving a nucleos(t)ide analog and have HBV DNA below Lower Limit of Normal (LLN) at screening are eligible** 16. **N**on-hematologic malignancy within the past 3 years except: a. Adequately treated basal cell or squamous cell skin cancer, b. Carcinoma in situ of the cervix, or c. Prostate cancer < Gleason Score 6 with stable prostate-specific antigen 17. Subjects with treatment-related myelodysplastic syndrome 18. Significant neuropathy (Grade 3, 4, or Grade 2 with pain) at the time of baseline evaluation 19. Subjects in whom the required program of fluid hydration is contraindicated, e.g., due to pre-existing pulmonary, cardiac, or renal impairment 20. Subjects with known or suspected amyloidosis 21. Subjects with pleural effusions requiring thoracentesis 22. Subjects with ascites requiring paracentesis 23. Any clinically significant medical disease or condition that, in the investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent 24. Female subjects who are pregnant or lactating, or are planning to become pregnant during treatment and for an additional 30 days after discontinuing carfilzomib 25. Serious psychiatric or medical conditions that could interfere with treatment
Overview of treatment and assessments:	Treatments will be administered in 28 day cycles. Details are provided in Appendix A (Schedule of Assessments).

Criteria for evaluation:	
Efficacy variables:	Disease response will be assessed per investigator every 4 weeks according to the International Myeloma Working Group – Uniform Response Criteria (IMWG-URC) (Durie, 2006; Rajkumar, 2011; **Kumar, 2016**; MR will be assessed as per ;**Kumar, 2016**). An IRC will assess best response after at least 6 and after at least 12 cycles of Kd, from which ORR, CBR, DOR, DCB, TTR, and PFS will also be determined. Subjects will be followed every 4 weeks for disease progression. After disease progression, subjects will be followed every 3 months (± 2 weeks) for OS for up to 3 years from the start of their study treatment.
Safety variables:	The safety and tolerability of carfilzomib will be assessed using the following measures: Incidence of AEs graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 4.03), blood counts, serum chemistries, and vital signs.
Pharmacokinetics:	Pharmacokinetics of carfilzomib will be assessed on Cycle 1 Day 1 and Cycle 2 Day 1 using noncompartmental methods. Following PK parameters will be determined: maximum observed plasma concentration (C_{max}), area under the plasma concentration curve up to the last measurable concentration (AUC_{last}), area under the plasma concentration curve extrapolated to infinity ($AUC_{0\text{-}inf}$), time to maximum concentration (T_{max}), terminal elimination half half-life ($T_{½}$), total plasma clearance (CL), volume of distribution ([V_{area}] and volume of distribution at steady state [V_{ss}]), and mean residence time (MRT).
Statistical methods and analyses:	All subjects who receive at least 1 dose of study treatment will be considered evaluable for both the efficacy and safety analyses (Safety Population). For the primary efficacy objective, an estimate of the ORR after at least 6 cycles of Kd, as assessed by the IRC, and its associated 2-sided 95% exact binomial confidence interval (CI) will be determined. Each subject's best overall response after at least 6 cycles will be determined by IRC assessment per IMWG-URC (Durie, 2006; Rajkumar, 2011; **Kumar, 2016**). Additionally, ORR based on investigator assessment of response after at least 6 cycles will be determined. Overall response rate after at least 12 cycles of Kd and the CBR will be determined based on both IRC and investigators response assessment, along with the associated 2-sided 95% exact binomial CI. **For the exploratory objectives, a validated computer algorithm (Onyx Response Computational Assessment [ORCA]) will be used to assess response and disease progression.** Time to event endpoints will include: • Duration of response, defined as the time from first evidence of PR or better to disease progression or death due to any cause. • Duration of clinical benefit, defined as the time from first evidence of MR or better to disease progression or death due to any cause. • Progression-free survival, defined as the time from first dose to the earlier of disease progression or death due to any cause. • Overall survival, defined as the time from the first dose to the date of death (due to any cause).

	The right-censored rule for time to event endpoints is described in Section 12.5.1.2. Analyses for time-to-events endpoints (DOR, DCB, PFS, and OS) will be performed using the Kaplan-Meier method. Medians and other quartiles for each time-to-event endpoint will be estimated in addition to the corresponding 2-sided 95% CIs. Time to response, defined as the time of start of study treatment to first confirmed response (PR or greater), will be assessed using descriptive statistics. Extent of exposure to the study treatment will be summarized using descriptive statistics. The number and percentage of subjects experiencing 1 or more AEs will be summarized, relationship of AE to study treatment and severity. Results of laboratory parameters and vital signs will be summarized. Laboratory parameters will be summarized using descriptive statistics, by post dose shifts relative to baseline, and a summary of the incidence of clinically significant abnormal values for key laboratory analytes. Laboratory values will be classified for severity using NCI-CTCAE, version 4.03. Vital signs will be summarized by changes from baseline values using descriptive statistics. The incidence and severity of adverse events including congestive heart failure (CHF), myocardial infarction, acute kidney injury, adult respiratory distress syndrome, pulmonary hypertension, dyspnea, hypertension, thromboembolic events, thrombocytopenia, hepatic toxicity, and thrombotic thrombocytopenia purpura/hemolytic uremic syndrome will be determined. Pharmacokinetic data analysis set will include all subjects who received at least 1 dose of carfilzomib and have adequate carfilzomib plasma concentration versus time data for the estimation of PK parameters by a noncompartmental analysis. Individual and mean plasma concentration versus time data will be tabulated and plotted for the subjects participating in the PK portion of the study. All PK parameters will be computed using actual elapsed time calculated relative to the start of dose administration.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
2-D	2-dimensional
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
$AUC_{0\text{-}inf}$	area under the curve extrapolated to infinity
$AUC_{0\text{-}last}$	area under the curve, from time 0 to the last concentration measured
AUC_{last}	area under the plasma concentration curve up to the last measurable concentration
BSA	body surface area
BUN	blood urea nitrogen
CBR	clinical benefit rate
CCSI	Company Core Safety Information
CFZ	carfilzomib [brand name: Kyprolis® (carfilzomib) for Injection
CHF	congestive heart failure
CI	confidence interval
CL	total plasma clearance
C_{max}	maximum observed plasma concentration
CR	complete response
CRF	case report form
CrCl	creatinine clearance
CT	computed tomography
CYP3A4/5	cytochrome P450 3A4/5
DOR	duration of response
DCB	duration of clinical benefit
EBMT	European Group for Blood and Marrow Transplantation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECHO	Echocardiogram
EDC	Electronic Data Capture
EOT	End of Treatment
EW	early withdrawal
FCBP	female of child-bearing potential
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization

Abbreviation	Definition
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GM-CSF	granulocyte macrophage-colony stimulating factor
H_A	alternative hypothesis
HBV	**Hepatitis B virus**
H_0	null hypothesis
HIV	human immunodeficiency virus
Hr	hour(s)
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	**Interferon alfa-2a**
IgM	immunoglobulin M
IMiD	immunomodulatory drug (thalidomide or lenalidomide)
IMWG	International Myeloma Working Group
IMWG-URC	International Myeloma Working Group Uniform Response Criteria
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IRC	Independent Review Committee
IPIM	Investigational Product Instruction Manual
IU	**International Units**
IV	intravenous(ly)
Kd	carfilzomib in combination with dexamethasone
LDH	lactate dehydrogenase
LFT	liver function test
LLN	**Lower limit of normal**
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MR	minimal response
MRI	Magnetic resonance imaging
MRT	mean residence time
MUGA	multiple gated acquisition scan
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
ORCA	**Onyx Response Computational Assessment**

Abbreviation	Definition
ORR	overall response rate
ORR6-IRC	Overall response rate after at least 6 cycles as determined by the IRC
OS	overall survival
PEG-IFN	**Peginterferon alfa-2a**
PD	progressive disease
PDn	pharmacodynamic(s)
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PO	orally, by mouth, *per os*
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PT	prothrombin time
aPTT	**activated** partial thromboplastin time
PTT	partial thromboplastin time
QT interval	QT interval is measured from the beginning of the QRS complex to the end of the T wave, representing the duration of ventricular electrical activity
QTc	corrected QT interval
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCR	stringent complete response
SFLC	serum-free light chain
SIFE	serum immunofixation electrophoresis
SPEP	serum protein electrophoresis
$T_{½}$	terminal elimination half-life or half-life
TLS	tumor lysis syndrome
T_{max}	time to maximum plasma concentration
TTP/HUS	thrombotic thrombocytopenic purpura / haemolytic uraemic syndrome
TTR	time to response
UIFE	urine immunofixation electrophoresis
ULN	upper limit of the normal
UPEP	urine protein electrophoresis
US	United States
USP	United States Pharmacopeia

Abbreviation	Definition
V_{area}	volume of distribution
V_{ss}	volume of distribution at steady state
VGPR	very good partial response
WBC	white blood cell

1 BACKGROUND INFORMATION

1.1 MULTIPLE MYELOMA

Multiple myeloma, a clonal neoplastic proliferation of plasma cells, is the second most common hematologic malignancy and is responsible for approximately 72,000 annual deaths worldwide (Ferlay 2010). There are an estimated 4,000 multiple myeloma deaths per year in China (Ferlay 2008), 11,000 deaths per year in the United States (US) and more than 19,000 deaths per year in Europe (American Cancer Society 2005; Boyle 2005). Multiple myeloma is characterized by anemia, bone destruction, monoclonal gammopathy, renal failure, hypercalcemia, and increased susceptibility to infections. Current treatment options in China commonly include combination chemotherapy with regimens using melphalan, bortezomib, and thalidomide (an immunomodulatory drug [IMiD]) with and without corticosteroids such as dexamethasone or prednisone. Eligible subjects 65 to 70 years old or younger frequently undergo induction therapy with myeloablative chemotherapy or radiation followed by autologous stem cell transplantation. Although improvements in progression-free survival (PFS) and overall survival (OS) have occurred in the past 5 years, even with the best available approved agents, essentially all patients eventually relapse. Median survival from the time of diagnosis is approximately 6 years (Kumar et al, 2014).

1.2 PROTEASOME BACKGROUND

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

1.3 CARFILZOMIB

1.3.1 *Preclinical Background*

Carfilzomib (formerly known as PX-171) is a tetrapeptide epoxyketone-based inhibitor of the chymotrypsin-like activity of the 20S proteasome. Carfilzomib, is structurally and mechanistically different from the dipeptide boronic acid proteasome inhibitor bortezomib.

Compared to bortezomib, carfilzomib showed less off-target activity when measured against a broad panel of proteases including metallo-, aspartyl-, and serine proteases. Bortezomib 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 preclinical studies comparing carfilzomib with bortezomib.

Based upon in vitro and in vivo studies, it is anticipated that a more intense and sustained proteasome inhibition can be achieved with carfilzomib relative to bortezomib, resulting in enhanced antitumor activity. Continuous 72-hour exposure to carfilzomib was associated with potent cytotoxic and pro-apoptotic activity across a broad panel of tumor-derived cell lines in culture (Demo 2007). Incubation of hematologic tumor cell lines with carfilzomib for as little as 1 hour led to rapid inhibition of proteasome activity followed by accumulation of polyubiquitinated proteins and induction of apoptotic cell death. Carfilzomib was also cytotoxic in bortezomib-resistant tumor cell lines (Suzuki 2011; Kuhn 2007).

Preclinical studies in rats and monkeys have been performed administering carfilzomib intravenously (IV) for 5 consecutive days followed by 9 days of rest for 2 cycles. Proteasome inhibition of more than 80% was achieved, suggesting that high-level inhibition of the proteasome with the epoxyketone class is possible, affording new opportunities to escalate dose to optimize antitumor effects (Onyx data on file, and Yang 2011). This finding was in contrast to preclinical testing with the boronate class of proteasome inhibitors that prohibited daily dosing due to substantial morbidity and mortality. Carfilzomib has also been administered to rats and monkeys for 6 and 9 months, respectively (once daily dosing for 2 consecutive days for 3 weeks on a 28-day cycle). In this setting, carfilzomib was well tolerated at doses resulting in more than 80% proteasome inhibition, with no behavioral or histological evidence of peripheral neuropathy and no neutropenia (Onyx data on file and Carfilzomib Investigator's Brochure [Carfilzomib IB]). In contrast, rats treated with bortezomib at doses causing 80% proteasome inhibition develop peripheral neuropathy (Meregalli et al, 2010).

1.3.2 *Clinical Background*

Carfilzomib entered clinical studies in September 2005.

On 20 July 2012, Kyprolis® (carfilzomib) for Injection, hereafter referred to as carfilzomib, was approved under the United States Food and Drug Administration's (US FDA) accelerated approval program for the treatment of patients with multiple myeloma who have received at least 2 prior therapies, including bortezomib and an 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 Phase 2 Study PX-171-003-A1 study (Siegel, 2012).

As of 19 July 2017, Carfilzomib for Injection has been approved in 31 countries/regions worldwide. It is estimated that the number of patients exposed to carfilzomib from launch in July 2012 through 19 July 2017 was 63,260 in the postmarketing setting. For a summary of all Onyx-sponsored studies along with the Ono-sponsored clinical program in Japan, please refer to the Carfilzomib IB for detailed information.

1.4 DOSE RATIONALE

The dose schedule selected for this study (20/27 mg/m^2) is based on the regimen that has been widely studied in patients with relapsed and refractory multiple myeloma. Evaluation of this dosing includes a pivotal single-arm Phase 2 Study PX-171-003A1 with 266 subjects that demonstrated efficacy and safety (Siegel, 2012) (see Section 1.3.2). Here, the dosing schedule is slightly modified to step up carfilzomib from 20 to 27 mg/m^2 on Cycle 1 Day 8 instead of Cycle 2 Day 1, to specify infusion over 30 minutes, and to include co-administration of low dose dexamethasone orally at 40 mg weekly (Papadopoulos, 2015).

The step up of carfilzomib on Cycle 1 Day 8, has been approved by the US FDA for the treatment of multiple myeloma in patients who have received at least 2 prior therapies, including bortezomib and an IMiD, and have demonstrated disease progression on or within 60 days of completion of the last therapy (Kyprolis Prescribing Information). **The carfilzomib dosing schedule used in this study is used in the ongoing global phase 3 study, "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 20140355).

1.5 STUDY RATIONALE

Clinical data to date demonstrate that carfilzomib has clinical activity in patients with multiple myeloma.

Of note, study PX-171-003A1 was a multicenter study conducted in the US and Canada which evaluated the efficacy and safety of carfilzomib monotherapy in 266 subjects with relapsed and refractory multiple myeloma (Siegel, 2012). Subjects were required to have had treatment with ≥ 2 prior lines of therapy, including bortezomib and an IMiD (either thalidomide or lenalidomide), a response to at least one prior line, and disease that was refractory to the most recent therapy. The median number of prior regimens for this study population was 5 (range: 1-20) and the median time from diagnosis of multiple myeloma until enrollment in Study 003A1 was 5.4 years.

Subjects received IV carfilzomib on Days 1, 2, 8, 9, 15, and 16 of 28-day cycles at a dose of 20 mg/m^2 for Cycle 1, increased to 27 mg/m^2 for subsequent treatment cycles. Subjects received premedication with 4 mg dexamethasone through Cycle 1, and carfilzomib was infused over 2 to 10 minutes.

The primary endpoint was overall response rate (ORR). Overall response rate was defined as stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) according to the International Myeloma Working Group - Uniform Response Criteria (IMWG-URC) (Durie, 2006).

The ORR with carfilzomib monotherapy in study PX-171-003A1 was 22.9% (95% confidence interval [CI]: 18.0, 28.5) and the proportion of patients who achieved a minimal response (MR) or better (i.e., clinical benefit rate [CBR]) was 35.7% (95% CI: 30.0, 41.8). Importantly, the median duration of response (DOR) was 7.8 months (95% CI: 5.6, 9.2) and the median duration of clinical benefit (DCB) was 8.3 months (95% CI: 6.5, 9.7), demonstrating a robust and durable response to carfilzomib therapy. Median OS was 15.4 months (95% CI: 12.5, 19.0).

Carfilzomib treatment was generally well tolerated by this population of patients with advanced and heavily pre-treated multiple myeloma.

This Phase 3 study (20140242 [CFZ005]), was originally designed to employ the same exact treatment regimen as that in study PX-171-003A1 to determine the magnitude and duration of response in relapsed and refractory multiple myeloma patients in China. However, multiple myeloma treatment has evolved and the protocol has been modified to evaluate carfilzomib given in accordance with current practice. Specifically: (a) carfilzomib will be given in combination with low dose dexamethasone (Kd), (b) carfilzomib will be infused over 30 minutes, and (c) after initial treatment with 20 mg/m^2 carfilzomib on Cycle 1 Days 1 and 2, carfilzomib will be raised to therapeutic dosing of 27 mg/m^2 beginning on Cycle 1 Day 8, in agreement with US FDA labelling.

Using a proteasome inhibitor in combination with low dose dexamethasone is a common clinical practice, and is anticipated to confer improved efficacy and tolerability as compared to single agent carfilzomib (Lendvai, 2014; Papadopoulos, 2015). In China, bortezomib, a proteasome inhibitor introduced before carfilzomib, is recommended for use in combination with dexamethasone for multiple myeloma patients (Guidelines on the Diagnosis and Management of Multiple Myeloma in China, 2013). Though carfilzomib is generally very well-tolerated, patients can experience dyspnea and fever during treatment. Tolerance improves when carfilzomib is infused over 30 minutes, rather than 2 to 10 minutes (Kortuem and Stewart, 2013). Thirty-minute infusions of carfilzomib yield equivalent proteasome inhibition as do shorter infusions (Papadopoulos, 2015), and will be used here.

To facilitate evaluation of response data, Multiple Myeloma disease response is assessed following the International Myeloma Working Group Uniform Response Criteria (IMWG-URC; Durie, 2006, Rajkumar, 2011; Kumar, 2016). The primary endpoint in this trial is ORR after each subject has had the opportunity to receive at least 6 cycles of therapy, with response as determined by review of subject data by an Independent Review Committee, following the IMWG-URC. CCI [redacted]

In summary, carfilzomib 20/27 mg/m^2 is an approved regimen for relapsed and refractory multiple myeloma in the United States. Its activity has been demonstrated in the PX-171-003-A1 study (n = 266) with an ORR of 23%. Its safety profile has been characterized across phase 1/2 studies (n = 598), and an estimated 20,000 patients have been treated with this regimen in the post-marketing setting. The ORR of Kd is estimated to be approximately 30% in relapsed and refractory multiple myeloma patients. Here, carfilzomib 20/27 mg/m^2 in combination with low dose dexamethasone will be evaluated in China.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objective of this study is to evaluate the ORR after at least 6 cycles of Kd in subjects with multiple myeloma who have previously received an alkylating agent or anthracycline, bortezomib and an IMiD, have relapsed after 2 or more lines of therapy, and are refractory to the most recently received therapy. Overall response rate is defined as the proportion of subjects with a best overall response of sCR, CR, VGPR, or PR. The ORR will be determined using best overall response as assessed by the Independent Review Committee (IRC) per IMWG-URC (Durie, 2006; Rajkumar, 2011; **Kumar, 2016**).

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are:

- To evaluate ORR after at least 6 cycles of Kd using investigator assessment of response
- To evaluate ORR after at least 12 cycles of Kd
- To estimate Clinical Benefit Rate (CBR, defined as the proportion of subjects with a best overall response of MR or better) after at least 6 cycles and after at least 12 cycles

- To estimate Duration of Response (DOR)
- To estimate Duration of Clinical Benefit (DCB)
- To estimate Progression Free Survival (PFS)
- To estimate Overall Survival (OS)
- To estimate time to response (TTR)
- To characterize pharmacokinetics (PK) in a subset of subjects

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives of this study are:

- **To evaluate ORR after at least 6 cycles of Kd using ORCA assessment of response**
- **To evaluate ORR after at least 12 cycles of Kd using ORCA assessment of response**
- **To estimate CBR after at least 6 and after at least 12 cycles of Kd using ORCA**
- **To estimate DOR, DCB, PFS and TTR using ORCA**

3 STUDY DESIGN

This Phase 3 study will be conducted as a multicenter, open-label, single-arm study at approximately 15 centers in China. The study is designed to evaluate the efficacy of carfilzomib in combination with low dose dexamethasone in subjects with multiple myeloma who have previously received an alkylating agent or anthracycline, bortezomib and an IMiD, relapsed following 2 or more therapies, and are refractory to the most recently received therapy.

Treatment cycles are every 28 days. In Cycle 1, subjects will receive carfilzomib 20 mg/m^2 infusion on Days 1 and 2. If well tolerated (defined as absence of any treatment-related adverse event [AE] requiring dose reduction, delay, or the dose to be held in Cycle 1 [see Section 8.2]), the dose will escalate to 27 mg/m^2 to be given Cycle 1 Day 8 and onward.

Dexamethasone 20 mg will be given to subjects on Days 1, 2, 8, 9, 15, 16, 22, and 23 on a schedule of every 28 days. On days when carfilzomib is administered, the dexamethasone is to be given 30 minutes to 4 hours prior to carfilzomib.

Subjects will receive treatment until disease progression, unacceptable toxicity, **initiation of new anti-myeloma therapy,** or discontinuation of study treatment for any other reason**,** whichever occurs first.

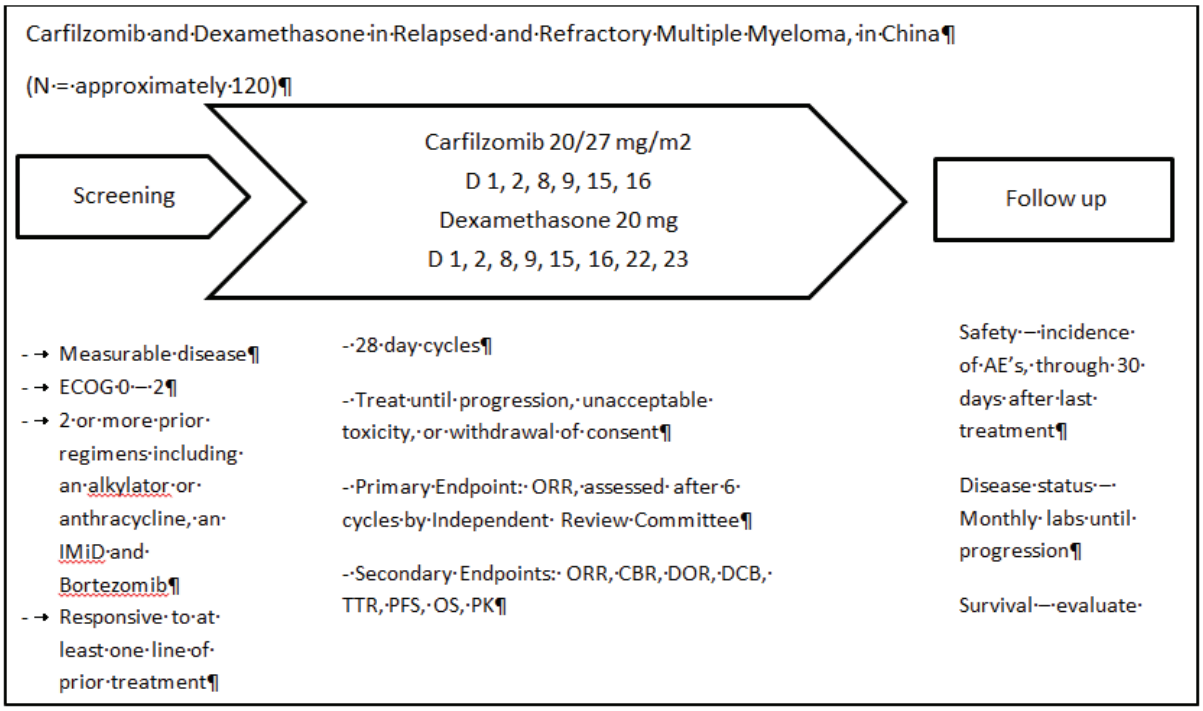
Dose reductions of carfilzomib and dexamethasone will be permitted per protocol guidelines (see Section 8.2).

Pharmacokinetic analyses will be characterized in a subset of approximately 15 subjects at selected sites. Subjects who do not provide all required PK assessments at Cycle 1 Day 1 and Cycle 2 Day 1 will be replaced.

3.1 TYPE/DESIGN OF STUDY

The design schema for this open-label, single-arm study is presented in Figure 1.

Figure 1: Study Design And Treatment Schema



Abbreviations: CBR = clinical benefit rate; DOR = duration of response; DCB = duration of clinical benefit; ECOG = Eastern Cooperative Oncology Group Performance Status; IMiD = immunomodulatory drug; N = number; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); TTR = Time to Treatment Response

3.2 MINIMIZING BIAS

3.2.1 *Randomization*

Not applicable; this is a single-arm study.

3.2.2 *Blinding*

Not applicable, this is an open-label study.

3.3 END OF STUDY

Primary Completion: The time when all subjects have had the opportunity to complete at least 6 cycles of Kd, or have withdrawn from study treatment.

End of Study: Three years after last subject initiates treatment or when all subjects have withdrawn consent or died, whichever occurs first.

4 SUBJECT SELECTION

A total of approximately 120 subjects are planned for this study.

4.1 INCLUSION CRITERIA

Subjects must meet all of the following inclusion criteria to be eligible for study enrollment.

1. Multiple myeloma
2. Subjects must have measurable disease, defined as 1 or more of the following:
   a. Serum M-protein ≥ 1 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 κ/λ ratio
3. Subjects must have been responsive (i.e., achieved a MR or better) to at least 1 of their prior treatment regimens
4. Refractory to the most recently received therapy. Refractory disease defined as ≤ 25% response to, or progressing during therapy or within 60 days after last therapy
5. Subjects must have received ≥ 2 prior regimens. Induction therapy and stem cell transplant (± maintenance) will be considered as 1 regimen **(as described in Section 9.1.2)**

6. Subjects must have received prior treatment with bortezomib and an IMiD
7. Subjects must have received an alkylating agent or anthracycline alone or in combination with other myeloma treatments (this may include high-dose melphalan as part of the conditioning regimen prior to stem cell transplant)
8. Males and females ≥ 18 years of age
9. Life expectancy of more than 3 months
10. Eastern Cooperative Oncology Group (ECOG) performance status of 0 – 2
11. Adequate hepatic function, with bilirubin < 2.0 times the upper limit of normal (ULN), and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3.0 times the ULN
12. Absolute neutrophil count (ANC) ≥ 1,000/mm^3, hemoglobin ≥ 8.0 g/dL, and platelet count ≥ 50,000/mm^3
    - Subjects should not have received platelet transfusions for at least 1 week prior to obtaining the screening platelet count
    - Screening ANC should be independent of granulocyte-colony stimulating factor (G-CSF) or granulocyte macrophage-colony stimulating factor (GM-CSF) support for ≥ 1 week and pegylated G-CSF for ≥ 2 weeks
    - Use of erythropoietic stimulating factors and red blood cell (RBC) transfusions per institutional guidelines is allowed; however, most recent RBC transfusion may not have been done within 7 days prior to obtaining screening hemoglobin
13. Calculated or measured creatinine clearance (CrCl) of ≥ 30 mL/min. Calculated CrCl should be performed by using a widely accepted equation (e.g., the Cockcroft and Gault formula: [(140 – Age) × Mass (kg) / (72 × Creatinine mg/dL)]; multiply result by 0.85 if female)
14. Left ventricular ejection fraction (LVEF) ≥ 40%; 2-dimentional (2-D) transthoracic echocardiogram (ECHO) is the preferred method of evaluation; multiple gated acquisition scan (MUGA) is acceptable if ECHO is not available
15. Written informed consent in accordance with national, local, and institutional guidelines
16. Female subjects of child-bearing potential (FCBP) must have a negative serum pregnancy test within 7 days prior to first dose of carfilzomib and agree to use an effective method of contraception during and for 30 days following last dose of carfilzomib (more frequent pregnancy tests may be conducted if required per local regulations). This protocol defines a FCBP as a sexually mature woman who: 1) has not undergone a hysterectomy, bilateral oophorectomy, or bilateral salpingectomy, or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

17. Male subjects must use an effective barrier method of contraception during the study and for 90 days following the last dose of carfilzomib if sexually active with a FCBP. Male subjects must not donate sperm during treatment and for an additional 90 days after last dose of carfilzomib. Male subjects with pregnant partners must practice sexual abstinence or use a condom during vaginal sex.

4.2 EXCLUSION CRITERIA

Subjects meeting any of the following exclusion criteria will not be eligible to enroll in this study.

1. Waldenström's macroglobulinemia or immunoglobulin M (IgM) multiple myeloma
2. Subjects who failed to achieve at least a confirmed MR on any of their prior regimens
3. Subjects with non-secretory multiple myeloma, defined as < 1 g/dL M-protein in serum and < 200 mg/**24-hour** M-protein in urine and SFLC ≤ 100 mg/L (involved light chain)
4. Glucocorticoid therapy (prednisone > 10 mg/day or equivalent) within 3 weeks prior to Cycle 1 Day 1
5. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
6. Plasma cell leukemia (> 2.0×10^9/L circulating plasma cells by standard differential)
7. Chemotherapy with approved or investigative anticancer therapeutics including steroid therapy within the 3 weeks prior to Cycle 1 Day 1
8. Radiation therapy or immunotherapy in the 4 weeks prior to Cycle 1 Day 1; localized radiation therapy within 1 week prior to Cycle 1 Day 1
9. Participation in an investigational therapeutic study within 3 weeks or within 5 drug half-lives ($T_{½}$) prior to Cycle 1 Day 1, whichever time is greater
10. Prior treatment with carfilzomib
11. Major surgery within 3 weeks before Cycle 1 Day 1
12. Congestive heart failure ([CHF] New York Heart Association Class III to IV), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention. **Subjects cannot have experienced a** myocardial infarction within 6 months prior to Cycle 1 Day 1
13. Uncontrolled hypertension (a sustained systolic blood pressure > 140 mmHg and/or diastolic BP > 90 mmHg)
14. Acute active infection requiring systemic **(either intravenous or oral)** antibiotics, antivirals, or antifungals; **the treatment must be completed at least** 2 weeks prior to Cycle 1 Day 1

15. Known HIV seropositive, hepatitis C infection, and/or hepatitis B (except for patients with hepatitis B surface antigen or core antibody receiving and responding to antiviral therapy directed at hepatitis B: these patients are allowed; **Note**: **patients who are HepB surface antigen negative at screening, or who are receiving interferon alfa-2a (IFN) or Peginterferon alfa-2a (PEG-IFN) and have Hepatitis B Virus (HBV) DNA < 2000 International Units (IU) at screening, or, are receiving a nucleos(t)ide analog and have HBV DNA below Lower Limit of Normal (LLN) at screening are eligible**
16. Non-hematologic malignancy within the past 3 years except:
    a. Adequately treated basal cell or squamous cell skin cancer,
    b. Carcinoma in situ of the cervix, or
    c. Prostate cancer < Gleason Score 6 with stable prostate-specific antigen
17. Subjects with treatment-related myelodysplastic syndrome
18. Significant neuropathy (Grade 3, 4, or Grade 2 with pain) at the time of baseline evaluation
19. Subjects in whom the required program of fluid hydration is contraindicated, e.g., due to pre-existing pulmonary, cardiac, or renal impairment
20. Subjects with known or suspected amyloidosis
21. Subjects with pleural effusions requiring thoracentesis
22. Subjects with ascites requiring paracentesis
23. Any clinically significant medical disease or condition, that in the investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent
24. Female subjects who are pregnant or lactating, or planning to become pregnant during treatment and for an additional 30 days after discontinuing carfilzomib.
25. Serious psychiatric or medical conditions that could interfere with treatment

5 SUBJECT SCREENING

A signed and dated informed consent form (ICF) will be obtained before any screening procedures are performed. All subjects who sign consent will be assigned a unique study number. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

Evaluations obtained as part of routine medical care and performed prior to informed consent may be used in place of the study-specific evaluations, provided they meet the time windows described **in Section 9.2.1.** Subjects will acknowledge and agree to the possible use of this

information for the study by giving informed consent. The screening period for a particular subject commences at the point at which the subject signs the ICF, and must be completed within 21 days.

6 SUBJECT ENROLLMENT

Only subjects who fulfill all eligibility criteria will be allowed to enroll into the study. The investigator is responsible for reviewing the subject's information before enrollment to ensure his or her eligibility.

Study sites that do not enroll a single subject within the first 3 months of opening the study may be subject to study site closure at the discretion of the sponsor.

7 STUDY DRUG

7.1 CARFILZOMIB

7.1.1 *Physical Description*

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

7.1.2 *Formulation*

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

7.1.3 *How Supplied*

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. Reordering clinical drug supplies will be managed through the

Interactive Voice Recognition System or Interactive Web Recognition System; details are provided in the Investigational Product Instruction Manual (IPIM).

7.2 DEXAMETHASONE

Dexamethasone is a commercially available drug. The description, how supplied, 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 they are using. Oral or IV dexamethasone may be utilized per site's standard practice.

7.3 STUDY DRUG ACCOUNTABILITY

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

8 DOSAGE AND TREATMENT ADMINISTRATION

Pretreatment and treatment administration details are outlined below in Section 8.1.
Dose modifications for toxicity are described in Section 8.2. Details on drug description, formulation, storage, and accountability of all study drugs are described in the IPIM.

8.1 GENERAL INSTRUCTIONS FOR ADMINISTRATION

8.1.1 *Oral and Intravenous hydration*

Intravenous hydration will be given immediately prior to and following carfilzomib administration during Cycle 1, and at the investigator's discretion in Cycle 2 and higher. If uric acid is elevated at Cycle 2, Day 1, then the recommended IV hydration should be repeated for all of Cycle 2, and, at the investigator's discretion, in conjunction with subsequent cycles. This will consist of 250 to 500 mL IV normal saline or other appropriate

IV fluid. The goal of the hydration program is to maintain robust urine output (e.g., ≥ 2 L/day). Subjects should be monitored periodically during this period for evidence of fluid overload. In subjects considered to be at risk for tumor lysis syndrome (TLS) at completion of Cycle 1, hydration should be continued into Cycle 2, if clinically indicated. Subjects in whom this program of oral and IV fluid hydration is contraindicated, e.g., due to pre-existing pulmonary, cardiac, or renal impairment, will not be eligible to participate in the clinical trial.

In addition, refer to Section 8.3.1 for optional medications including allopurinol (or other approved uric acid-lowering agent) for patients considered to be at high risk for TLS.

Patients should be well hydrated to reduce risk of TLS and decline in renal function; refer to Section 8.4.3 for safety guidance regarding TLS.

8.1.2 *Carfilzomib Administration*

Information regarding drug description, formulation, storage, and accountability of carfilzomib is provided in Section 7 and in the IPIM.

Carfilzomib is administered as an IV infusion over approximately 30 minutes (± 5 minutes). Note: On days of PK sampling (Cycle 1 Day 1 and Cycle 2 Day 1), carfilzomib must be administered over 30 ± 1 minutes. Subjects should have a dedicated line for drug administration whenever possible, and PK samples may not be collected from the same line that is used for carfilzomib administration. The dedicated infusion line or the existing infusion line (when a dedicated line is not available) must be flushed as specified in the IPIM.

Each dose will consist of carfilzomib administered on a mg/m^2 basis, and should be based on the subject's actual calculated body surface area (BSA) at baseline. Subjects with a BSA > 2.2 m^2 will receive a dose based upon a 2.2 m^2 BSA (Mosteller 1987).

Carfilzomib administration may be performed ± 2 days from the scheduled administration day. Every effort should be made to maintain consecutive dosing days. Anticipated

treatment delays of greater than 2 days must be discussed with the study medical monitor or designee. Procedures for dose reductions and adjustments are summarized in Section 8.2.

8.1.3 *Dexamethasone Administration*

Dexamethasone (20 mg) will be administered on Days 1, 2, 8, 9, 15, 16, 22, and 23 on a 28 day cycle. **Note: Days 22 and 23 dosing may be ± 2 days from the scheduled administration day. Every effort should be made to maintain consecutive dosing days**. It will be given at least 30 minutes (but no more than 4 hours) prior to carfilzomib infusion. On non-clinic days, PO dexamethasone may be self-administered at home.

Procedures for dose reductions and adjustments are summarized in Section 8.2.

8.2 DOSE MODIFICATION GUIDELINES

In the event of a possible drug-related AE, the investigator will to the best of his/her ability, assess its relationship to carfilzomib and/or dexamethasone.

For cycles where Day 1 is delayed, the entire cycle should shift to accommodate the delay. If a mid-cycle dose is missed, that dosing day should be skipped and not made up.

If carfilzomib dosing is permanently stopped due to toxicity per dose modification guidelines listed in Section 8.2.1, dexamethasone dosing will also be stopped and the subject assessed for disease status per protocol-specified disease response criteria, and followed per protocol specified guidelines (**Section 9.4.1**) prior to initiating new antimyeloma therapies.

8.2.1 *Carfilzomib Dose Modification Guidelines*

Dose reduction guidelines for carfilzomib include guidelines where the dose of carfilzomib is decreased based on the observed toxicity. Administration of carfilzomib will be discontinued in the event of a treatment-related toxicity that, in the opinion of the investigator, warrants discontinuation. Exceptions to the dose modification guidelines are permitted with prior written approval from the study medical monitor or designee.

Treatment guidelines for specific toxicities are outlined in Section 8.2.2. If a subject requires a hold of therapy for more than 6 consecutive weeks due to unresolved toxicity, the subject

should be removed from study treatment and followed for survival and disease progression. Exceptions to this should be discussed with the study medical monitor or designee.

A maximum of 2 dose reductions are allowed (Table 1) if the carfilzomib dose is reduced during the previous cycle, the reduced dose level will be continued on Day 1 of the new cycle. If the reduced dose level is well tolerated for a complete cycle, the subject may, at the investigator's discretion, be rechallenged at the dose prior to the reduction at the start of the next cycle.

Table 1: Dose Decrements for Carfilzomib

Starting Dose	Reduced Carfilzomib Doses	
	First Dose Reduction Dose –1	Second Dose Reduction Dose –2
20 mg/m^2	15 mg/m^2	11 mg/m^2
27 mg/m^2	20 mg/m^2	15 mg/m^2

Note: Infusions remain as 30-minute infusions during dose reduction(s).

8.2.1.1 Missed Doses

Missed doses will not be replaced during a cycle.

8.2.1.2 Changes in Body Surface Area

Dose adjustments do not need to be made for weight gains/losses of ≤ 20%. Study subjects with a BSA of > 2.2 m^2 will receive a maximal dose of 44 mg of carfilzomib (at the 20 mg/m^2 dose level) or 59 mg of carfilzomib (at the 27 mg/m^2 dose level).

8.2.2 *Carfilzomib: Guidelines for Treatment-Emergent Toxicities*

Guidelines for the management of hematologic and non-hematologic treatment emergent toxicities in subjects receiving carfilzomib are summarized in Table 2 and Table 3, respectively. For conditions that do not require dose reduction, refer to Section 8.2.4.

For both hematologic and non-hematologic treatment-emergent toxicities, no more than 2 dose reductions will be permitted in an individual subject in the study; if toxicity continues, the subject should discontinue study treatment and begin follow-up (Section 9.2.16).

Table 2: Guidelines for Hematologic Treatment Emergent Toxicities in Carfilzomib Patients

Hematologic Toxicity	Recommended Action	
Thrombocytopenia		
When platelets first fall to ≤ 30×10^9/L	If platelets 10–30×10^9/L without evidence of bleeding	Continue at same dose*.
	If evidence of bleeding or platelets < 10×10^9/L	Hold dose until platelets return to ≥ 10×10^9/L and/or bleeding is controlled, then resume at same dose.
For each subsequent drop to ≤ 30×10^9/L	If platelets 10–30×10^9/L without evidence of bleeding	Continue at same dose.
	If evidence of bleeding or platelets < 10×10^9/L	Hold dose until platelets return to ≥ 10×10^9/L and/or bleeding is controlled, then resume at 1 dose decrement.
Neutropenia		
When ANC first falls to **< 0.5** × 10^9/L	If ANC < 0.5×10^9/L	Hold dose until ANC returns to ≥ 0.5×10^9/L, then resume at same dose.*
For each subsequent drop to **< 0.5** × 10^9/L	If ANC < 0.5×10^9/L	Hold dose until ANC returns to ≥ 0.5×10^9/L, then resume at 1 dose decrement.
Neutropenic fever	If < 1×10^9/L and single temperature > 38.3ºC *OR* temperature > 38.0 ºC for more than 1 hour	Hold dose until ANC returns to baseline grade, then resume at same dose.

ANC = absolute neutrophil count *** If the first fall in platelet count or in ANC is observed before D8C1, then administer the protocol-specified 27 mg/m2 on D8C1**

Table 3: Guidelines for Non-hematologic Treatment Emergent Toxicities in Carfilzomib Patients

Nonhematologic Toxicities, All Days and Cycles		
Symptom	**Findings**	**Recommended Action[a]**
Tumor Lysis Syndrome	3 or more of the following: increase in creatinine of ≥ 50% increase in uric acid of ≥ 50% increase in phosphate of ≥ 50% increase in potassium of ≥ 30% decrease in calcium OR increase in LDH of ≥ 2-fold from baseline	Hold carfilzomib until all abnormalities in serum chemistries have resolved; resume at same dose[b]
Infection	Grade 3 or 4	**Hold carfilzomib. Once infection is controlled and the subject is without infection-related symptoms, and if ANC > 0.5 × 10^9/L, resume at full dose. If ANC < 0.5 × 10^9/L, follow hematologic toxicities dose reduction guidelines.**
Neuropathy	Grade 2 treatment-emergent with pain, or Grade 3	Hold carfilzomib until resolved to ≤ Grade 2 without pain; then resume at 1 dose decrement
	Grade 4	Discontinue
Dyspnea	Grade 3 or 4	Hold carfilzomib until resolution to baseline, then resume at 1 dose decrement
Renal Dysfunction	Serum creatinine clearance < 15 mL/min (or CrCl decreases to ≤ 50% of baseline), or need for dialysis	Hold carfilzomib and continue monitoring renal function If attributable to carfilzomib, resume when renal function has recovered to within 25% of baseline, resume at 1 dose level reduction If not attributable to carfilzomib, dosing may be resumed at the discretion of the treating physician If tolerated, reduced dose may be raised to the previous dose at the discretion of the treating physician. For patients on dialysis receiving carfilzomib, the dose is to be administered after dialysis

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Footnotes defined on last page of the table.

Table 3: Guidelines for Non-hematologic Treatment Emergent Toxicities in Carfilzomib Patients

Nonhematologic Toxicities, All Days and Cycles		
Symptom	**Findings**	**Recommended Action[a]**
Elevation in Liver Function Tests	≥ Grade 3 (AST, ALT, or total bilirubin)	Hold carfilzomib until all abnormalities in liver functions resolve to baseline. Resume carfilzomib at 1 dose decrement.
Congestive Heart Failure	N/A	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 6 weeks, the subject will be withdrawn from all study treatment
Hypertensive crisis	Hypertensive urgency defined as sustained or persistent SBP ≥ 180 mmHg or DBP ≥ 110 mmHg. Hypertensive emergency with values as before and evidence of end organ damage.	Hold carfilzomib until resolution to baseline[c] and restart at 1 dose decrement.
Pulmonary toxicity	Interstitial lung disease, acute respiratory failure, ARDS	Hold carfilzomib until resolution to baseline and restart at 1 dose decrement.
Pulmonary Hypertension	Presence of mean pulmonary arterial pressure ≥ 25 mmHg at rest	Hold carfilzomib until resolution to baseline and restart at 1 dose decrement
Posterior Reversible Encephalopathy Syndrome	Headaches, altered mental status, seizures, visual loss, and hypertension	If PRES is suspected, hold carfilzomib. Consider evaluation with neuroradiological imaging for onset of visual or neurological symptoms suggestive of PRES. If the diagnosis of PRES is excluded, carfilzomib administration may resume if clinically appropriate.

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Footnotes defined on last page of the table.

Table 3: Guidelines for Non-hematologic Treatment Emergent Toxicities in Carfilzomib Patients

Nonhematologic Toxicities, All Days and Cycles		
Symptom	**Findings**	**Recommended Action[a]**
Thrombotic Microangiopathy	Fever, microangiopathic hemolytic anemia, renal failure, thrombocytopenia, neurological manifestations	If the diagnosis is suspected, stop carfilzomib and manage per standard of care including plasma exchange as clinically appropriate. If the diagnosis is excluded, carfilzomib can be restarted.
Other Nonhematologic Toxicity	Assessed as carfilzomib-related and ≥ Grade 3	Hold dose until toxicity resolves to ≤ Grade 1 or baseline; restart at 1 dose decrement

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ALT = alanine aminotransferase; ANC = absolute neutrophil count; ARDS = acute respiratory distress syndrome; AST = aspartate aminotransferase; CrCl = creatinine clearance; DPB = diastolic blood pressure; LDH = lactate dehydrogenase; PRES = posterior reversible encephalopathy; SBP = systolic blood pressure.

[a] The maximum allowed interruption of carfilzomib is 6 consecutive weeks.

[b] **If the Tumor Lysis Syndrome laboratory finding is observed before D8C1, administer the protocol-specified 27 mg/m2 when dosing is resumed.**

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

Please refer to Section 8.2.4 for additional conditions that do NOT require dose reductions.

8.2.3 *Dexamethasone Toxicities and Treatment*

Guidelines for dexamethasone dose modifications are summarized in Table 4 and Table 5. In the event that carfilzomib is permanently discontinued, dexamethasone should also be discontinued.

Two dose reduction levels are defined for dexamethasone, as illustrated in Table 4 below.

Table 4: Dose Decrements for Dexamethasone

Nominal Dose	**Reduced Dexamethasone Doses**	
	Dose –1	**Dose –2**
20 mg	12 mg	8 mg

In the event of additional dexamethasone-related dose-limiting toxicity, dexamethasone will be permanently discontinued after 2 dose reductions. At the investigator's discretion, dexamethasone may be tapered prior to complete discontinuation. If the dexamethasone dose is reduced during the previous cycle, the reduced dose level will be continued on day 1 of the new cycle. If the reduced dose level is well tolerated for a complete cycle, the patient may,

at the investigator's discretion, be rechallenged with the dose level used prior to the reduction, at the start of the next cycle.

Table 5: Treatment Guidelines for Dexamethasone-related Toxicity

Body System	Symptom	Recommended Action
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, or gastritis Grade 1–2 (requiring medical management)	Continue dexamethasone at same dose and treat with therapeutic doses of H2 blockers, or proton pump inhibitor. May consider adding sucralfate or other antiulcer treatment as clinically indicated. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, or gastritis ≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms return to baseline. Restart dexamethasone at 1 dose decrement along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone permanently.
Gastrointestinal	Acute pancreatitis	Discontinue dexamethasone permanently.
General disorders	Edema > Grade 3 (> 30% limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self-care activities of daily living (ADL)	Hold dexamethasone until symptoms return to baseline. Diuretics as needed, and restart dexamethasone at 1 dose decrement; if edema persists despite above measures, decrease dose another level. Discontinue dexamethasone permanently if symptoms persist despite second reduction.
Psychiatric Disorders	Confusion or mood alteration > Grade 2 (interfering with function ± interfering with activities of daily living)	Hold dexamethasone until symptoms return to baseline. Restart dexamethasone at 1 dose decrement. If symptoms persist despite above measures, reduce by another dose decrement.
Musculoskeletal	Muscle weakness > Grade 2 (symptomatic and interfering with function ± interfering with activities of daily living)	Hold dexamethasone until symptoms return to baseline. Restart dexamethasone at 1 dose decrement. If weakness persists, decrease dose by 1 more dose level. Discontinue dexamethasone permanently if symptoms persist.
Metabolism and Nutrition Disorders	Hyperglycemia ≥ Grade 3 (fasting glucose > 250 mg/dL)	Hold dexamethasone until glucose is < Grade 2 (< 250 mg/dL) and treat with insulin or other hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by 1 dose level until ≤ Grade 2 (< 250 mg/dL)
All Other	Other nonhematologic toxicity ≥ Grade 3 felt related to dexamethasone	Hold dexamethasone dose. Resume at 1 dose decrement when toxicity has resolved to Grade 2 or less or to baseline. If toxicity recurs, hold dexamethasone dose until toxicity has resolved to Grade 2 or less or to baseline and resume dexamethasone dose by 1 more dose decrement. If toxicity recurs despite 2 dose decrements, discontinue dexamethasone permanently.

8.2.4 *Conditions Not Requiring Dose Reduction*

The following conditions are exceptions to the above guidelines. Carfilzomib and dexamethasone do not need to be skipped or withdrawn in the following cases:

- Grade 3 nausea, vomiting, or diarrhea (unless persisting more than 3 days after adequate treatment with antiemetics or antidiarrheal agents)
- Grade 3 fatigue (unless persisting for > 14 days)
- Any grade anemia or lymphopenia
- Alopecia

8.3 CONCOMITANT MEDICATIONS

A concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins, supplements, and Traditional Chinese Medicines. All concomitant medications must be recorded on the subject's case report form (CRF) from informed consent to 30 days following the last dose of study drug **or initiation of new anti-myeloma therapy, whichever comes first**. Blood or blood products are not considered concomitant medications and must be recorded on the appropriate CRF.

8.3.1 *Required and Optional Concomitant Medications*

Antiviral Prophylaxis:

Valacyclovir (or equivalent antiviral) is a required concomitant medication. Valacyclovir 500 mg orally, daily (or equivalent antiviral) should continue for the duration of treatment. **Antiviral prophylaxis is recommended to be initiated at least 24 hours before the first dose of carfilzomib.**

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

Allopurinol (or other approved uric acid-lowering agent) in patients at high risk for TLS due to high tumor burden may be prescribed at the investigator's discretion. Glucocorticoids < 10 mg oral prednisone (or equivalent) per week are permitted for non-malignant conditions (e.g., asthma, inflammatory bowel disease, etc.) as needed.

Subjects may receive antiemetics and antidiarrheal agents as necessary. Myeloid growth factors (e.g., G-CSF) may be used if neutropenia occurs in accordance with American

Society of Clinical Oncology 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 medical monitor or designee.

8.3.2 *Excluded Concomitant Medications*

Concurrent therapy with a marketed or investigational anticancer therapeutic (including steroids at a higher dose than this protocol specifies) or radiation to large marrow reserves for either a palliative or therapeutic intent is not allowed. **If a patient requires radiation therapy and wishes to remain on study, the radiation plan must be shared and written approval of the study medical monitor must be obtained prior to the initiation of radiation therapy.** Additionally, alternative anticancer therapy including Chinese herbal medicine with curative intent (other than that administered in the study), or other investigational agents are not allowed prior to confirmed progressive disease (PD).

8.3.3 *Additional Considerations Regarding Concomitant Medications*

In an in vitro human microsome system, carfilzomib demonstrated direct, time-dependent inhibition of cytochrome CYP3A4/5 activity (Yang 2012). Carfilzomib did not induce human CYP1A2 and CYP3A4 in cultured fresh human hepatocytes. Carfilzomib was primarily metabolized via peptidase and epoxide hydrolase activities. Cytochrome P450–mediated mechanisms played a minor role in the overall metabolism of carfilzomib. The PK profile of carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors and inducers. Carfilzomib showed marginal inhibitory effects on P-glycoprotein (P-gp) in a Caco-2 monolayer system, but was determined to be a P-gp substrate. Given that carfilzomib is administrated IV and is extensively metabolized, the PK profile of carfilzomib is unlikely to be affected by P-gp inhibitors or inducers.

A clinical study of 17 subjects using PO midazolam as a CYP3A probe demonstrated that the PK of midazolam were unaffected by concomitant carfilzomib administration. Carfilzomib

is not expected to inhibit CYP3A4/5 activities and/or affect the exposure to CYP3A4/5 substrates.

8.4 SAFETY GUIDANCE FOR INVESTIGATORS

8.4.1 *Infusion Reactions and Adverse Events Experienced Within a Day of Dosing of Carfilzomib*

True infusion reactions have been reported but are rare. Should an infusion reaction occur, glucocorticoids, IV fluids, vasopressors, oxygen, bronchodilators, and acetaminophen are to be available for immediate use and instituted as medically indicated. Adverse events that have been commonly observed within a day of carfilzomib administration include mild fever, chills, dyspnea, and/or rigors occurring in the evening following the first day of infusion during the first cycle of therapy. This can be associated with an increase in serum creatinine level on the subsequent day. Refer to the CCSI for detailed information.

8.4.2 *Renal Function*

Grade 1 and 2 reversible increases in serum creatinine have been reported in subjects treated carfilzomib on clinical trials. Renal insufficiency has been reported less frequently. It is not known if there is a clear association between renal failure and carfilzomib. In Phase 2 studies, cases of renal failure were confounded by documented or suspected TLS, sepsis/infections, light-chain disease, and disease progression. Renal function will be monitored prior to each dose. Refer to Table 3 for guidance regarding dose reduction in subjects with compromised renal function and the CCSI for additional details.

8.4.3 *Tumor Lysis Syndrome*

Suspected or documented TLS has been observed in some subjects treated with carfilzomib early in the Phase 2 studies, which resulted in the institution of TLS prophylaxis guidelines. Subjects with high tumor burden or compromised renal function (e.g., International Staging System Stage II/III or rapidly increasing M-protein or light chains or compromised renal function [CrCl < 50 mL/minute]) may be at elevated risk and must be closely monitored, and uric acid levels normalized prior to initiation of treatment, if appropriate. Intravenous hydration must be given to all subjects in Cycle 1; premedication with allopurinol or other approved uric acid-lowering agent is optional. Following Cycle 1, pre-carfilzomib IV

hydration is only required if indicated by the subject's condition and/or risk factors, and the reason for hydration must be documented on the CRF. Refer to the CCSI for detailed information.

8.4.4 *Thrombocytopenia and Neutropenia*

Carfilzomib has been associated with thrombocytopenia. The thrombocytopenia pattern is cyclical with nadirs following the second dose each week and typically recovering prior to the initiation of the next treatment, similar to that observed with Bortezomib. The severity of thrombocytopenia is related to the pretreatment platelet counts. Transfusions may be considered. The incidence of significant bleeding is < 5%. At minimum, platelet counts are to be monitored on Days 1, 8, and 15 of each cycle. Severe neutropenia has been reported and may occur during treatment but is uncommon. Please refer to dose modification recommendations for hematologic toxicity in Table 2.

8.4.5 *Cardiac Disorders*

Safety data reported from single-arm Phase 2 studies of carfilzomib in heavily pretreated subjects has shown acute development or exacerbation of CHF and new onset of decreased left ventricular function. Death due to cardiac arrest has occurred within a day of carfilzomib administration (< 1%). Subjects with risk factors for or evidence of existing heart disease are to be closely monitored throughout their treatment with carfilzomib. A follow-up ECHO is to be conducted in patients who develop clinically significant CHF or clinically important signs/symptoms indicative of decreased ventricular function. Carfilzomib must be held if CHF develops or appears to be exacerbated by treatment (refer to Table 3), and may be resumed once the symptoms resolve.

Dyspnea may or may not occur in association with cardiac disorders. Subjects who experience dyspnea are to be evaluated for the presence of associated conditions and management should be tailored to the appropriate treatment for the underlying disorder. Refer to the CCSI for detailed information.

8.4.6 *Gastrointestinal Events*

Carfilzomib treatment can cause nausea, vomiting, diarrhea, or constipation, sometimes requiring the use of antiemetics or antidiarrheals. Fluid and electrolyte replacement is to be administered to prevent dehydration. Routine premedication with medications to treat nausea and vomiting is not required.

8.4.7 *Hepatic Impairment*

Three cases of hepatic failure (including 2 cases that were fatal, with both cases occurring in the context of progressive disease [PD]) and 1 case of veno-occlusive disease have been reported with the use of carfilzomib at the time of finalization of this protocol, at which time more than 2000 subjects have received carfilzomib in Onyx-sponsored studies. Non-serious and serious (Grades 1 to 3) elevations of serum transaminase levels have been reported infrequently. The use of carfilzomib has not been characterized in subjects with moderate or severe hepatic impairment. See Table 3 for dose reduction information related to hepatic toxicities. Refer to the CCSI for detailed information.

8.4.8 *Pulmonary Events*

Dyspnea was reported in 35% of patients treated on carfilzomib Phase 2 clinical trials, was predominantly Grade 1 or Grade 2 in severity, transient, and did not require intervention. Grade 3 events occurred in 5% of subjects; no Grade 4 events, and one Grade 5 event was reported. Grade 3 or 4 dyspnea, especially if occurring within a day of carfilzomib dosing, is to be evaluated immediately and appropriate medical management given.

Pulmonary hypertension was reported in 2% of subjects in Phase 2 studies, and was ≥ Grade 3 in < 1% of subjects. In most cases, insufficient diagnostic evidence was available to definitively confirm the diagnosis of pulmonary hypertension, and the cases reported occurred primarily in the context of CHF. Refer to the CCSI for detailed information.

8.4.9 *Posterior reversible encephalopathy syndrome*

Cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving carfilzomib. Posterior reversible encephalopathy syndrome is a rare, neurological disorder, which can present with seizure, headache, lethargy, confusion,

blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension, and the diagnosis is confirmed by neuro-radiological imaging. Carfilzomib should be discontinued if PRES is suspected.

8.4.10 *Thrombotic microangiopathy*

Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome (TTP/HUS) have been reported in patients who received carfilzomib. Some of these events have been fatal. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, treatment should be interrupted. If diagnosis of TTP/HUS is excluded, carfilzomib can be restarted.

8.4.11 *Venous thrombosis*

Cases of venous thromboembolic events, including deep vein thrombosis and pulmonary embolism with fatal outcomes, have been reported in patients who received carfilzomib. Patients with known risk factors for thromboembolism, including prior thrombosis, should be closely monitored. Action should be taken to try to minimise all modifiable risk factors (e.g., smoking, hypertension, and hyperlipidaemia). Caution should be used in the concomitant administration of other agents that may increase the risk of thrombosis (e.g., erythropoietic agents or hormone replacement therapy). Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, haemoptysis, arm or leg swelling or pain. Thromboprophylaxis should be considered based on an individual benefit/risk assessment.

9 STUDY PROCEDURES

Study-specific procedures are described below in Section 9.1. The schedule of study assessments is outlined in Section 9.2 and tabulated in Appendix A.

Appropriate written informed consent must be obtained before any study-specific tests may be performed.

9.1 DESCRIPTION OF STUDY-SPECIFIC PROCEDURES

9.1.1 *Medical History*

Medical history will include recording of significant medical conditions, prior cancer surgery/radiation therapy, transplant, tobacco history (years of tobacco use; packs per day of cigarettes), alcohol history (current number of alcoholic drinks per week), and neuropathy history.

9.1.2 *Multiple Myeloma History and Prior Lines of Therapy Assessment*

Subjects must have confirmed and verifiable diagnosis of multiple myeloma and documented relapse after 2 or more therapies for multiple myeloma. Prior therapies must have included an alkylating agent or anthracycline, bortezomib, and an IMiD. 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 for the disease.

- 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.

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)

Investigators are responsible for maintaining documentation of prior lines of multiple myeloma therapy.

9.1.3 *Vital Signs*

Vital signs will include: heart rate, blood pressure, respiratory rate, and temperature. The subject should be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position possible (this request is recommended in all following assessments). The position selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF.

9.1.4 *Eastern Cooperative Oncology Group Performance Status*

Eastern Cooperative Oncology Group performance status grades and descriptions are tabulated in Appendix C.

9.1.5 *Complete and Routine Physical Examinations*

A complete physical examination should include: examination of cardiovascular and respiratory systems, abdominal examination, neurologic physical exam, weight, BSA, and height (height measurement will be performed only at screening physical examination). Body surface area is determined by a standard formula such as the Mosteller Formula: BSA (m^2) = ([Height (cm) × Weight (kg)]/ 3600)^{½} (Mosteller 1987).

A routine physical examination should include examination of cardiovascular and respiratory systems.

9.1.6 *Electrocardiogram*

Twelve-lead electrocardiograms (ECGs) including corrected QT interval (QTc; representing the corrected duration of ventricular electrical activity) will be performed. Electrocardiograms will be required in all subjects at screening and at the end of treatment only.

9.1.7 *Echocardiogram*

A 2-D transthoracic ECHO to assess LVEF will be performed at Screening. If transthoracic ECHO is not available, MUGA will be acceptable.

9.1.8 *Laboratory Evaluation*

Laboratory tests, including hematology, blood chemistries, and coagulation tests will be performed as outlined in Section 9.2.1 and **9.2.16** and the Schedule of Assessments (Appendix A). Unscheduled or additional laboratory samples may be collected and analyzed if immediate results are necessary for management of treatment emergent AEs or dosing determination.

9.1.8.1 Chemistry

The chemistry panel to be used is displayed below in **Table 6** Chemistry panels will be performed at the local laboratory.

Table 6: Laboratory Tests: Chemistry Panel

Chemistry Panel	
Albumin	Glucose
Alkaline Phosphatase	LDH
ALT	Magnesium
AST	Phosphorus
Bicarbonate **or Total CO_2**	Potassium
BUN	Sodium
Calcium	Total Bilirubin
Chloride	Total Protein
Creatinine	Uric Acid

Abbreviations: ALT= alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, LDH = lactate dehydrogenase.

9.1.8.2 Hematology

Table 7 displays the hematology tests that will be conducted. Hematology tests will be performed at the local laboratory.

Table 7: Laboratory Tests: Hematology

Hematology Panel
Hemoglobin
Hematocrit
WBCs with complete manual or automated differential[a] to include: • Total neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
RBCs
Platelet count

Abbreviations: RBCs = red blood cells, WBCs = white blood cells.

[a] Absolute or percent counts will be acceptable.

9.1.8.3 Coagulation Panel

Coagulation panel will be performed at baseline, at the local laboratory (see **Table 8**).

Table 8: Laboratory Tests: Coagulation Panel

Coagulation Panel
PT
aPTT or PTT
INR

Abbreviations: PT = Prothrombin time, aPTT = activated partial thromboplastin time, INR = international normalized ratio

9.1.9 *Pregnancy Evaluation and Contraception Considerations*

For FCBPs, a serum pregnancy test that is confirmed negative is required for eligibility. This protocol defines a FCBP as a sexually mature woman who: 1) has not undergone a hysterectomy, bilateral oophorectomy, or bilateral salpingectomy, or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

In addition to the pregnancy test conducted for eligibility, a serum or urine pregnancy test must be confirmed negative on Day 1 of each cycle prior to dosing and at end of therapy (EOT). More frequent pregnancy tests may be conducted if required per local regulations. Pregnancy testing will be done at the local laboratory.

9.1.10 *Multiple Myeloma Disease Assessments*

9.1.10.1 Plasmacytoma Evaluations

All subjects are required to have a clinical assessment in consideration of formal plasmacytoma evaluation at screening. Further evaluation for extramedullary plasmacytoma evaluation is required at screening only if a lesion is suspected clinically. The baseline plasmacytoma evaluation may consist of palpation, ultrasound, computed tomography (CT) scan, magnetic resonance imaging (MRI), or positron emission tomography with diagnostic CT (PET/CT). **Bone scintigraphy is not an acceptable method of plasmacytoma imaging**. At baseline, the greatest diameter, and the greatest orthogonal cross diameter must be measured. If an extramedullary plasmacytoma is detected at Screening, imaging evaluation must be repeated during treatment only if required to confirm a new response of PR or better, a new response of CR or better, or to confirm PD, per the IMWG response criteria (Durie, 2006; Rajkumar, 2011) (Appendix E). The same technique should be employed for each measurement of plasmacytoma dimensions. Bi-dimensional lesion measurements must be performed and recorded in the designated CRF.

9.1.10.2 Skeletal Survey

Skeletal survey **by plain radiography** will include lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. **Skeletal survey may be done by X-ray, CT, CT/PET, or MRI. Bone scintigraphy is not an acceptable method of skeletal imaging.** The skeletal survey will be conducted at screening and will be repeated if worsening clinical symptoms suggest PD, or as clinically indicated.

9.1.10.3 Bone Marrow Aspirate and/or Biopsy

All subjects will have a baseline bone marrow aspirate and/or biopsy done and evaluated locally for percent plasma cell involvement**.** Multiple myeloma-specific interphase **F**luorescent **I**n **S**itu **H**ybridization (FISH) testing is optional.

A bone marrow aspirate and/**or** biopsy, evaluated locally, is required to confirm a **laboratory** response of CR or sCR .

9.1.10.4 Disease Response and Progression Assessments

Subjects will be evaluated by the investigator for disease response according to the IMWG-URC assessment parameters as outlined in Appendix E on Day 1 of Cycles 2 and higher through to EOT and during Active Follow-up (Durie, 2006; Rajkumar, 2011**; Kumar, 2016**). Minimal response will **also** be assessed (**Kumar, 2016;** Appendix F). The following clinical response assessments will be completed at the protocol specified time points.

9.1.10.4.1 Laboratory Assessments of Disease - Screening

All subjects must have SPEP, serum immunofixation electrophoresis (SIFE), SFLC, beta-2 microglobulin, serum calcium, quantitative immunoglobulins, and **24-**hour urine collection for UPEP, and urine immunofixation electrophoresis (UIFE) at baseline. NOTE: UPEP with immunofixation (on a 24-hour collection) is required. No substitute method is acceptable.

If multiple disease assessment measurements are available before initiation of therapy, the measurement closest to Cycle 1, Day 1 will be used as baseline (Kumar, 2016).

Laboratory assessments of disease, listed above, will be performed at the central laboratory. For details of collection, please refer to the study Central Laboratory Manual.

9.1.10.4.2 Laboratory Assessments of Disease – During Treatment Period and Active Follow-Up

Day 1, Cycles 2 and Higher, EOT, and Active Follow-Up

- Serum M-protein: Subjects with serum positive for M-protein levels measured by SPEP (> 1 g/dL at baseline) –must have SPEP and SIFE done on Day 1 of each cycle (± 3 days) from Cycle 2 and beyond, at EOT, and during Active Follow-up. SPEP and SIFE will be performed at the central laboratory.
- Urine M-protein: All **s**ubjects must have a **24-hour** urine for UPEP and UIFE done on day 1 of each cycle (± 3 days) from Cycle 2 and beyond, at EOT, and during active follow-up. UPEP and UIFE will be performed at the central laboratory.
- Serum and Urine M-protein: Subjects with both serum and urine positive for M-protein levels (> 1 g/dL in serum and > 200 mg/24 hours in urine at baseline) – must have both SPEP, SIFE, and a **24-hour** urine for UPEP and UIFE done on Day 1 of each cycle

(± 3 days) from Cycle 2 and beyond, at EOT, and during Active Follow-up. These tests will be performed at the central laboratory.

- Serum-free light chains: All subjects must have SFLC assay drawn at Screening and EOT. Subjects with < 1 g/dL serum M-protein and < 200 mg/24 hours urine M-protein at baseline must have SFLC drawn on day 1 of each cycle (± 3 days) from Cycle 2 onwards, at EOT, and during Active Follow-up. Subjects in CR must have SFLC drawn. SFLC test will be performed at the central laboratory.
- Serum calcium must be tested on all subjects at the central laboratory on day 1 (± 3 days) of Cycles 2 and higher, at EOT, and during Active Follow-up

9.1.10.4.3 Response Assessments

In addition to the above-described assessments of multiple myeloma disease marker levels in serum and urine, the following response assessments are required to confirm all response categories (PR, VGPR, CR, sCR, MR):

- Two consecutive laboratory assessments of M-protein level (serum and/or urine) drawn at any time before the start of new (off protocol) myeloma therapy. **No minimum interval is required for SPEP, SIFE, SFLC, it can be done on the same day, however to confirm response or progressive disease, 2 discrete samples are required; testing cannot be based on the splitting of a single sample.**
- A plasmacytoma evaluation: if present at baseline, a ≥ 50% reduction in the size of plasmacytomas is required to confirm a new response of PR or better (to be done within 6 weeks of first laboratory evidence of PR or better). Disappearance of plasmacytoma is required to confirm a new response of CR or better (to be done within 6 weeks of first laboratory evidence of CR or better).
- No known evidence of progressive or new bone lesions on skeletal survey if radiographic studies are performed after baseline; **however, radiology examination is not a scheduled assessment after baseline unless clinically indicated.**

In addition, the following assessments are required to confirm a VGPR or better:

- UIFE in subjects being followed by serum M-protein or SFLC (even if UPEP and UIFE were not measurable at baseline). This test will be performed at the central laboratory. A repeat confirmatory UIFE is required to allow classification of response.

In addition to all of the above, the following assessments are required to confirm a CR or sCR:

- SFLC assay and confirmatory SFLC. A normal κ/λ ratio is required to confirm a sCR. This test will be performed at the central laboratory.
- SIFE and UIFE must be repeated and be negative, to confirm CR or sCR, regardless of the level of baseline M-protein in the serum or urine. These tests will be done at the central laboratory.
- Bone marrow aspirate and/or biopsy is required to confirm **laboratory evidence of** CR or sCR (Appendix E). Bone marrow biopsy must be done within 2 weeks of confirmatory laboratory evidence of CR or sCR and will be evaluated at the local pathology laboratory.
- Document disappearance of any soft tissue plasmacytomas, if present at baseline.

9.1.10.4.4 **Progressive Disease**

Progressive disease requires 2 consecutive laboratory assessments of M-protein level before classification as relapse or disease progression and/or the institution of any new therapy. These tests will be done at the central laboratory.

9.1.11 *Adverse Events*

For all subjects, all AEs, regardless of causality, must be recorded in the designated CRF from the first dose of IP **through** 30 days following the last dose of all study drugs **or initiation of new anti-myeloma therapy, whichever comes first.**

9.1.12 *Concomitant Medications*

All concomitant medications must be recorded in the designated CRF from informed consent to 30 days following the last dose of all study drugs **or initiation of new anti-myeloma therapy, whichever comes first.**

9.1.13 *Pharmacokinetic Measurements*

Blood samples will be collected at selected sites to measure plasma concentration of carfilzomib. The PK sampling times are outlined below in **Table 9.**

Note: On days of PK sampling (Cycle 1 Day 1 and Cycle 2 Day 1), carfilzomib must be administered over 30 ± 1 minutes.

Table 9: Blood Sample Collection for Pharmacokinetics

Blood Sample Collection (To measure plasma concentration of carfilzomib)		
Cycle	**Days**	**Timing of Sample Collection**
1 and 2	1	• Pre dose (within 15 minutes before the start of carfilzomib infusion) • 5 minutes post start of carfilzomib infusion • Immediately (within **2** minute**s**) before the end of infusion • At 5, 15, and 30 minutes (± 2 minutes for all time points), and 1, 2, and 4 hours (± 5 minutes for all time points) after the end of carfilzomib infusion

Note: Carfilzomib must be administered over 30 ± 1 minutes on days of PK sampling

9.2 SCHEDULE OF STUDY ASSESSMENTS

Screening assessments (eligibility tests) and all protocol-required assessments, along with their chronology, are tabulated in Appendix A. The timing of all study assessments is provided below in Sections 9.2.1 through Section 9.2.**15**.

9.2.1 *Screening Assessments*

The Screening period for a particular subject commences once the subject signs informed consent. A unique subject number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject (data for screen-failures will be captured).

The following screening assessments must be performed between Days –21 and –1:

- Written informed consent (to be signed before any protocol-specific tests or procedures are conducted)
- Obtain medical history, including prior cancer surgery/radiotherapy, transplant, tobacco history (years of tobacco use; packs per day of cigarettes) and alcohol history (current number of alcoholic drinks per week), neuropathy history, **and ECOG**
- Document multiple myeloma treatment history
- Perform complete physical examination, including neurologic assessment and plasmacytoma assessment
- Obtain height, weight, and BSA
- Measure blood pressure, heart rate, respiratory rate, and temperature

- Perform 12-lead ECG including QTc interval
- 2-D ECHO. Multiple gated acquisition scan is acceptable if ECHO is not available. Repeat ECHO only required for subjects who develop clinically significant CHF. Note: Study does not need to be repeated if previously done within 30 days of informed consent
- Obtain blood sample for chemistry panel (**Table 6**) Note: Tests do not need to be repeated if performed prior to informed consent but within 21 days prior to Cycle 1 Day 1
- Obtain blood sample for hematology panel (**Table 7**) Note: Tests do not need to be repeated if performed prior to informed consent but within 21 days prior to Cycle 1 Day 1
- Obtain blood sample for coagulation tests (PT, **aPTT or PTT** and INR) (**Table 8**). Note: Tests do not need to be repeated if performed prior to informed consent but within 21 days prior to Cycle 1 Day 1
- Perform serum pregnancy test within 7 days of first dose for FCBP
- Obtain blood for SPEP, SIFE, SFLC, quantitative immunoglobulins, beta-2 microglobulin, and serum calcium. Obtain 24-hour urine sample for UPEP and UIFE and urine immunofixation. NOTE: UPEP with UIFE (on a 24-hour collection) is required. No substitute method is acceptable
- Perform bone marrow biopsy and/or aspirate, documenting percent plasma cells in the marrow. Performing FISH is preferred but optional. Note: **Bone marrow assessment does not need to be repeated if it is conducted within 30 days of informed consent**.
- Obtain skeletal survey. **Note: skeletal assessment does not need to be repeated if done within 30 days of informed consent**
- Record concomitant medications
- Determine eligibility according to Inclusion/Exclusion criteria (see Section 4)

9.2.2 *Cycle 1 Days -2 and -1*

- Consider oral hydration for patients with high tumor burden and a risk of TLS. See Section 8.1.1 for additional details. **Antiviral prophylaxis is recommended to be initiated at least 24 hours before the first dose of carfilzomib.**

  Cycle 1 Day 1

The following assessments must be completed on Cycle 1 Day 1 (defined as first day of dosing):

- Obtain weight, and BSA
- Perform physical examination
- Measure blood pressure, heart rate, respiratory rate, and temperature within 1 hour prior to carfilzomib dosing
- Urine or serum pregnancy test must be confirmed negative prior to Cycle 1 Day 1 dose

- Obtain blood sample for chemistry up to 1 day prior to Cycle 1 Day 1 and review results prior to carfilzomib dose
- Obtain blood sample for hematology panel up to 1 day prior to Cycle 1 Day 1 and review results prior to carfilzomib dose
- In subjects participating in the PK sub-study, obtain serial blood samples. See Section 9.3 and Appendix B for additional details.
- Administer IV hydration predose
- Administer dexamethasone 30 minutes to 4 hours prior to carfilzomib
- Administer carfilzomib dose 20 mg/m^2
- Repeat blood pressure and heart rate postdose (between 5 and 60 minutes after carfilzomib infusion is completed)
- Administer IV hydration postdose
- Record AEs
- Record concomitant medications

9.2.3 *Cycle 1 Day 2*

The following assessments must be completed on Cycle 1 Day 2:

- Measure blood pressure, heart rate, respiratory rate, and temperature within 1 hour prior to carfilzomib dosing
- Obtain optional blood sample for serum chemistry
- Administer IV hydration pre carfilzomib dose
- Administer dexamethasone 30 minutes to 4 hours prior to carfilzomib dose
- Administer carfilzomib dose
- Repeat blood pressure and heart rate postdose (between 5 and 60 minutes after carfilzomib infusion is completed)
- Administer IV hydration postdose
- Record AEs
- Record changes in concomitant medications

9.2.4 *Cycle 1 Day 8*

If 20 mg/m^2 carfilzomib is well tolerated (defined as absence of any treatment-related AE requiring dose reduction or delay), the dose will be escalated to 27 mg/m^2 on Cycle 1 Day 8 and thereafter.

The following assessments must be completed on Cycle 1 Day 8:

- Measure blood pressure, heart rate, respiratory rate, and temperature within 1 hour prior to carfilzomib dosing
- Obtain blood sample for serum chemistry (review results up to 1 day prior to carfilzomib dosing)
- Obtain blood sample for hematology panel (review results up to 1 day prior to carfilzomib dosing)
- Administer IV hydration predose
- Administer dexamethasone 30 minutes to 4 hours prior to carfilzomib dose
- Administer carfilzomib dose
- Repeat blood pressure and heart rate postdose (between 5 and 60 minutes after carfilzomib infusion is complete)
- Administer IV hydration postdose
- Record AEs
- Record changes in concomitant medications

9.2.5 *Cycle 1 Day 9*

The following assessments must be completed on Cycle 1 Day 9:

- Measure blood pressure, heart rate, respiratory rate, and temperature within 1 hour prior to carfilzomib dosing
- Obtain optional blood sample for serum chemistry
- Administer IV hydration predose
- Administer dexamethasone 30 minutes to 4 hours prior to carfilzomib dose
- Administer carfilzomib dose
- Repeat blood pressure and heart rate postdose (between 5 and 60 minutes after carfilzomib infusion is completed)
- Administer IV hydration postdose
- Record AEs
- Record changes in concomitant medications

9.2.6 *Cycle 1 Day 15*

The following assessments must be completed on Cycle 1 Day 15:

- Measure blood pressure, heart rate, respiratory rate, and temperature within 1 hour prior to carfilzomib dosing
- Obtain blood sample for serum chemistry (review results up to 1 day prior to carfilzomib dosing)
- Obtain blood sample for hematology (review results up to 1 day prior to carfilzomib dosing)
- Administer IV hydration predose
- Administer dexamethasone 30 minutes to 4 hours prior to carfilzomib
- Administer carfilzomib dose
- Repeat blood pressure and heart rate postdose (between 5 and 60 minutes after carfilzomib infusion is completed)
- Administer IV hydration postdose
- Record AEs
- Record changes in concomitant medications

9.2.7 *Cycle 1 Day 16*

The following assessments must be completed on Cycle 1 Day 16:

- Measure blood pressure, heart rate, respiratory rate, and temperature within 1 hour prior to carfilzomib dosing
- Obtain optional blood sample for serum chemistry
- Administer IV hydration predose
- Administer dexamethasone 30 minutes to 4 hours prior to carfilzomib
- Administer carfilzomib dose
- Repeat blood pressure and heart rate post dose (between 5 and 60 minutes after carfilzomib infusion is completed)
- Administer IV hydration postdose
- Record AEs
- Record changes in concomitant medications

9.2.8 *Cycle 1 Days 22 and 23*

Administer dexamethasone. Oral dexamethasone may be self-administered at home.

9.2.9 *Cycle 2 (and Higher) Day 1*

Please note that though disease assessment laboratories are drawn on day 1 of each cycle, the results of disease assessment labs will not be reported until several days later. Initiation of a cycle may begin while the results of disease assessment laboratories for that cycle are pending.

Response assessments based upon the laboratory results are to be made once the disease assessment laboratory results become available, **following guidelines in Appendix E.** All response assessments require confirmation with 2 consecutive assessments to confirm response or progression (Durie, 2006, **Rajkumar, 2011; Kumar, 2016**).

The following assessments must be completed on Day 1 of Cycle 2 and higher:

- Obtain weight and BSA
- Perform routine physical examination
- Measure blood pressure, heart rate, respiratory rate, and temperature within 1 hour prior to carfilzomib dosing
- Urine or serum pregnancy test must be confirmed negative prior to start of each cycle of therapy for FCBP
- Obtain blood sample for chemistry panel (review results up to 1 day prior to carfilzomib dosing)*
- Obtain blood sample for hematology panel (review results up to 1 day prior to carfilzomib dosing)
- Obtain disease response assessment as outlined in Section 9.1.10.4.2 (± 3-day window, response labs must be drawn prior to administration of Kd)
- If a subject has entered a PR or better or a CR or better, and had a plasmacytoma at baseline, a plasmacytoma evaluation (using the modality used at baseline) must be done to classify response.
- If a subject has entered a CR or better, a bone marrow aspirate and/**or** biopsy is required to confirm response
- In subjects participating in the PK sub-study, obtain serial blood samples (Cycle 2). See Section 9.3 and Appendix B for additional details.
- Administer dexamethasone 30 minutes to 4 hours prior to carfilzomib
- Administer carfilzomib dose
- Repeat blood pressure and heart rate postdose (between 5 and 60 minutes after carfilzomib infusion is completed)

- Record AEs
- Record changes in concomitant medications

* If uric acid is elevated at Cycle 2 (and higher) Day 1, then the recommended IV hydration should be repeated for all of Cycle 2, and, at the investigator's discretion, in conjunction with subsequent cycles.

9.2.10 *Cycle 2 (and Higher) Day 2*

The following assessments must be completed on Day 2 of Cycle 2 and higher:

- Measure blood pressure, heart rate, respiratory rate, and temperature within 1 hour prior to carfilzomib dosing
- Obtain optional blood sample for serum chemistry*
- Administer dexamethasone 30 minutes to 4 hours prior to carfilzomib
- Administer carfilzomib dose
- Repeat blood pressure and heart rate postdose (between 5 and 60 minutes after carfilzomib infusion is completed)
- Record AEs
- Record changes in concomitant medications

* If uric acid was elevated at Cycle 2 (and higher) Day 1, then the recommended IV hydration should be repeated for all of Cycle 2, and, at the investigator's discretion, in conjunction with subsequent cycles.

9.2.11 *Cycle 2 (and Higher) Day 8*

The following assessments must be completed on Day 8 of Cycle 2 and higher:

- Measure blood pressure, heart rate, respiratory rate, and temperature within 1 hour prior to carfilzomib dosing
- Obtain blood sample for serum chemistry (review results up to 1 day prior to carfilzomib dosing)*
- Obtain blood sample for hematology panel (review results up to 1 day prior to carfilzomib dosing)
- Administer dexamethasone 30 minutes to 4 hours prior to carfilzomib
- Administer carfilzomib dose
- Repeat blood pressure and heart rate postdose (between 5 and 60 minutes after carfilzomib infusion is completed)
- Record AEs
- Record changes in concomitant medications

* If uric acid was elevated at Cycle 2 (and higher) Day 1, then the recommended IV hydration should be repeated for all of Cycle 2, and, at the investigator's discretion, in conjunction with subsequent cycles.

9.2.12 *Cycle 2 (and Higher) Day 9*

The following assessments must be completed on Day 9 of Cycle 2 and higher:

- Measure blood pressure, heart rate, respiratory rate, and temperature within 1 hour prior to carfilzomib dosing
- Obtain optional blood sample for serum chemistry*
- Administer dexamethasone 30 minutes to 4 hours prior to carfilzomib
- Administer carfilzomib dose
- Repeat blood Pressure and heart rate postdose (between 5 and 60 minutes after carfilzomib infusion is completed)
- Record AEs
- Record changes in concomitant medications

* If uric acid was elevated at Cycle 2 (and higher) Day 1, then the recommended IV hydration should be repeated for all of Cycle 2, and, at the investigator's discretion, in conjunction with subsequent cycles.

9.2.13 *Cycle 2 (and Higher) Day 15*

The following assessments must be completed on Day 15 of Cycle 2 and higher:

- Measure blood pressure, heart rate, respiratory rate, and temperature within 1 hour prior to carfilzomib dosing
- Obtain blood sample for serum chemistry (review results up to 1 day prior to carfilzomib dosing)*
- Obtain blood sample for hematology panel (review results up to 1 day prior to carfilzomib dosing)
- Administer dexamethasone 30 minutes to 4 hours prior to carfilzomib
- Administer carfilzomib dose
- Repeat blood pressure and heart rate postdose (between 5 and 60 minutes after carfilzomib infusion is completed)
- Record AEs
- Record changes in concomitant medications

* If uric acid was elevated at Cycle 2 (and higher) Day 1, then the recommended IV hydration should be repeated for all of Cycle 2, and, at the investigator's discretion, in conjunction with subsequent cycles.

9.2.14 *Cycle 2 (and Higher) Day 16*

The following assessments must be completed on Day 16 of Cycle 2 and higher:

- Measure blood pressure, heart rate, respiratory rate, and temperature within 1 hour prior to carfilzomib dosing
- Obtain optional blood sample for serum chemistry*
- Administer dexamethasone 30 minutes to 4 hours prior to carfilzomib
- Administer carfilzomib dose
- Repeat blood pressure and heart rate postdose (between 5 and 60 minutes after carfilzomib infusion is completed)
- Record AEs
- Record changes in concomitant medications

* If uric acid was elevated at Cycle 2 (and higher) Day 1, then the recommended IV hydration should be repeated for all of Cycle 2, and, at the investigator's discretion, in conjunction with subsequent cycles.

9.2.15 *Cycle 2 (and Higher) Days 22 and 23*

Administer dexamethasone. Oral dexamethasone may be self-administered at home.

9.2.16 *End of Treatment Assessment (within 30 days of Treatment discontinuation)*

Patients may withdraw from study treatment at any time. Reasons for discontinuation include: Adverse event, pregnancy, withdrawal by subject, and progressive disease.

A patient who develops progressive disease per IMWG-URC (Durie, 2006; **Rajkumar, 2011**; **Kumar, 2016**) must discontinue study treatment. Any patient who misses more than 6 consecutive weeks of study treatment must discontinue study treatment. The reason for discontinuation of study treatment will be documented in the CRF.

The following EOT assessments must be completed within 30 days of treatment discontinuation and prior to initiation of any new antimyeloma therapy:

- Obtain weight and ECOG
- Perform complete physical examination, including neurologic assessment
- Measure blood pressure, heart rate, respiratory rate, and temperature
- Urine or serum pregnancy test must be confirmed negative in FCBP
- Obtain blood sample for chemistry panel
- Obtain blood sample for hematology panel

- Obtain disease response assessment labs as outlined in Section 9.1.10.4.2
- Obtain beta-2 microglobulin and quantitative immunoglobulins
- Record AEs
- Record changes in concomitant medications
- **Obtain ECG as described in Section 9.1.6**

9.3 PHARMACOKINETIC SAMPLING SCHEDULE

Blood samples will be collected from a subset of subjects for PK analysis on Cycle 1 Day 1 and Cycle 2 Day 1 at the following time points **(Appendix B)**:

- Predose (within 15 minutes of initiation of carfilzomib infusion)
- 5 minutes post start of carfilzomib infusion
- Immediately (within **2** minute**s**) before the end of carfilzomib infusion
- At 5, 15, and 30 minutes (± 2 minutes for all time points), and 1, 2, and 4 hours (± 5 minutes for all time points) after the end of carfilzomib infusion

9.4 FOLLOW–UP VISITS

9.4.1 *Active Follow-up*

All subjects who discontinue study treatment for reasons other than PD will be followed in active follow-up every 4 weeks (± 4 days; first visit should be 4 weeks after EOT visit) for disease progression until confirmed PD, withdrawal of consent for further participation, loss to follow-up, **initiation of new, non-protocol anti-myeloma therapy,** death or study closure. During active follow-up subjects will be evaluated every 4 weeks (± 4 days). Multiple myeloma disease assessment will be performed with laboratory evaluations as specified in Section 9.1.10.4.2. **Physical and laboratory assessments will be performed as clinically indicated.**

9.4.2 *Long Term Survival Follow-up*

After disease progression **or initiation of new non-protocol anti-myeloma therapy**, subjects will be followed every 3 months (± 2 weeks) for survival for up to 3 years from start

of study treatment, or until the subject has withdrawn consent for further participation, is lost to follow up, has died, or the sponsor makes the decision to close the study.

10 STUDY DISCONTINUATION

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records. Subjects who withdraw from treatment will be monitored for AEs as described in Section 11 and Appendix D (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE], version 4.03).

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly.

Subjects may withdraw from the study at any time.

The sponsor may elect to discontinue the study at any time.

The investigator may discontinue study treatment for any of the following reasons:

- Disease progression (PD must be verified with 1 set of confirmatory labs
- Unacceptable toxicity
- Subject noncompliance with study procedures, including use of non-protocol therapies
- Requirement for alternative therapy
- Intercurrent illness or worsening of a chronic condition

Subjects who discontinue therapy will be followed for survival and disease status (if discontinuation is prior to progression).

If the reason for withdrawal is an AE, the subject will be followed by the investigator as described in Section 11 until such events resolve, stabilize, and, according to the investigator's judgment, there is no need for further safety follow-up.

If a subject is withdrawn for PD, the date of the laboratory test or procedure indicating disease progression will be used as the date of PD.

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

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

11 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

11.1 ADVERSE EVENT REPORTING

11.1.1 *Definitions*

An AE is any untoward medical occurrence in a study subject administered an investigational product(s) 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 receives the first dose of carfilzomib 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).

Whenever possible, the NCI-CTCAE, version 4.03 should be used to describe the event and for assessing the severity of AEs. For AEs not adequately addressed in the NCI-CTCAE, version 4.03, **Table 10** below should be used.

Table 10: Toxicity Grading for Adverse Events Not Covered in the NCI-CTCAE (Version 4.03)

Severity	Description
GRADE 1 – Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
GRADE 2 – Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental 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

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the current CCSI or prescribing information for a marketed compound or is not listed at the specificity or severity that has been observed. Adverse events or suspected adverse reactions that are mentioned in the CCSI 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 CCSI would be considered "unexpected." Any condition, laboratory abnormality, or physical finding with an onset date prior to the subject receiving the first dose of carfilzomib is considered to be pre-existing in nature and part of the subject's medical history.

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.

11.2 CAUSALITY

A suspected adverse reaction means any AE for which there is reasonable possibility that carfilzomib or dexamethasone caused the AE. "Reasonable possibility" means that there is evidence to suggest a causal relationship between the drug and the AE. An adverse reaction means any AE caused by a drug. The relationship of the AE to the study drug should assessed using the following criteria:

YES: The event is suspected to be related if:

- There is a clinically plausible time sequence between the AE onset and administration of study treatment; and/or
- There is a biologically plausible mechanism for the study treatment to cause or contribute to the AE; and/or
- 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); and/or
- The AE cannot be reasonably attributed to concurrent or underlying illness, other drugs, or procedures.

NO: The event is not suspected to be related if:

- The AE is more likely to be explained by the subject's clinical state, underlying disease, concomitant medical, study or non-study procedure; and/or
- The time occurrence of the AE is not reasonably related to administration of study treatment; and/or
- The event is not related to the investigational product(s)

11.3 ADVERSE EVENTS REPORTING PROCEDURES

11.3.1 *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 receives the first dose of carfilzomib must be promptly documented on the AE CRF. Details of the event must include severity, relationship to study drug(s), duration, action taken, and outcome. Whenever possible, reporting specific diagnosis is preferred when reporting AEs in the AE CRF rather than reporting individual signs and symptoms.

All AEs will be collected from the time the subject receives the first dose of carfilzomib through 30 days after receiving the last dose of carfilzomib, **or until initiation of a new anti-cancer therapy after receiving the last dose of carfilzomib, whichever comes first.** 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 CRF.

The investigator must assess whether the AE is possibly related to carfilzomib or to dexamethasone. This relationship is indicated by a "yes" or "no" response to the question:

"Is there a reasonable possibility that the event may have been caused by a study activity/procedure"? Please refer to Section 11.2 for causality assessment.

All AE severity changes will be recorded on the AE CRF as separate events.

All AEs that are considered related to study drug and all serious adverse events (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 a new AE. 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. 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 sub-investigators and must ensure that these sub-investigators are qualified to perform these duties under the supervision of the investigator.

11.3.2 *Disease Progression*

Discontinuation of treatment due to progression of disease should be recorded on the treatment discontinuation CRF as "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 (eg, 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.** Additional details of the event (such as the contributory causes of death) should be reported on the Death CRF.

11.4 SERIOUS ADVERSE EVENTS DEFINITIONS

An SAE is an AE that meets one 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-patient hospitalization or prolongation of an existing hospitalization (except scheduled hospitalizations for a non-acute, 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)
- 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 one of the outcomes listed in this definition.

11.5 SERIOUS ADVERSE EVENT REPORTING AND DOCUMENTATION REQUIREMENTS

The investigator is responsible for ensuring that all SAEs observed by the investigator or observed by the subject that occur after signing the ICF through 30 days after the last dose of carfilzomib **or initiation of new anti-myeloma therapy** are recorded in the subjects' medical record and are reported to the sponsor.

Sponsor 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. See Appendix J for the SAE contingency form in the event that electronic data capture (EDC) is unavailable. Please refer to the SAE Reporting Guidelines in the study reference manual.

New information relating to a previously reported SAE must be submitted to the sponsor. All new information for SAEs must be sent to sponsor Global Patient Safety within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from

the medical record. Information provided about the SAE must be consistent with that recorded on the Event CRF.

There is no requirement to monitor study subjects for SAEs following the protocol-required reporting period or after the end of study. However, these SAEs can be reported to the sponsor if investigators become aware of such events. If SAEs are reported, the investigator is to report them to Sponsor Global Patient Safety within 24 hours following the investigator's knowledge of the event.

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

The investigator must assess whether the SAE is possibly related to any study-mandated activity or procedure. The relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure"?

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 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 Event CRF.

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

11.6 PREGNANCY AND BREASTFEEDING REPORTING

Pregnancy occurring in a female subject while enrolled in this trial through 30 days after the last dose of carfilzomib received or in a male subject's partner while enrolled in this clinical trial through 90 days after the last dose of carfilzomib received, although not considered an SAE, must be reported to Sponsor Global Patient Safety within 24 hours of the investigator, designee or site personnel learning of the event on a Pregnancy Notification Worksheet

(Appendix I). If the subject is pregnant, all study treatment must be discontinued immediately and the pregnancy must be reported to the investigator within 24 hours. The sponsor will request consent to obtain pregnancy and birth outcome information.

In the event of a pregnancy in the partner of a male subject, the pregnant partner will be asked to complete an informed consent/authorization form for the pregnant partner prior to the collection of any pregnancy data.

If the outcome of the pregnancy meets an SAE criterion (e.g., spontaneous abortion, stillbirth, neonatal death, or fetal or neonatal congenital anomaly), the investigator will report the SAE through the usual processes.

If a female subject breastfeeds while taking carfilzomib, report the lactation case to Sponsor Global Patient Safety within 24 hours of the investigator's knowledge of the event. Report a lactation case on the Lactation Notification Worksheet (Appendix I). The sponsor will request authorization to obtain health information for both the mother and the infant.

12 STATISTICAL CONSIDERATIONS

This section describes the statistical analysis that will be employed for assessing each of the efficacy and safety endpoints considered in the trial. Specifics of the analyses will be provided in the Statistical Analysis Plan (SAP). 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.

12.1 STUDY ENDPOINTS

12.1.1 *Primary Endpoint*

The primary endpoint of this study is:

- Overall response rate after at least 6 cycles of Kd based on best response assessment by the IRC.
- The ORR is defined as the proportion of subjects with a best overall response per IMWG-URC criteria (Durie, 2006; Rajkumar, 2011; **Kumar, 2016**) (Appendix E) of sCR, CR, VGPR, or PR.

12.1.2 *Secondary Endpoints*

The secondary endpoints of this study are:

- ORR after at least 6 cycles of Kd based on response assessed by the investigator
- ORR after at least 12 cycles of Kd based on both investigator and IRC assessment of best response
- CBR after at least 6 cycles and after at least 12 cycles, based on IRC and investigator assessments of best response. Clinical benefit rate is defined as the proportion of subjects with the best overall response of MR or better (Durie, 2006; Rajkumar 2011; **Kumar, 2016**) (Appendix E and Appendix F)
- Duration of response, defined as the time from first evidence of PR or better to disease progression or death due to any cause based on both investigator and IRC response assessments
- Duration of clinical benefit, defined as the time from first evidence of MR or better to disease progression or death due to any cause based on both investigator and IRC response assessments
- Progression-free survival, defined as the time from first dose to the earlier of disease progression or death due to any cause based on both investigator and IRC response assessments
- Overall survival, defined as the time from first dose to the date of death (due to any cause)
- Time to response, defined as the time from the start of study treatment until the start of the first confirmed response (PR or greater) based on both investigator and IRC response assessments
- Pharmacokinetics of carfilzomib

12.1.3 *Exploratory Endpoints:*

Efficacy endpoints related to response and disease progression will be determined based on a validated computer algorithm (ORCA) are:

- **ORR after at least 6 cycles of Kd and after at least 12 cycles**
- **CBR after at least 6 cycles and after at least 12 cycles**
- **Duration of response**
- **Duration of clinical benefit**
- **Progression-free survival**
- **Time to response**

12.2 DETERMINATION OF SAMPLE SIZE

CCI [redacted]

This study will enroll approximately 120 subjects with relapsed and refractory multiple myeloma. CCI [redacted]

CCI [redacted]

CCI

12.3 ANALYSIS POPULATION

The Safety Population is defined as all enrolled patients who received at least 1 dose of carfilzomib. The Safety Population will be the primary population for all efficacy and safety data presented.

12.4 PLANNED ANALYSES

12.4.1 *Primary Analysis*

Primary analysis will be performed when all of the enrolled subjects have received at least 6 cycles of Kd or have discontinued treatment with Kd.

12.4.2 *Final Analysis*

Final analysis will be performed when all of the enrolled subjects have received at least 12 cycles of Kd or have discontinued the treatment with Kd.

Study treatments will be administered until disease progression, unacceptable toxicity, or discontinuation of study treatment for any other reason, whichever occurs first. Dose reductions of carfilzomib and dexamethasone will be permitted per protocol guidelines.

Upon discontinuation of study treatment for reasons other than disease progression, subjects will be followed **as described in Section 9.4.1.**

After disease progression, each subject will be followed **as described in Section 9.4.2**

12.4.3 *Estimated Study Duration*

Enrollment is expected to be completed approximately 16 months after opening.

The duration of screening for each subject is approximately 21 days. The duration of treatment will vary for each subject, with an approximately 12 month estimated median duration of treatment. Patients will be followed until withdrawal of consent, death, loss to follow-up, or the sponsor makes a decision to close the study, whichever occurs first.

Estimated study duration is **about** 48 months.

12.4.4 *Independent Review Committee*

The membership criteria and operational details of the IRC will be described in the IRC charter. The IRC will centrally review the disease related laboratory tests and plasmacytoma assessments. The outcomes determined by the IRC will serve as the primary data source for the primary analysis for ORR6-IRC. Responses will be assessed using the IMWG-URC (Durie, 2006; **Kumar, 2016**) (Appendix E) and minimal response **will be evaluated following IMWG-URC** (**Kumar, 2016,** Appendix F).

12.5 STATISTICAL METHODS

12.5.1 *Efficacy Analyses*

The analysis of all efficacy endpoints will be based on the Safety Population.

12.5.1.1 Primary Efficacy Analysis

Overall response rate after at least 6 cycles of Kd, defined as the proportion of subjects with the best overall response of PR or better, will be determined along with the corresponding 95% exact binomial. Responses will be assessed by the IRC according to the IMWG-URC criteria (ORR6-IRC) (Durie, 2006; Rajkumar, 2011; **Kumar, 2016**).

12.5.1.2 Secondary Efficacy Analyses

Overall response rate (after at least 6 cycles of Kd), based on the investigator's assessment of best response according to IMWG-URC criteria (Durie, 2006; Rajkumar, 2011; **Kumar, 2016**) (**Appendix E**) will be determined along with the corresponding 95% exact binomial.

Overall response rate (after at least 12 cycles of Kd), based on both IRC and investigator assessment of best overall response will be determined along with the corresponding 95% exactly binomial.

Clinical benefit rate, defined as the proportion of subjects with the best overall response (per the investigator) of MR or better, will be determined along with the 95% exact binomial CI. Minimal response will be defined according to **IMWG** criteria (**Kumar, 2016**;Appendix F). Clinical benefit rate will be calculated after at least 6 and after at least 12 cycles of therapy and determined for both investigator and IRC response assessments.

Duration of response (DOR) is defined as the time from first evidence of PR or better to disease progression or death due to any cause. Duration of response will be determined based on both investigator and IRC assessment. Duration of response will be right-censored for subjects who achieve at least a PR based on the censoring conventions defined in Table 12 for PFS. Duration of clinical benefit (DCB) is defined as the time from first evidence of MR or better to disease progression or death due to any cause. Duration of clinical benefit will be right-censored for subjects who at least achieve at least an MR based on the censoring conventions defined in Table 12 for PFS.

Progression-free survival (PFS) is defined as the time from first dose to the earlier of disease progression or death due to any cause. Progression-free survival will be determined based on both investigator and IRC assessment of response. For purposes of calculating PFS, the start

date for PD is the date at which progression is first observed. The duration of PFS will be right-censored for subjects who meet 1 of the conditions **described in Table 12**. For such subjects, the analysis of PFS will be right-censored according to the conventions described in Table 12.

Table 12: Date of Progression or Censoring for Progression-free Survival

Situation	Date of Progression or Censoring	Outcome
No baseline disease assessments	Date of first dose	Censored
New anticancer therapy started before documentation of PD or death	Date of last disease assessment prior to start of new anticancer therapy	Censored
Death or PD immediately after more than 1 consecutively missed disease assessment visit	Date of last disease assessment visit without documentation of PD that is before the first missed visit	Censored
Alive and without PD documentation	Date of last disease assessment	Censored
Death or PD between planned disease assessments	Date of death or first disease assessment showing PD, whichever occurs first	Progressed
Death before first disease assessment	Date of death	Progressed

Overall survival (OS) is defined as the time from the first dose to the date of death due to any cause. Subjects who are alive or lost to follow-up as of the data analysis cutoff date will be right-censored at the subject's date of last contact (last known to be alive). **If the date last known to be alive is after the data analysis cutoff date, the subject will be censored at the data analysis cutoff date.**

Analyses for all time-to-event secondary endpoints (DOR, DCB, PFS, and OS) will be performed using the Kaplan-Meier method, and calculated using both IRC and investigator response assessments. Medians and other quartiles for each endpoint will be estimated in addition to the corresponding two-sided 95% CIs. **Duration of** follow-up for PFS and OS will also be estimated according to the Kaplan-Meier estimate of potential follow-up also termed "reverse Kaplan-Meier" (Schemper 1996).

Time to response is the time from the start of study treatment until the start of the first confirmed response (PR or greater) and will be determined based on both investigator and IRC assessment. The mean, standard deviation, minimum, and maximum will be calculated for time to response.

12.5.1.3 Exploratory Efficacy Analyses

Efficacy endpoints related to response and disease progression determined by ORCA will be analyzed per the methods described in Section 12.5.1.1 and Section 12.5.1.2

12.6 SAFETY ANALYSIS

The analysis of all safety endpoints will be based on the Safety Population.

Safety and tolerability assessments will include extent of exposure to study treatment, AEs (including SAEs), laboratory values, vital sign results, and ECGs. Safety data will be examined on an ongoing basis to ensure subject safety.

Extent of exposure to the study treatment will be summarized using descriptive statistics (number, mean, standard deviation, median, and range). Percent of subjects and number of cycles with doses held (i.e., delayed or missed) and dose reductions will be calculated by treatment group.

Treatment-emergent adverse events are defined as AEs occurring from the first dose of study treatment through 30 days after the last dose of study treatment **or initiation of new anti-myeloma therapy, whichever comes first**. Adverse events will be summarized by MedDRA system organ class and preferred term for the number and percentage of subjects who experienced the event. A subject reporting the same AE more than once will be counted only once when calculating 1) within a given system organ class and 2) within a given system organ class and preferred term combination. For such cases, the maximum NCI-CTCAE toxicity grade and strongest causal relationship to study treatment for the event will be used in the incidence calculations. Treatment-emergent AEs will be tabulated to examine their frequency, severity, and relationship to study treatment. Additional summaries will be provided for SAEs and events resulting in the permanent discontinuation of treatment. All AEs will also be included in individual subject listings. Adverse event reporting will include incidence and severity of congestive heart failure, myocardial infarction, acute kidney injury, adult respiratory distress syndrome, pulmonary hypertension, dyspnea, hypertension, thromboembolic events, thrombocytopenia, hepatic toxicity, and thrombotic microangiopathy/hemolytic uremic syndrome.

Laboratory parameters will be summarized using descriptive statistics, by post-dose shifts relative to baseline, and a summary of the incidence of clinically significant abnormal values for key laboratory analytes. Vital sign results will also be summarized descriptively for each scheduled protocol time point. Changes will be calculated relative to the values collected at Baseline, defined as the last assessment taken prior to the first dose of study drug on Day 1 of Cycle 1.

The analysis of the locally performed ECGs will involve descriptive statistics.

12.7 PHARMACOKINETIC ANALYSES

Pharmacokinetic data analysis set will include **approximately** 15 subjects who received carfilzomib given as a 30 ± 1 minute IV infusion, and have adequate carfilzomib plasma concentration versus time data for the estimation of PK parameters by a noncompartmental analysis. Individual and mean plasma concentration versus time data will be tabulated and plotted for the subjects participating in the PK portion of the study. The following PK parameters will be determined when possible for carfilzomib:

- Maximum plasma concentration (C_{max}, observed)
- Time of maximum plasma concentration (T_{max}, observed)
- Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration and to infinity ($AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$, respectively)
- Terminal elimination half-life ($T_{½}$)
- Plasma clearance (CL)
- Volume of distribution (V_{area})
- Volume of distribution at steady state (V_{ss})
- Mean residence time (MRT)

All PK parameters will be computed using actual elapsed time calculated relative to the start of dose administration.

13 ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

13.1 COMPLIANCE STATEMENT

This study will be conducted in accordance with the protocol and with ICH GCP guidelines, as well as all applicable country and regional regulatory requirements. The investigator is responsible for ensuring that this protocol, the site's informed consent form, and any other information that will be presented to potential subjects are reviewed and approved by the appropriate IRB or IEC prior to the enrollment of any study subjects.

13.2 INSTITUTIONAL REVIEW BOARD OR INDEPENDENT ETHICS COMMITTEE

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

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

13.3 INFORMED CONSENT AND HUMAN SUBJECT PROTECTION

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

The sponsor or its designated representative will provide the investigator with a sample 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 shall be documented in the subject case histories and by the use of a written consent form 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 ICF will be given to the subject or subject's legally authorized representative. The original signed ICF must be maintained by the investigator and available for inspection by the sponsor, its designated representative, or regulatory authority at any time.

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

The study will be carried out in keeping with applicable local laws and regulations. This may include an inspection by sponsor representatives/designees, and/or regulatory authority representatives at any time. The investigator/institution must agree to the inspection of study-related records by the regulatory authority/sponsor representatives/designees, and must allow direct access to source documents to the regulatory authority/sponsor representatives/ designees/IRB/IEC. The investigator must allocate time (investigator and study staff) to discuss findings and relevant issues with the regulatory authority/sponsor representatives.

13.5 DATA COLLECTION AND HANDLING

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

Data collection will involve a data capture system, to which only authorized personnel will have access.

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

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

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to assure subject confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (e.g., copies of CRFs, regulatory documents) will be retained at the study site, along with adequate source documentation. The study file and all source data should be retained until written notification is given by the sponsor or designee for destruction.

13.6 CONFIDENTIALITY

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

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

available for inspection will be handled in strictest confidence and in accordance with applicable local data protection laws.

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

The investigator will maintain a list to enable subjects' records to be identified.

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APPENDIX A: SCHEDULE OF ASSESSMENTS

Table 13: Schedule of Assessments for Subjects in Screening and Cycle 1

Assessments	Visit								
	Screening	Study Cycle 1							
	Day –21 to –1	Day 1	Day 2	Day 8	Day 9	Day 15	Day 16	Day 22	Day 23
Written Informed Consent	×								
Inclusion/Exclusion Criteria	×								
Medical History[a]	×								
Previous treatment history	×								
Complete Physical Examination and ECOG	×								
Height, Weight, and Body Surface Area	×	×							
Substance History[b]	×[q]								
Routine Physical Evaluation		×							
Blood Pressure, Heart Rate, Respiratory Rate and Temperature[c]	×	×	×	×	×	×	×		
12-lead Electrocardiogram, including QT_c	×								
2-D ECHO[d]	×								
Pregnancy Test[e] (for FCBP, Day -7 to -1 and Day 1)	(×)	(×)							
Chemistry Panel[f]	×	×	(×)	×	(×)	×	(×)		
Coagulation tests	×								
Hematology Panel[g]	×	×		×		×			
Beta-2 microglobulin and quantitative immunoglobulins	×								
IV Hydration[h]		×	×	×	×	×	×		
Dexamethasone Dosing[i]		×	×	×	×	×	×	×	×
Carfilzomib Dosing[j]		×	×	×	×	×	×		
Blood pressure, Heart Rate postdose		×	×	×	×	×	×		
Required Disease Assessment Labs[k]	×								
Bone Marrow Biopsy, Aspirate, FISH[l]	×								
Skeletal Survey[m]	×								
Plasmacytoma Evaluation[n] (if clinically indicated)	(×)								
Adverse Events[o]	x	×	×	×	×	×	×		
Concomitant Medications	×	×	×	×	×	×	×		
Pharmacokinetic Assessments[p]		x							

Abbreviations: CRF = case report form; ECHO = echocardiogram; ECOG = Easter Cooperative Oncology Group; FCBP = females of child bearing potential; FISH = fluorescence in situ hybridization; IV = intravenous; PO = orally; SFLC = serum-free light chain; SIFE = serum immunofixation electrophoresis; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis

Footnotes to Table 13

a. Medical history, including prior cancer surgery/radiotherapy, transplant and neuropathy history.
b. Substance History: Record number of alcoholic drinks per week, number of years of tobacco use, and number of packs of cigarettes smoked per day.
c. Measure blood pressure, heart rate, respiratory rate, and temperature within 1 hour prior to dose of carfilzomib. Blood pressure and heart rate will be measured 5 to 60 minutes after completing infusion. The subject should be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position possible (this request is recommended in all following assessments). The position selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF.
d. ECHO is required during screening. Multiple gated acquisition scan is acceptable if ECHO is not available. The screening studies do not need to be repeated if previously done within 30 days of consent. Repeat ECHO only required for subjects who develop clinically significant CHF.
e. For FCBP, obtain serum pregnancy test within 7 days of first dose of carfilzomib. Urine or serum pregnancy test must be confirmed negative locally on Day 1 of each cycle prior to dosing.
f. Obtain chemistry panel (**Table 6)** up to 1 day prior to administration of carfilzomib on Days 1, 8, and 15. A chemistry panel on Days 2, 9 and 16 is optional. Results of local laboratory studies must be reviewed and deemed acceptable prior to administration of carfilzomib.
g. Obtain hematology panel (**Table 7**) up to 1 day prior to administration of carfilzomib on Days 1, 8, and 15. Results must be reviewed and deemed acceptable prior to administration of carfilzomib.
h. IV hydration: 250–500 mL of normal saline (or other IV formulation) before and after each carfilzomib infusion is required during cycle 1
i. Dexamethasone must be administered at least 30 minutes (but no more than 4 hours) prior to carfilzomib on Days 1, 2, 8, 9, 15, and 16. On Days 22 and 23, PO dexamethasone may be self-administered orally at home **(± 2 days).**
j. Carfilzomib is administered at 20 mg/m^2 in Cycle 1 Days 1 and 2; at 27 mg/m^2 in Cycle 1 Days 8, 9, 15, and 16**.**
k. See Section **9.1.10.4.2**for required disease assessment labs (sent to central study laboratory). Obtain blood for SPEP, SIFE, serum calcium, and SFLC and **24-hour** urine sample for UPEP and UIFE. NOTE: UPEP with immunofixation (on a 24-hour collection) is required; no substitute method is acceptable. Details can be found within the study procedures manual.
l. Bone marrow biopsy and/or aspirate documenting percent marrow involvement. FISH is optional at screening. The screening studies do not need to be repeated if previously done within 30 days of consent.
m. Skeletal Survey does not need to be repeated if previously done within 30 days of consent. Skeletal survey includes: lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri.
n. All subjects are required to have a clinical assessment in consideration of formal plasmacytoma evaluation at screening (see Section 9.1.10.1 and Section 9.2.1). If present at baseline, the plasmacytoma(s) should be monitored throughout the study, as clinically appropriate and in accordance with Section-**9.1.10.4.3.**
o. Record all AEs from time of first administration of carfilzomib through 30 days post-last dose of study drug or initiation of a new anti-cancer therapy. Note: All Serious Adverse Events (SAEs) should be collected after signing of the informed consent form (ICF). Record concomitant medications from 21 days before Day 1. Any changes in the subject's concomitant medications during the study, must be recorded on the CRF.
p. Pharmacokinetic (PK) analyses will be characterized in a subset of approximately 15subjects at selected sites. Subjects who do not provide all required PK assessments at Cycle 1 Day 1 and Cycle 2 Day 1 will be replaced. See Section 9.1.13, Section 9.3, or Appendix B for more details.

Table 14: Schedule of Assessments for Subjects in Cycles 2 and Higher

	Visit								EOT/EW[a] Within 30 days	AFU[l]	LTFU[m]
	Study Cycle 2+										
Assessments	**Day 1**	**Day 2**	**Day 8**	**Day 9**	**Day 15**	**Day 16**	**Day 22**	**Day 23**			
Complete Physical Examination									×		
Weight and Body Surface Area	×								×		
Routine Physical Examination	×										
ECOG									×		
Blood Pressure, Heart Rate, Respiratory Rate, and Temperature[b]	×	×	×	×	×	×			×		
12-lead Electrocardiogram including QTc									×		
Pregnancy Test (for FOCB)[c]	(×)								(×)		
Chemistry Panel[d]	×	**(×)**	×	**(×)**	×	**(×)**			×		
Hematology Panel[e]	×		×		×				×		
Beta-2 microglobulin and quantitative immunoglobulin									×		
IV Hydration[f]	(×)	(×)	(×)	(×)	(×)	**(×)**					
Dexamethasone Dosing[g]	×	×	×	×	×	×	×	×			
Carfilzomib Dosing[h]	×	×	×	×	×	×					
Required Disease Response Assessment Labs[i]	×								×	×	
Plasmacytoma Evaluation[j] If present at baseline and entered PR or better or CR or better	(×)										
Bone marrow aspirate and/**or** biopsy if patient has entered a new CR or sCR	(×)										
Adverse Events[k]	×	×	×	×	×	×			×		
Concomitant Medications	×	×	×	×	×	×			×		
Pharmacokinetic Assessments[n]	**x**										
Survival										×	×

Abbreviations: AFU = active follow-up; CR = complete response; ECOG = Easter Cooperative Oncology Group; EOT = End of Treatment; EW = early withdrawal; FOCB = females of child-bearing potential; LTFU = long-term follow-up; PO = orally; sCR = stringent complete response; SFLC = serum-free light chain; SIFE = serum immunofixation electrophoresis; SPEP = serum protein electrophoresis; UIFE = urine immunofixation electrophoresis; UPEP = urine protein electrophoresis;

Footnotes to Table 14

- **a.** All EOT assessments must be performed within 30 days of treatment discontinuation and prior to initiation of any new anti-myeloma treatment.
- **b.** Measure blood pressure, heart rate, respiratory rate, and temperature within one hour prior to carfilzomib dose. The subject should be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position possible (this request is recommended in all following assessments). The position selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. Measure blood pressure and heart rate within 1 hour after completing carfilzomib infusion.
- **c.** Urine or serum pregnancy test must be confirmed negative locally on Day 1 of each cycle prior to dosing and at End of Treatment.
- **d.** Obtain chemistry panel (**Table 6)** up to 1 day prior to administration of carfilzomib on Days 1, 8, 15, and EOT. Results of laboratory studies must be reviewed and deemed acceptable prior to administration of carfilzomib. A chemistry panel on Days 2, 9, and 16 is optional.
- **e.** Obtain hematology panel (**Table 7**) up to 1 day prior to administration of carfilzomib on Days 1, 8, 15, and End of Treatment. Results must be reviewed and deemed acceptable prior to administration of carfilzomib.
- **f.** If uric acid is elevated at Cycle 2 (and higher) Day 1, then the recommended IV hydration should be repeated for all of Cycle 2, and, at the investigator's discretion, in conjunction with the subsequent cycles.
- **g.** Dexamethasone must be administered at least 30 minutes (but no more than 4 hours) prior to carfilzomib on Days 1, 2, 8, 9, 15, and 16. On Days 22 and 23, PO dexamethasone may be self-administered at home **(± 2 days**).
- **h.** Carfilzomib is administered at 27 mg/m^2 for Cycle 2 and subsequent cycles on Days 1, 2, 8, 9, 15, and 16.
- **i.** See Section **9.1.10.4.2** for required labs. Obtain blood for SPEP, SIFE, serum calcium, and SFLC and 24 hour urine sample for UPEP and UIFE. NOTE: UPEP with immunofixation (on a 24-hour collection) is required; no substitute method is acceptable. Details can be found within the study procedures manual.
- **j.** All subjects are required to have a plasmacytoma assessment at Screening (see Section 9.2.1). If present at baseline, the plasmacytoma(s) should be monitored throughout the study, as clinically appropriate and in accordance with Section **9.1.10.4.3**
- **k.** Record all AEs from first administration of carfilzomib through 30 days post-last dose of carfilzomib or initiation of a new anti-cancer therapy. Note: All Serious Adverse Events (SAEs) should be collected after signing of the informed consent form (ICF). Record concomitant medications from 21 days before Day 1. If there is any change in the subject's concomitant medications during the study, it must be recorded on the CRF.
- **l.** AFU – Active follow-up occurs upon discontinuation of therapy in patients who do not have progression of disease. AFU evaluations with disease response assessment labs are required every 4 weeks (± 4 days) until disease progression, death, or withdrawal of consent.
- **m.** LTFU - In long-term follow-up, upon progressive disease, subjects will be followed every 3 months (± 2 weeks) for survival for up to 3 years from start of study treatment.
- **n.** Pharmacokinetic (PK) analyses will be characterized in a subset of approximately 15 subjects at selected sites. Subjects who do not provide all required PK assessments at Cycle 1 Day 1 and Cycle 2 Day 1 will be replaced. See Section 9.1.13, Section 9.3, or Appendix B for more details.

APPENDIX B: PHARMACOKINETIC SAMPLING SCHEDULE

		Pharmacokinetic Sampling Time points[1]								
Cycle	**Day**	**Predose[5]**	**5 min Post Start of Infusion**	**End of Infusion[2]**	**5 min End of Infusion[3]**	**15 min End of Infusion[3]**	**30 min End of Infusion[3]**	**1 hour End of Infusion[4]**	**2 hour End of Infusion[4]**	**4 hour End of Infusion[4]**
1	1	×	×	×	×	×	×	×	×	×
2	1	×	×	×	×	×	×	×	×	×

* All timepoints are relative to the start and end of carfilzomib

1. Carfilzomib must be administered over 30 ± 1 minutes on days of PK sampling
2. Immediately (within **2** minute**s**) before end of infusion
3. The 5, 15, and 30 minute sampling time points after the end of infusion have a window of ± 2 minutes
4. The 1, 2, and 4 hour sampling time points after the end of infusion have a window of ± 5 minutes
5. Within 15 minutes of starting the infusion

APPENDIX C: EASTERN COOPERATIVE ONCOLOGY GROUP (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

APPENDIX D: 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

Publish Date: 28 May 2009

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

APPENDIX E: INTERNATIONAL UNIFORM RESPONSE CRITERIA FOR MULTIPLE MYELOMA

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

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

(cont'd)

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

PD	• Increase of 25% from lowest response value in any of the following:
	  ○ Serum M-component (absolute increase must be ≥ 0.5 g/dL) and/or
	  ○ Urine M-component (absolute increase must be ≥ 200 mg per 24 hours)
	  ○ Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL)
	• Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in size of existing bone lesions or soft tissue plasmacytomas
	• Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.875 mmol/L) attributed solely to the plasma cell proliferative disorder*

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

All response categories (CR, sCR, VGPR, PR) require 2 consecutive laboratory assessments made at any time before the institution of any new therapy **(no minimum interval is required, it can be done the same day, however, to confirm response or progressive disease two discrete samples are required),** 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 assessments are not required to be confirmed by repeat testing.

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.

Response criteria for all categories and subcategories of response except CR and VGPR are applicable only to patients that have "measurable" disease defined by at least one of SPEP ≥ 1 g/dL or UPEP ≥ 200 mg per 24 hours; except for assessment of sCR, CR, or VGPR.

Determination of PD while on study requires two consecutive assessments made at any time **(no minimum interval is required, it can be done the same day, however, to confirm response or progressive disease two discrete samples are required)** 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.

***Development of hypercalcemia attributed soley to the plasma cell proliferative disorder is considered PD when confirmed with two consecutive assessments made at any time (Rajkumar, 2011).**

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. The requirement for bi-directional measurements applies only to plasmacytomas. The plasmacytoma specifications for PD are based on the sponsor's interpretation of the IMWG-URC and practical considerations for study execution.

Sources: Durie 2006; Rajkumar 2011; **Kumar, 2016**.

APPENDIX F: DEFINITION OF MINIMAL RESPONSE PER IMWG CRITERIA

Minimal Response	
Response Subcategory	**Response Criteria**
MR	25% to 49% reduction in the level of serum M-protein **and** a 50% to 89% reduction in 24-hour urinary M-protein, which still exceeds 200 mg /24 hr **If present at baseline, a >50% reduction in the size of soft tissue plasmacytomas is also required**

Abbreviations: hr = hour(s), MR = minimal response.
Sources: **Kumar, 2016**

APPENDIX G: 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 H: SAMPLE DEXAMETHASONE PRESCRIBING INFORMATION

http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Roxane/Dexamethasone/Dexamethasone+Tablets+Solution+and+Intensol.pdf

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=DEXAMETHASONE

APPENDIX I: PREGNANCY AND LACTATION NOTIFICATION WORKSHEETS

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

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

Print 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: _____

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 J: SAE CONTINGENCY FORM

ATTENTION: CONTACT PVOPS CSL PRODUCT REPRESENTATIVE FOR STUDY SPECIFIC 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

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.

not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

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.*

AMGEN Study # XXXXXXXX AMG XXX	**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	Event serious?	If Serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? <Device> No ✓ / Yes ✓	<Device> No ✓ / Yes ✓	<Device> No ✓ / Yes ✓	<Device> No ✓ / Yes ✓	Outcome of Event 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; 06 Congenital anomaly / birth defect; 08 Other medically important serious event

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

IP/Amgen Device:		Prior to, or at time of Event Date of Initial Dose Day Month Year	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/Device>>	☐blinded ☐open label							Lot # _____ ☐Unknown Serial # _____ ☐Unavailable / Unknown
<<IP/Device>>	☐blinded ☐open label							Lot # _____ ☐Unknown Serial # _____ ☐Unavailable / Unknown

AMGEN Study # XXXXXXXX AMG XXX	**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:

Test / Unit / Date (Day Month Year)											

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 # XXXXXXXX AMG XXX	**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 K: SUMMARY OF CHANGES

SUMMARY OF CHANGES Superseding Amendment 1.0 - 12 April 2018 to Amendment 3 23 March 2018

This summary of changes includes changes to the study synopsis and the body of the protocol to maintain consistency.

Section(s)	Changed from	Changed to	Rationale
Title Page	**n/a**	**Date of Superseding Amendment 1.0 12 April 2018**	
Protocol Acceptance Page	n/a	**Superseding Amendment 1.0/12 April 2018**	
Synopsis	For the exploratory objectives, a validated computer algorithm (Onyx Response Computational Assessment [ORCA]) will be used to assess response and disease progression. Time to event endpoints will include: • Duration of response, defined as the time from first evidence of PR or better to disease progression or death due to any cause~~; or will be censored at date of the last valid assessment~~ • Duration of clinical benefit, defined as the time from first evidence of MR or better to disease progression or death due to any cause~~; or will be censored at date of the last valid assessment~~ • Progression-free survival, defined as the time from first dose to the earlier of disease progression or death due to any cause~~; or will be censored at date of the last valid assessment~~ • Overall survival, defined as the time from the first dose to the date of death (due to any cause)~~; or will be censored at date of the last valid assessment~~	**n/a** **The right-censored rule for time to event endpoints is described in Section 12.5.1.2.**	Update to maintain consistency with section 12 Statistical considerations
Section 2.3 Exploratory Objectives	**To estimate ~~ORR,~~ DOR, DCB, PFS and TTR using ORCA**	**n/a**	s/a

Section(s)	Changed from	Changed to	Rationale
Section 5 Subject Screening	Evaluations obtained as part of routine medical care and performed prior to informed consent may be used in place of the study-specific evaluations, provided they meet the time windows described ~~below~~	Evaluations obtained as part of routine medical care and performed prior to informed consent may be used in place of the study-specific evaluations, provided they meet the time windows described **in Section 9.2.1.**	Maintain consistency throughout the body of the protocol
Section 12.4.2 Final Analysis	Upon discontinuation of study treatment for reasons other than disease progression, subjects will be followed ~~every 4 weeks until disease progression or withdrawal of consent.~~ After disease progression, each subject will be followed ~~every 3 months (± 2 weeks) for OS for up to 3 years from the start of their study treatment, or until the subject has withdrawn from further participation, is lost to follow up, has died, or the sponsor makes a decision to close the study.~~	Upon discontinuation of study treatment for reasons other than disease progression, subjects will be followed **as described in Section 9.4.1** After disease progression, each subject will be followed **as described in Section 9.4.2.**	Maintain consistency throughout the body of the protocol
Section 12.4.3 Estimated Study Duration	**n/a**	Estimated study duration is **about** 48 months.	Provide clarification
Section 12.5.1.2 Secondary Efficacy Analyses	The duration of PFS will be right-censored for subjects who meet 1 of the ~~following~~ conditions~~: 1) starting a new anticancer therapy before documentation of disease progression or death; 2) death or disease progression immediately after more than 1 consecutively missed disease assessment visit or; 3) alive without documentation of disease progression before the data cutoff date.~~ ~~Median~~ follow-up for PFS and OS will also be estimated according to the Kaplan-Meier estimate of potential follow-up also termed “reverse Kaplan-Meier” (Schemper 1996).	The duration of PFS will be right-censored for subjects who meet 1 of the conditions **described in Table 12.** **If the date last known to be alive is after the data analysis cutoff date, the subject will be censored at the data analysis cutoff date.** **Duration of** follow-up for PFS and OS will also be estimated according to the Kaplan-Meier estimate of potential follow-up also termed “reverse Kaplan-Meier” (Schemper 1996).	Maintain consistency throughout the body of the protocol

SUMMARY OF CHANGES Amendment 2 (09 November 2016) to Amendment 3 (23 March 2018)

This Summary of Changes outlines noteworthy changes from Amendment 2.0 to Amendment 3.0, and includes rationales for the changes. Revisions to the main body of the protocol have also been made in the synopsis. Deletions of text are presented in strikethrough; added text is presented in bold format. Minor and editorial changes are not listed in the following table.The main purposes for revising the 20140242 (CFZ005) protocol are to:

1. **Include the NCT number on the title page**
2. **Update the name and contact number of the Study Medical Monitor**
3. **Include new references throughout the document**
4. **Add Exploratory Objectives**
5. **Clarify the description of prior regimens**
6. **Clarify the exclusion criteria for prior myocardial infarction**
7. **Clarify the exclusion criteria for subjects with Hepatitis B**
8. **Clarify the exclusion criteria regarding the treatment of active infection**
9. **Clarify the guidelines for toxicity management (Tables 2, 3, and 6[removed])**
10. **Clarify the initiation of antiviral prophylaxis**
11. **Provide a 2 day window for the administration of dexamethasone on days 22 and 23**
12. **Clarify the requirements for receiving radiation therapy and reporting Concomitant Medications.**
13. **Include additional laboratory parameters**
14. **Add ECOG to the screening assessment**
15. **Clarify requirements for skeletal surveys**
16. **Clarify acceptable imaging modalities for plasmacytomas**
17. **Clarify and update the response criteria**
18. **Clarify the criteria for discontinuation of study treatment**
19. **Clarify the reporting period for adverse events**
20. **Clarify the requirements for active and long term follow up**
21. **Increase the window for obtaining the first PK specimen**
22. **Include Amgen templated language re withdrawal of consent**
23. **Update Schedule of Assessments to be consistent with the above revisions**
24. **Make minor editorial revisions**

Summary of Changes Amendment 2 to Amendment 3

Section(s)	Changed from	Changed to	Rationale
Throughout the document	n/a	Additional references added: **Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016; 17:e328-46.** Citations updated throughout the protocol: **Kumar, 2016; Blade, 1998; Kyle, 2009** Minor editorial revisions: e.g., spelling, grammar, bolding	Update to include current references
Cover Page	n/a	**NCT Number NCT03029234**	Regulatory requirement
	PPD [redacted] ~~, MD~~ ~~One Amgen Center Drive~~ ~~Thousand Oaks, CA 91320 USA~~ PPD [redacted]	PPD [redacted] **, MD PhD** One Amgen Center Drive Thousand Oaks, CA 91320 USA PPD [redacted]	Change in Study Medical Monitor
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS	n/a	Added: **aPTT activated partial thromboplastin time** **HBV Hepatitis B virus** **IFN Interferon alfa-2a** **IU International Units** **LLN Lower limit of normal** **ORCA Onyx Response Computational Assessment** **PEG-IFN Peginterferon alfa-2a**	
Synopsis Efficacy variables	Disease response will be assessed per investigator every 4 weeks according to the International Myeloma Working Group – Uniform Response Criteria (IMWG-URC) (Durie, 2006; Rajkumar, 2011; MR will be assessed as per ~~the modified European Group for Blood and Marrow Transplantation [EBMT] criteria, Bladé, 1998; Kyle, 2009~~). An IRC will assess best response after at least 6 and after at least 12 cycles of Kd, from which ORR, CBR,	Disease response will be assessed per investigator every 4 weeks according to the International Myeloma Working Group – Uniform Response Criteria (IMWG-URC) (Durie, 2006; Rajkumar, 2011; Kumar**, 2016);** MR will be assessed as per **Kumar, 2016**. An IRC will assess best response after at least 6 and after at least 12 cycles of Kd, from which ORR, CBR, DOR, DCB, TTR, and PFS will also be determined.	To support exploratory endpoints

Section(s)	Changed from	Changed to	Rationale
	DOR, DCB, TTR, and PFS will also be determined ~~using investigator assessment of response.~~		
Section 1.3.2 Clinical Background	n/a	**As of 19 July 2017, Carfilzomib for Injection has been approved in 31 countries/regions worldwide. It is estimated that the number of patients exposed to carfilzomib from launch in July 2012 through 19 July 2017 was 63 260 in the post marketing setting.**	Updated for clarity
Section 1.4 Dose Rationale	n/a	**The carfilzomib dosing schedule used in this study is used in the ongoing global phase 3 study, "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 20140355).**	Updated for clarity
Section 1.5 Study Rationale	n/a	**To facilitate evaluation of response data, Multiple Myeloma disease response is assessed following the International Myeloma Working Group Uniform Response Criteria (IMWG-URC; Durie 2006, Rajkumar, 2011; Kumar 2016). The primary endpoint in this trial is ORR after each subject has had the opportunity to receive at least 6 cycles of therapy, with response as determined by review of subject data by an Independent Review Committee, following the IMWG-URC.** CCI [redacted] CCI	To support new exploratory endpoints

Section(s)	Changed from	Changed to	Rationale
Section 2.3 Exploratory Objectives	n/a	**2.3 EXPLORATORY OBJECTIVES** **The exploratory objectives of this study are:** **• To evaluate ORR after at least 6 cycles of Kd using ORCA assessment of response** **• To evaluate ORR after at least 12 cycles of Kd using ORCA assessment of response** **• To estimate CBR after at least 6 and after at least 12 cycles of Kd using ORCA** **• To estimate ORR, DOR, DCB, PFS and TTR using ORCA**	Include additional objectives to explore ORCA response criteria
Section 3 Study Design	n/a	Subjects will receive treatment until disease progression, unacceptable toxicity, **initiation of new anti-myeloma therapy**, or discontinuation of study treatment for any other reason, whichever occurs first.	Updated for clarity
Section 4.1 Inclusion Criteria	2. c. In subjects without ~~detectable~~ serum or urine M protein, SFLC > 100 mg/L (involved light chain) and an abnormal κ/λ ratio	2. c. In subjects without **measurable** serum or urine M protein, SFLC > 100 mg/L (involved light chain) and an abnormal κ/λratio 5. Subjects must have received ≥ 2 prior regimens. Induction therapy and stem cell transplant (± maintenance) will be considered as 1 regimen **(as described in 9.1.2)**	Updated for clarity
Section 4.2 Exclusion Criteria	12. Congestive heart failure ([CHF] New York Heart Association Class III to IV), symptomatic ischemia, conduction abnormalities, uncontrolled by conventional intervention ~~or~~ myocardial infarction within 6 months prior to Cycle 1 Day 1	12. Congestive heart failure ([CHF] New York Heart Association Class III to IV), symptomatic ischemia, conduction abnormalities, uncontrolled by conventional intervention. **Subjects cannot have experienced a** myocardial infarction within 6 months prior to Cycle 1 Day 1	Updated for clarity
Section 4.2 Exclusion Criteria	14. Acute active infection requiring systemic antibiotics, antivirals, or antifungals; ~~within~~ 2 weeks prior to Cycle 1 Day 1	14. Acute active infection requiring systemic **(either intravenous or oral)** antibiotics, antivirals, or antifungals; **the treatment must be completed at least** 2 weeks prior to Cycle 1 Day 1	Updated for clarity
Section 4.2 Exclusion Criteria	n/a	15. Known HIV seropositive, hepatitis C infection, and/or hepatitis B (except for patients with hepatitis B surface antigen or core antibody receiving and responding to	Updated for clarity

<table>
<tr><th>Section(s)</th><th>Changed from</th><th>Changed to</th><th>Rationale</th></tr>
<tr><td></td><td></td><td>antiviral therapy directed at hepatitis B: Note: patients who are HepB surface antigen negative at screening, or are receiving IFN or PEG-IFN and have HBV DNA < 2000 IU at screening, or, are receiving a nucleos(t)ide analog and have HBV DNA below LLN at screening are eligible</td><td></td></tr>
<tr><td>Section 8.1.3 Dexamethasone Administration</td><td>n/a</td><td>Note: Days 22 and 23 dosing may be ± 2 days from the scheduled administration day. Every effort should be made to maintain consecutive dosing days.</td><td>Updated for clarity</td></tr>
<tr><td>Table 2: Guidelines for Hematologic Treatment Emergent Toxicities…</td><td>
<table>
<tr><th colspan="3">Neutropenia</th></tr>
<tr><td>When ANC first falls to ~~≤ 0.5~~ × 10^9/L</td><td>If ANC < 0.5 × 10^9/L</td><td>Hold dose until ANC returns to ≥ 0.5 × 10^9/L, then resume at same dose.</td></tr>
<tr><td>For each subsequent drop to ~~≤ 0.5~~ × 10^9/L</td><td>If ANC < 0.5 × 10^9/L</td><td>Hold dose until ANC returns to ≥ 0.5 × 10^9/L, then resume at 1 dose decrement.</td></tr>
</table>
</td><td>
<table>
<tr><th colspan="3">Neutropenia</th></tr>
<tr><td>When ANC first falls to < 0.5 × 10^9/L</td><td>If ANC < 0.5 × 10^9/L</td><td>Hold dose until ANC returns to ≥ 0.5 × 10^9/L, then resume at same dose.*</td></tr>
<tr><td>For each subsequent drop to <0.5 × 10^9/L</td><td>If ANC < 0.5 × 10^9/L</td><td>Hold dose until ANC returns to ≥ 0.5 × 10^9/L, then resume at 1 dose decrement.</td></tr>
</table>
* If the first fall in platelet count or in ANC is observed before D8C1, then administer the protocol-specified 27 mg/m2 on D8C1
</td><td>Updated for clarity</td></tr>
</table>

<table>
<tr><th>Section(s)</th><th>Changed from</th><th>Changed to</th><th>Rationale</th></tr>
<tr><td>Table 3: Guidelines for Non-hematologic Treatment Emergent Toxicities…</td><td><table><tr><td>Infection</td><td>Grade 3 or 4</td><td>Hold carfilzomib ~~until systemic treatment for infection is complete. If ANC > 1.0 × 10^9/L, resume both drugs at same dose. If ANC < 1.0 × 10^9/L,~~ follow hematologic toxicities dose reduction guidelines</td></tr></table></td><td><table><tr><td>Infection</td><td>Grade 3 or 4</td><td>Hold carfilzomib. Once infection is controlled and the subject is without infection-related symptoms, and if ANC > 0.5 × 10^9/L, resume at full dose. If ANC < 0.5 × 10^9/L, follow hematologic toxicities dose reduction guidelines.</td></tr></table></td><td>Updated for clarity</td></tr>
<tr><td>Table 3: Guidelines for Non-hematologic Treatment Emergent Toxicities…</td><td></td><td><table><tr><td>Tumor Lysis Syndrome</td><td>3 or more of the following: …</td><td>Hold carfilzomib until all abnormalities in serum chemistries have resolved; resume at same dose[b]</td></tr></table>[b] If the Tumor Lysis Syndrome laboratory finding is observed before D8C1, administer the protocol-specified 27 mg/m2 when dosing is resumed.</td><td></td></tr>
</table>

Section(s)	Changed from	Changed to	Rationale
Section 8.3 Concomitant Medications	n/a	All concomitant medications must be recorded on the subject's case report form (CRF) from informed consent to 30 days following the last dose of study drug **or initiation of new anti-myeloma therapy, whichever comes first.**	Updated for clarity
Section 8.3.1 Required and Optional Concomitant Medications	n/a	Valacyclovir 500 mg orally, daily (or equivalent antiviral) should continue for the duration of treatment. **Antiviral prophylaxis is recommended to be initiated at least 24 hours before the first dose of carfilzomib.**	Updated for clarity
Section 8.3.2 Excluded Concomitant Medications	n/a	Concurrent therapy with a marketed or investigational anticancer therapeutic (including steroids at a higher dose than this protocol specifies) or radiation to large marrow reserves for either a palliative or therapeutic intent is not allowed. **If a patient requires radiation therapy and wishes to remain on study, the radiation plan must be shared and written approval of the study medical monitor must be obtained prior to the initiation of radiation therapy.**	Updated for clarity
Table 6: Dose Modifications During Carfilzomib Treatment	Deleted	n/a	Table was not consistent with Tables 2 and 3: • Guidelines for Hematologic Treatment Emergent Toxicities in Carfilzomib Patient • Guidelines for Non-hematologic Treatment Emergent Toxicities in Carfilzomib Patients

Section(s)	Changed from	Changed to	Rationale
Section 9.1.8.1 Table 6: Laboratory Tests: Chemistry Panel	n/a	Bicarbonate **or Total CO_2**	Total Co_2 commonly measured in China
Section 9.1.8.3 Table 8: Laboratory Tests: Coagulation Panel	n/a	**aPTT** **Activated partial thromboplastin time** **Abbreviations: PT = Prothrombin time, aPTT = activated partial thromboplastin time, INR = international normalized ratio**	
Section 9.1.10.1 Plasmacytoma Evaluation	n/a	The baseline plasmacytoma evaluation may consist of palpation, ultrasound, computed tomography (CT) scan, magnetic resonance imaging (MRI), or positron emission tomography with diagnostic CT (PET/CT). **Bone scintigraphy is not an acceptable method of plasmacytoma imaging.**	Updated for clarity
Section 9.1.10.2 Skeletal Survey	n/a	Skeletal survey **by plain radiography** will include lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. **Skeletal survey may be done by X-ray, CT, CT/PET, or MRI. Bone scintigraphy is not an acceptable method of skeletal imaging.** The skeletal survey will be conducted at screening and will be repeated if worsening clinical symptoms suggest PD, or as clinically indicated.	Updated for clarity
Section 9.1.10.3 Bone Marrow Aspirate and/or Biopsy	n/a. .	A bone marrow aspirate and/or biopsy, evaluated locally, is required to confirm a **laboratory** response of CR or sCR. .	Updated for clarity
Section 9.1.10.4 Disease Response and Progression Assessments	Minimal response will be assessed using the ~~European Group for Blood and Marrow Transplant (EBMT) criteria (Appendix F).~~	Minimal response will **also** be assessed (**Kumar 2016**; Appendix F.)	Updated for clarity

Section(s)	Changed from	Changed to	Rationale
9.1.10.4.1 Laboratory Assessments of Disease - Screening	n/a	**If multiple disease assessment measurements are available before initiation of therapy, the measurement closest to Cycle 1, Day 1 will be used as baseline (Kumar, 2016).**	Updated for clarity
9.1.10.4.3 Response Assessments	Two consecutive laboratory assessments of M protein level (serum and/or urine), ~~made at least 24 hours apart and assessed at the central study lab~~, drawn at any time before the start of new (off protocol) myeloma therapy. No known evidence of progressive or new bone lesions on skeletal survey if radiographic studies are performed after baseline. SFLC assay and confirmatory SFLC ~~(24 hours to 28 days later)~~. A normal κ/λ ratio is required to confirm a sCR. This test will be performed at the central laboratory Bone marrow aspirate and/or biopsy is required to confirm CR or sCR (Appendix E).	Two consecutive laboratory assessments of M protein level (serum and/or urine) drawn at any time before the start of new (off protocol) myeloma therapy. **No minimum interval is required for SPEP, SIFE, SFLC, it can be done on the same day, however to confirm response or progressive disease, 2 discrete samples are required; testing cannot be based on the splitting of a single sample.** No known evidence of progressive or new bone lesions on skeletal survey if radiographic studies are performed after baseline; **however, radiology examination is not a scheduled assessment after baseline unless clinically indicated.** SFLC assay and confirmatory SFLC. A normal κ/λ ratio is required to confirm a sCR. This test will be performed at the central laboratory Bone marrow aspirate and/or biopsy is required to confirm **laboratory evidence of** CR or sCR (Appendix E).	Updated for clarity
9.1.10.4.4 Progressive Disease	Progressive disease requires 2 consecutive laboratory assessments of M protein level ~~made at least 24 hours apart~~ before classification as relapse or disease progression and/or the institution of any new therapy.	Progressive disease requires 2 consecutive laboratory assessments of M protein level before classification as relapse or disease progression and/or the institution of any new therapy.	Updated for clarity
Section 9.1.11 Adverse events	For all subjects, all AEs, regardless of causality, must be recorded in the designated CRF from the first dose of IP ~~to~~ 30 days following the last dose of all study drugs.	For all subjects, all AEs, regardless of causality, must be recorded in the designated CRF from the first dose of IP **through** 30 days following the last dose of all study drugs **or the initiation of new anti-myeloma therapy**	To be consistent with Section 11
Section 9.1.12 Concomitant Medications	n/a	All concomitant medications must be recorded in the designated CRF from informed consent to 30 days	Updated for clarity

Section(s)	Changed from	Changed to	Rationale
		following the last dose of all study drugs **or initiation of new anti-myeloma therapy, whichever comes first.**	
Section 9.1.14 Survival	Section Deleted: ~~Upon study treatment discontinuation, subjects who have not progressed will be followed in Active Follow up every 4 weeks ± 4 days to monitor for disease progression. Active Follow Up will end upon confirmed PD, withdrawal of consent for further participation, loss to follow up, death, or study closure. After disease progression, subjects will be followed in Long Term Follow Up every 3 months (± 2 weeks) for survival for up to 3 years from start of Cycle 1 Day 1, or until the subject has withdrawn from further participation, is lost to follow up, has died, or the sponsor makes a decision to close the study.~~	n/a	Section incorporated into Section 9.4 Follow-up
Section 9.1.3 and Table 9	Timing of Sample Collection • Immediately (within ~~1~~ minute) before the end of infusion	Timing of Sample Collection • Immediately (within **2** minute**s**) before the end of infusion	To accommodate clinical practice
Section 9.2.1 Screening Assessments	• n/a • Obtain blood sample for coagulation tests (PT, PPT, and INR) • Perform bone marrow biopsy and/or aspirate, documenting percent plasma cells in the marrow. Performing FISH is preferred but optional. Note: ~~Studies do not need to be repeated if previously done within 30 days of informed consent~~. • Obtain skeletal survey. ~~Study does not need to be repeated if previously done within 30 days of informed consent.~~	• Obtain medical history, including prior cancer surgery/radiotherapy, transplant, tobacco history (years of tobacco use; packs per day of cigarettes) and alcohol history (current number of alcoholic drinks per week), neuropathy history, **and ECOG** • Obtain blood sample for coagulation tests (PT, **aPTT, or** PTT**,** and INR) • Perform bone marrow biopsy and/or aspirate, documenting percent plasma cells in the marrow. Performing FISH is preferred but optional. Note: **Bone marrow assessment does not need to be repeated if it is conducted within 30 days of informed consent**	Updated for clarity

Section(s)	Changed from	Changed to	Rationale
		• Obtain skeletal survey. Note**: skeletal assessment does not need to be repeated if done within 30 days of informed consent**	
Section 9.2.2 Cycle 1 Days -2 and -1	n/a	**Antiviral prophylaxis is recommended to be initiated at least 24 hours prior to the first dose**	Updated for clarity
Section 9.2.2 Cycle 2 (and higher) Day 1	n/a	Response assessments based upon the laboratory results are to be made once the disease assessment laboratory results become available, **following guidelines in Appendix E.**	
Section 9.2.16 End of Treatment Assessment…	n/a	**• Obtain ECG as described in Section 9.1.6**	To be consistent with schedule of assessments
Section 9.2.9 Cycle 2 (and higher) Day 1	~~n/a~~	Response assessments based upon the laboratory results are to be made once the disease assessment laboratory results become available, **following guidelines in Appendix E.**	To clarify that response is per protocol
Section 9.4	~~Long Term~~ Follow-up Visits	Follow-up Visits	Updated for clarity
Section 9.4.1	n/a	All subjects who discontinue study treatment for reasons other than PD will be followed in active follow-up every 4 weeks (+or- 4 days; first visit should be 4 weeks after EOT visit) for disease progression until confirmed PD, withdrawal of consent for further participation, loss to follow-up, **initiation of new, non-protocol anti-myeloma therapy,** death, or study closure. During active follow-up, subjects will be evaluated every 4 weeks (+or- 4 days). Multiple myeloma disease assessment will be performed with laboratory evaluations as specified in Section 9.1.10.4.2. **Physical and laboratory assessments will be performed as clinically indicated.**	Updated for clarity

Section(s)	Changed from	Changed to	Rationale
Section 9.4.2 Long Term Follow-up	n/a	After disease progression **or initiation of new non-protocol anti-myeloma therapy,** subjects will be followed every 3 months (± 2 weeks) for survival for up to 3 years from start of study treatment, or until the subject has withdrawn consent for further participation, is lost to follow up, has died, or the sponsor makes the decision to close the study.	Updated for clarity
Section 10 Study Discontinuation	Subjects who withdraw from treatment will be monitored for AEs as described in Section 11 and Appendix D (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE], version 4.03). The investigator may discontinue study treatment for any of the following reasons: •Disease progression (PD must be verified with 1 set of confirmatory labs ~~drawn at least 1 day following initial PD labs)~~	**Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records.** Subjects who withdraw from treatment will be monitored for AEs as described in Section 11 and Appendix D (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE], version 4.03). **If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly.** The investigator may discontinue study treatment for any of the following reasons: •Disease progression (PD must be verified with 1 set of confirmatory labs.	To be consistent with Amgen templated language
Section 11.3.1 General	n/a	All AEs will be collected from the time the subject receives the first dose of carfilzomib through 30 days after	Updated for clarity

Section(s)	Changed from	Changed to	Rationale
		receiving the last dose of carfilzomib**, or until initiation of a new anti-cancer therapy after receiving the last dose of carfilzomib, whichever comes first.**	
Section 11.3.2 Disease Progression	Discontinuation of treatment due to progression of disease should be recorded ~~on the treatment discontinuation CRF as "Disease Progression." If the progression of disease meets any of the serious criteria, as outlined in Section 11.4, it should also be recorded as a SAE in the AE CRF. All disease progression related deaths occurring from the time of signing of the ICF through 30 days after last dose of study drug(s) must be reported on the AE CRF as a SAE using the verbatim term "Disease Progression" rather than signs and/or symptoms that may have been the immediate cause of death.~~ Additional details of the event (such as the contributory causes of death) should be reported on the Death CRF.	Discontinuation of treatment due to progression of disease should be recorded on the treatment discontinuation CRF as "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.** Additional details of the event (such as the contributory causes of death) should be reported on the Death CRF.	Update to be consistent with ARROW protocol
Section 11.5 Serious Adverse Event Reporting and Documentation Requirements	n/a	The investigator is responsible for ensuring that all SAEs observed by the investigator or observed by the subject that occur after signing the ICF through 30 days after the last dose of carfilzomib **or initiation of new anti-myeloma therapy** are recorded in the subjects' medical record and are reported to the sponsor.	New Exploratory endpoints
Section 12.1.3 Exploratory Endpoints	n/a	**12.1.3 Exploratory Endpoints:** **Efficacy endpoints related to response and disease progression will be determined based on a validated computer algorithm (Onyx Response Computational Assessment; [ORCA]) are:** **•ORR after at least 6 cycles of Kd and after at least 12 cycles**	

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<tr><th>Section(s)</th><th>Changed from</th><th>Changed to</th><th>Rationale</th></tr>
<tr><td></td><td></td><td>•CBR after at least 6 cycles and after at least 12 cycles
•Duration of response
•Duration of clinical benefit
•Progression-free survival
•Time to response</td><td></td></tr>
<tr><td>Section 12.4.4. Independent Review Committee</td><td>Responses will be assessed using the IMWG-URC (Durie, 2006; <s>Rajkumar, 2011</s>) (Appendix E) and minimal response as defined by <s>EBMT criteria, Blade, 1998.</s></td><td>Responses will be assessed using the IMWG-URC (Durie, 2006; Kumar, 2016) (Appendix E) and minimal response will be evaluated following IMWG-URC (Kumar, 2016, Appendix F).</td><td></td></tr>
<tr><td>Section 12.5.1.2 Secondary Efficacy Analyses</td><td>Clinical benefit rate, defined as the proportion of subjects with the best overall response (per the investigator) of MR or better, will be determined along with the 95% exact binomial CI. Minimal response will be defined according to <s>EBMT</s> criteria</td><td>Clinical benefit rate, defined as the proportion of subjects with the best overall response (per the investigator) of MR or better, will be determined along with the 95% exact binomial CI. Minimal response will be defined according to IMWG criteria</td><td>Update</td></tr>
<tr><td>Section 12.5.1.3 Exploratory Efficacy analysis</td><td>n/a</td><td>Efficacy endpoints related to response and disease progression determined by ORCA will be analyzed per the methods described in Section 12.5.1.1 and 12.5.1.2</td><td>To support exploratory endpoints</td></tr>
<tr><td>Section 12.6 Safety Analysis</td><td>n/a</td><td>Treatment-emergent adverse events are defined as AEs occurring from the first dose of study treatment through 30 days after the last dose of study treatment or initiation of new anti-myeloma therapy, whichever comes first.</td><td>Updated for clarity</td></tr>
<tr><td>Section 12.7 Pharmacokinetic Analyses</td><td>n/a</td><td>Pharmacokinetic data analysis set will include approximately 15 subjects who received carfilzomib.</td><td>To account for simultaneous collection at multiple sites</td></tr>
<tr><td>Appendix E International Uniform Response Criteria For Multiple Myeloma</td><td><table><tr><td>PR</td><td>• ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours
• If the serum and urine M-protein are not measurable, a decrease ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria.</td></tr></table></td><td><table><tr><td>Stable Disease</td><td>Not meeting criteria for CR, VGPR, PR, MR or PD</td></tr></table></td><td>Patients with unmeasurable serum and urine M protein are not eligible for this trial</td></tr>
</table>

Section(s)	Changed from	Changed to	Rationale
	• ~~If the serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥ 50% reduction in bone marrow PCs is required in place of M-protein, provided baseline percentage was ≥ 30%.~~ • In addition to the above criteria, if present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required. .		
	PD: • Increase of 25% from lowest response value in any of the following: • Serum M-component (absolute increase must be ≥ 0.5 g/dL) and/or • Urine M-component (absolute increase must be ≥ 200 mg per 24 hours) ~~and/or~~ • Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) • ~~Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥ 10%)~~		Revised for clarity (the FLC rules do not directly relate to the above rules for PD)

Section(s)	Changed from	Changed to	Rationale
	• Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.875 mmol/L) attributed solely to the plasma cell proliferative disorder* .		
Appendix E footnotes	All response categories (CR, sCR, VGPR, PR) require 2 consecutive laboratory assessments made ~~at least 24 hours apart~~ at any time before the institution of any new 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 assessments are not required to be confirmed by repeat testing. Response criteria for all categories and subcategories of response except CR and VGPR are applicable only to patients that have "measurable" disease defined by at least one of SPEP ≥ 1 g/dL or UPEP ≥ 200 mg per 24 hours; except for assessment of sCR, CR, or VGPR~~; patients with measurable disease restricted to SPEP will need to be followed only by SPEP. Correspondingly, patients with measurable disease restricted to UPEP will need to be followed only by UPEP.~~ Determination of PD while on study requires two consecutive assessments made at any time ~~at least 24~~	All response categories (CR, sCR, VGPR, PR) require 2 consecutive laboratory assessments made at any time before the institution of any new therapy **(no minimum interval is required, it can be done the same day, however, to confirm response or progressive disease two discrete samples are required),** 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 assessments are not required to be confirmed by repeat testing. n/a Determination of PD while on study requires two consecutive assessments made at any time **(no minimum interval is required, it can be done the same day, however, to confirm response or progressive disease two discrete samples are required)** 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. ***Development of hypercalcemia attributed solely to the plasma cell proliferative disorder is considered PD**	Clarifying language added from Kumar, 2016 Clarifying language added from Kumar, 2016

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<tr><th>Section(s)</th><th>Changed from</th><th>Changed to</th><th>Rationale</th></tr>
<tr><td></td><td>~~hours apart~~ 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.</td><td>when confirmed with two consecutive assessments made at any time (Rajkumar, 2011).</td><td>Clarification due to revision of IMWG-URC – protocol amendment 3 continues to follow the Rajkumar 2011 hypercalcemia definition. Rajkumar 2011 specifies Hypercalcemia, corrected serum calcium >11.5 mg/dL to fulfill criteria for PD. Kumar 2016 does not define PD based on hypercalcemia (hypercalcemia to >11 mg/dL fulfils definition of ‘Clinical Relapse’ per Kumar 2016)</td></tr>
<tr><td>Appendix F Definition of Minimal Response</td><td>DEFINITION OF MINIMAL RESPONSE PER ~~EBMT~~ CRITERIA<table><tr><th colspan="2">Minimal Response</th></tr><tr><th>Response Subcategory</th><th>Response Criteria</th></tr></table></td><td>DEFINITION OF MINIMAL RESPONSE PER IMWG CRITERIA<table><tr><th colspan="2">Minimal Response</th></tr><tr><th>Response Subcategory</th><th>Response Criteria</th></tr></table></td><td>To be consistent with IMWG-URC criteria

Minimal response is not a component of</td></tr>
</table>

Section(s)	Changed from	Changed to	Rationale
	MR: 25% to 49% reduction in the level of serum M-protein ~~or~~ a 50% to 89% reduction in 24-hour urinary M-protein, which still exceeds 200 mg /24 hr, ~~maintained for a minimum of 8 weeks.~~ ~~25% to 49% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination)~~ Abbreviations: ~~EBMT = European Group for Blood and Marrow Transplantation,~~ hr = hour(s), MR = minimal response. Sources: ~~Bladé 1998; Kyle 2009.~~	MR: 25% to 49% reduction in the level of serum M-protein **and** a 50% to 89% reduction in 24-hour urinary M-protein, which still exceeds 200 mg /24 hr **If present at baseline, a >50% reduction in the size of soft tissue plasmacytomas is also required** **Abbreviations: IMWG = International Myeloma Working Group.** hr = hour(s), MR = minimal response**.** **Sources: Kumar, 2016**	the primary endpoint, ORR, but is a component of the secondary endpoints, CBR and DCB. Minimal response was not previously defined in IMWG URC. With the inclusion of MR in the Kumar 2016 IMWG URC, this definition of MR is used in PA3. This change does not impact trial conduct as subjects in minimal response are to continue therapy per protocol.
Tables 13 and 14 Schedule of Assessments	n/a	Footnotes updated to reflect the changes described above	..

This Summary of Changes outlines noteworthy changes from the original protocol to Amendment 2.0, and includes rationales for the changes. Minor and editorial changes are not listed in the following table.

The main purposes for revising the 20140242 (CFZ005) protocol are to:

1. Add a (-1) day to the collection window for chemistry on Day 1, 8 and 15. The chemistry panel for Days 2, 9 and 16 were made optional. Collection of blood on day of dosing does not reflect normal practice. Hence, the requirement of collecting blood on Day 2, 9 and 16 could lead to protocol deviations and/or affect patient enrollment.
2. Remove the requirement to perform FISH analysis, and made it optional. This was done because not all the participating sites are able to perform FISH, so is has been confirmed that this requirement will lead to protocol deviations.
3. Remove language that suggest x-ray for plasmacytoma imaging. X-ray is not used for plasmacytoma imaging and hence, has been removed as a possible imaging technique.
4. Change "Bone Marrow Aspirate and Biopsy" to "Bone Marrow Aspirate and/or Biopsy". Not all the participating sites can do both bone marrow aspirate and biopsy. Hence the wording was update to "and/or" to avoid protocol deviations.
5. Update the primary objective to clarify that the overall response rate (ORR) will be evaluated after "at least" 6 cycles of carfilzomib in combination with dexamethasone (Kd), and a second ORR evaluation will be evaluated after "at least" 12 cycles.
6. Update the End Of Study definitions. Some of the changes include:
    a. Changed primary completion to change it from when all subjects "complete", to "have had the opportunity to complete"
    b. End of Trial was updated to End of Study and the definition was clarified.
7. Clarify in the subject design that subjects "must have received at least two prior regiments".
8. Clarify in the study design that subjects will receive treatment until disease progression, unacceptable toxicity, or discontinuation of study treatment for any other reason, "whichever occurs first".
9. Clarify that subjects of child-bearing potential (FCBP) must have a negative serum pregnancy test within 7 days prior to first dose of carfilzomib, instead of within 21 days prior to enrollment.
10. Clarify that intravenous hydration will be given immediately prior and following carfilzomib administration during Cycle 1. If uric acid is elevated at Cycle 2, Day 1, then the recommended IV hydration should be repeated for all of Cycle 2, and, at the investigator's discretion, in conjunction with subsequent cycles.
11. The excluded concomitant medication was updated to clarify that no alternative anticancer therapy are allowed prior to confirmed progressive disease.
12. Added information regarding Posterior Reversible Encephalopathy Syndrome, Thrombotic Microangiopathy, and Venous Thrombosis to the Safety Guidance for Investigators section
13. Serious Adverse Events are now being collected at the time of signing of the ICF, while the Adverse Events are still being collected at time of first dose.

14. Update the background information
15. Study Medical Monitor information and details regarding sponsor was updated

SUMMARY OF CHANGES Amendment 1 (10 May 2016) to Amendment 2 (09 November 2016)

Significant changes are described in the table below. The revisions done in protocol main body also applies to protocol synopsis. Deletions of text are presented in strikethrough format. Added text is presented in bold format.

Section(s)	Changed from	Changed to	Rationale
Global	10 May 2016	**09 November** 2016	Administrative
Global	To evaluate ORR after 6 cycles of Kd To evaluate ORR after 12 cycles of Kd	To evaluate ORR after **at least** 6 cycles of Kd To evaluate ORR after **at least** 12 cycles of Kd	Clarification
Global	Bone marrow aspirate and biopsy	Bone marrow aspirate and/**or** biopsy	Clarification
Cover page	Sponsor: Onyx Therapeutics, Inc. One Amgen Center Drive Thousand Oaks, CA 91320 USA Study Medical Monitors: PPD, MD Room 1501-1506, No 233 Platinum Tower Taicing Road Shanghai 200020 China PPD PPD, MD, PhD One Amgen Center Drive Thousand Oaks, CA 91320 USA PPD	Sponsor: Onyx Therapeutics, Inc., **an Amgen subsidiary**. One Amgen Center Drive Thousand Oaks, CA 91320 USA Study Medical Monitors: PPD **, MD** One Amgen Center Drive Thousand Oaks, CA 91320 USA PPD	Administrative updates
Cover page	N/A	Add: **Date of Protocol Amendment 2.0** **09 November 2016**	Administrative update

Cover page, Confidentiality Statement	This material is the property of Amgen**,** Inc**.** The material is highly confidential and is to be used only in connection with matters authorized by a senior representative of Amgen, Inc., and no part of it is to be disclosed to a third party without the express prior written permission of Amgen, Inc.	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 Amgen, Inc.	Administrative update
Cover page, Compliance Statement	This study will be conducted in accordance with Protocol 20140242 **(**CFZ005**)**, the International Conference on Harmonisation (ICH), Good Clinical Practice (GCP) guidelines, and the applicable country and regional regulatory requirements.	This study will be conducted in accordance with Protocol 20140242 **(**CFZ005**)**, **the relevant Onyx Therapeutics, Inc., an Amgen Inc. subsidiary, policies and procedures,** the International Conference on Harmonisation (ICH), Good Clinical Practice (GCP) guidelines, and the applicable country and regional **(local)** regulatory requirements.	Administrative update
Protocol Acceptance Page	Issue/Date: 20140242 (CFZ005)/Protocol Amendment 1.0/10 May 2016	Issue/Date: 20140242 (CFZ005)/Protocol Amendment **2.0/09 November** 2016	Administrative update
Synopsis, Name of sponsor/ company:	Amgen, Inc.	**Onyx Therapeutics**, Inc. **(Subsidiary of Amgen, Inc.)**	Administrative update
Synopsis, Study Design, Paragraph 1	N/A	Add: Subjects **must have received at least two prior regimens and** are required to have previous treatment with an alkylating agent or anthracycline, bortezomib, and an IMiD.	Clarification
Synopsis, Study Design, Paragraph 3, 4, and 5	Study treatments will be administered until disease progression, unacceptable toxicity, or discontinuation of study treatment for any other reason. Dose reductions of carfilzomib and dexamethasone will be permitted per protocol guidelines. The enrollment period is anticipated to be approximately 16 months.	Study treatments will be administered until disease progression, unacceptable toxicity, or discontinuation of study treatment for any other reason**, whichever occurs first**. Dose reductions of carfilzomib and dexamethasone will be permitted per protocol guidelines. The enrollment period is anticipated to be approximately 16 months. Upon discontinuation of study treatment for reasons other than disease progression, subjects will be followed every **4 weeks** until disease progression, **or** withdrawal of consent.	Wording changed to secure clarification

	Upon discontinuation of study treatment for reasons other than disease progression, subjects will be followed every month until disease progression, withdrawal of consent, or initiation of new, non-protocol antimyeloma therapy, whichever occurs first.		
Synopsis, Treatment regimen(s):	N/A	Add: Carfilzomib and dexamethasone treatments will be administered in 28-day cycles until disease progression, unacceptable toxicity, or discontinuation from study treatment for any other reason**, whichever occurs first**.	Clarification
Synopsis, Inclusion Criteria	4. Refractory to the most recently received therapy. Refractory disease defined as ≤ 25% response to, or progressing during therapy or within 60 days after completion of therapy	14 Refractory to the most recently received therapy. Refractory disease defined as ≤ 25% response to, or progressing during therapy or within 60 days after **last** therapy	Clarification
Synopsis, Exclusion Criteria	15. Written informed consent in accordance with federal, local, and institutional guidelines 16. Female subjects of child-bearing potential (FCBP) must have a negative serum pregnancy test within 21 days prior to enrollment and agree to use an effective method of contraception during and for 30 days following last dose of carfilzomib. 17. Male subjects must use an effective barrier method of contraception during the study and for 3 months following the last dose of carfilzomib if sexually active with a FCBP.	15. Written informed consent in accordance with **national**, local, and institutional guidelines 16. Female subjects of child-bearing potential (FCBP) must have a negative serum pregnancy test within **7** days prior to **first dose of carfilzomib** and agree to use an effective method of contraception during and for 30 days following last dose of carfilzomib. 17. Male subjects must use an effective barrier method of contraception during the study and for **90 days** following the last dose of carfilzomib if sexually active with a FCBP.	Correction of wording Requirement changed to reflect 003A1 protocol

<table>
<tr><td>Synopsis, Exclusion Criteria</td><td>N/A</td><td>Add:
9. Participation in an investigational therapeutic study within 3 weeks or within 5 drug half-lives (T½) prior to Cycle 1 Day 1, whichever time is greater</td><td>Clarification</td></tr>
<tr><td>Synopsis, Exclusion Criteria</td><td>N/A</td><td>Delete:
19. Subjects in whom the required program of <s>PO and IV</s> fluid hydration is contraindicated, e.g., due to pre-existing pulmonary, cardiac, or renal impairment</td><td>Clarification</td></tr>
<tr><td>Synopsis, Criteria for evaluation, Efficacy variables</td><td>An IRC will assess best response after 6 and after 12 cycles of Kd, from which ORR, CBR, DOR, DCB, TTR, and PFS will also be determined using investigator assessment of response. Subjects will be followed every month for disease progression</td><td>An IRC will assess best response after at least 6 and after at least 12 cycles of Kd, from which ORR, CBR, DOR, DCB, TTR, and PFS will also be determined using investigator assessment of response. Subjects will be followed every 4 weeks for disease progression</td><td>Clarification</td></tr>
<tr><td>Synopsis, Statistical methods and analyses, Paragraph 7</td><td>N/A</td><td>Delete:
<s>OS analysis will be performed at the end of study.</s></td><td>Clarification</td></tr>
<tr><td>List of Abbreviations and Definitions of Terms</td><td>N/A</td><td>Add:<table><tr><td>PD</td><td>progressive disease</td></tr><tr><td>PRES</td><td>posterior reversible encephalopathy syndrome</td></tr><tr><td>TTP/HUS</td><td>thrombotic thrombocytopenic purpura / haemolytic uraemic syndrome</td></tr></table></td><td>Addition of lacking abbreviation</td></tr>
<tr><td>1.1 Multiple Myeloma</td><td>Multiple myeloma, a clonal neoplastic proliferation of plasma cells, is the second most common hematologic malignancy and is responsible for approximately 72,000 annual deaths</td><td>Multiple myeloma, a clonal neoplastic proliferation of plasma cells, is the second most common hematologic malignancy and is responsible for approximately 72,000 annual deaths worldwide (Ferlay 2010). There are an estimated 4,000 multiple myeloma deaths per year in China (Ferlay 2008), 11,000 deaths per year in the United States (US) and</td><td>Clarification and updated data</td></tr>
</table>

	worldwide (Ferlay 2010). There are an estimated 4,000 multiple myeloma deaths per year in China (Ferlay 2008), 11,000 deaths per year in the United States (US) and more than 19,000 deaths per year in Europe (American Cancer Society 2005; Boyle 2005). Multiple myeloma is characterized by anemia, bone destruction, monoclonal gammopathy, renal failure, hypercalcemia, and increased susceptibility to infections. The disease is systemic and chemotherapy is indicated for management of symptomatic myeloma. Current treatment options in China commonly include combination chemotherapy with regimens using melphalan, bortezomib, and thalidomide (an immunomodulatory drug [IMiD]) with and without corticosteroids such as dexamethasone or prednisone and other agents. Eligible subjects 65 to 70 years old or younger frequently undergo consolidation therapy with myeloablative chemotherapy or radiation followed by autologous stem cell transplantation. Although improvements in progression-free survival (PFS) and overall survival (OS) have occurred in the past 5 years, even with the best available approved agents, essentially all patients eventually relapse. Median survival from diagnosis was reported at 42 months (Jawed 2007).	more than 19,000 deaths per year in Europe (American Cancer Society 2005; Boyle 2005). Multiple myeloma is characterized by anemia, bone destruction, monoclonal gammopathy, renal failure, hypercalcemia, and increased susceptibility to infections. Current treatment options in China commonly include combination chemotherapy with regimens using melphalan, bortezomib, and thalidomide (an immunomodulatory drug [IMiD]) with and without corticosteroids such as dexamethasone or prednisone. Eligible subjects 65 to 70 years old or younger frequently undergo **induction** therapy with myeloablative chemotherapy or radiation followed by autologous stem cell transplantation. Although improvements in progression-free survival (PFS) and overall survival (OS) have occurred in the past 5 years, even with the best available approved agents, essentially all patients eventually relapse. Median survival **from the time of diagnosis is approximately 6 years (Kumar et al, 2014)**.	

1.2 Proteasome Background	The proteasome is a multicatalytic proteinase complex that is responsible for degradation of a wide variety of protein substrates within normal and transformed cells. Intracellular proteins targeted for degradation by the proteasome are first ubiquitinated via the ubiquitin conjugation system. Ubiquitinated proteins are cleaved within the proteasome by 1 or more of 3 separate N-terminal threonine protease activities: a chymotrypsin-like activity, a trypsin-like activity, and a caspase-like activity.	The proteasome is a multicatalytic proteinase complex that is responsible for degradation of a wide variety of protein substrates within **both** normal and **malignant** transformed cells. Intracellular proteins targeted for degradation by the proteasome are first ubiquitinated via the ubiquitin conjugation system. Ubiquitinated proteins are cleaved within the proteasome by 1 or more of 3 separate N-terminal threonine protease activities: a chymotrypsin-like, a trypsin-like, and a caspase-like activity.	Clarification
1.3.1 Preclinical Background, Paragraph 1	Carfilzomib (formerly known as PR-171) is a tetrapeptide epoxyketone-based inhibitor of the chymotrypsin-like activity of the 20S proteasome. Carfilzomib, which is structurally and mechanistically different from the dipeptide boronic acid proteasome inhibitor 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).	Carfilzomib (formerly known as PR-171) is a tetrapeptide epoxyketone-based inhibitor of the chymotrypsin-like activity of the 20S proteasome. Carfilzomib, is structurally and mechanistically different from the dipeptide boronic acid proteasome inhibitor bortezomib**. Compared to bortezomib, carfilzomib** showed less off-target activity when measured against a broad panel of proteases including metallo-, aspartyl-, and serine proteases**. B**ortezomib showed off-target inhibitory activity in the nanomolar range against several serine proteases (Arastu-Kapur 2009).	Clarification
1.3.1 Preclinical Background, Paragraph 3	This finding was in contrast to preclinical testing with the boronate class of inhibitors that prohibited uninterrupted daily dosing due to substantial morbidity and mortality. Carfilzomib has also been administered to rats and monkeys for	This finding was in contrast to preclinical testing with the boronate class of **proteasome** inhibitors that prohibited daily dosing due to substantial morbidity and mortality. Carfilzomib has also been administered to rats and monkeys for 6 and 9 months, respectively (once daily dosing for 2 consecutive days for 3 weeks on a 28-day cycle). **In this setting, c**arfilzomib was well tolerated at doses resulting in more than 80% proteasome inhibition, with no behavioral or histological evidence of	Clarification

	6 and 9 months, respectively (once daily dosing for 2 consecutive days for 3 weeks on a 28-day cycle). Carfilzomib was well tolerated at doses resulting in more than 80% proteasome inhibition, with no behavioral or histological evidence of peripheral neuropathy and no neutropenia (Onyx data on file and Carfilzomib Investigator's Brochure [Carfilzomib IB]).	peripheral neuropathy and no neutropenia (Onyx data on file and Carfilzomib Investigator's Brochure [Carfilzomib IB]).	
3 Study Design, Paragraph 4	N/A	Add: Subjects will receive treatment until disease progression, unacceptable toxicity, or discontinuation of study treatment for any other reason**, whichever occurs first**.	Clarification
3.3 End of Study	Primary Completion: The time when all subjects complete the IRC assessment of ORR after 6 cycles of Kd, or have withdrawn from study treatment. End of Trial: The time when the last subject completes 3 years of monitoring after initiation of study treatment, withdraws consent, or dies.	Primary Completion: The time when all subjects **have had the opportunity to complete at least** 6 cycles of Kd, or have withdrawn from study treatment. End of **Study**: **Three years after last subject initiates treatment or when all subjects have withdrawn consent or died, whichever occurs first.**	Clarification Clarification

4.1 Inclusion Criteria	4. Refractory to the most recently received therapy. Refractory disease defined as ≤ 25% response to, or progressing during therapy or within 60 days after completion of therapy 15. Written informed consent in accordance with federal, local, and institutional guidelines 16. Female subjects of child-bearing potential (FCBP) must have a negative serum pregnancy test within 21 days prior to enrollment and agree to use an effective method of contraception during and for 30 days following last dose of drug (more frequent pregnancy tests may be conducted if required per local regulations). 17. Male subjects must use an effective barrier method of contraception during the study and for 3 months following the last dose of carfilzomib if sexually active with a FCBP. Male subjects must not donate sperm during treatment and for an additional 90 days thereafter. Male subjects with pregnant partners must practice sexual abstinence or use a condom during vaginal sex.	4. Refractory to the most recently received therapy. Refractory disease defined as ≤ 25% response to, or progressing during therapy or within 60 days after **last** therapy 15. Written informed consent in accordance with **national**, local, and institutional guidelines 16. Female subjects of child-bearing potential (FCBP) must have a negative serum pregnancy test within **7** days prior to **first dose of carfilzomib** and agree to use an effective method of contraception during and for 30 days following last dose of **carfilzomib** (more frequent pregnancy tests may be conducted if required per local regulations). 17. Male subjects must use an effective barrier method of contraception during the study and for **90 days** following the last dose of carfilzomib if sexually active with a FCBP. Male subjects must not donate sperm during treatment and for an additional 90 days **after last dose of carfilzomib**. Male subjects with pregnant partners must practice sexual abstinence or use a condom during vaginal sex.	Clarification Correction of wording Clarification of requirement Clarification, changed to secure consistency

4.2 Exclusion CriteriaCriteria	N/A	Delete: 19. Subjects in whom the required program of ~~PO or IV~~ fluid hydration is contraindicated, e.g., due to pre-existing pulmonary, cardiac, or renal impairment	Clarification
7.3 Study Drug Accountability	N/A	Delete: 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.	Clarification, not required to document
8.1.1 Oral and Intravenous Hydration	Intravenous hydration will be given immediately prior to carfilzomib administration during Cycle 1 and at the investigator's discretion in Cycle 2 and higher. This will consist of 250 to 500 mL IV normal saline or other appropriate IV fluid. The goal of the hydration program is to maintain robust urine output (e.g., ≥ 2 L/day). Subjects should be monitored periodically during this period for evidence of fluid overload (refer to Company Core Safety Information [the CCSI]). For subjects thought to be at particularly high risk for the development of tumor lysis syndrome (TLS)**,** based on high tumor burden, PO hydration up to 48 hours before starting carfilzomib should be given.	Intravenous hydration will be given immediately prior to **and following** carfilzomib administration during Cycle 1**,** and at the investigator's discretion in Cycle 2 and higher. **If uric acid is elevated at Cycle 2, Day 1, then the recommended IV hydration should be repeated for all of Cycle 2, and, at the investigator's discretion, in conjunction with subsequent cycles.** This will consist of 250 to 500 mL IV normal saline or other appropriate IV fluid. The goal of the hydration program is to maintain robust urine output (e.g., ≥ 2 L/day). Subjects should be monitored periodically during this period for evidence of fluid overload. **In** subjects **considered** to be at risk for tumor lysis syndrome (TLS) **at completion of Cycle 1**, **hydration should be continued into Cycle 2, if clinically indicated. Subjects in whom this program of oral and IV fluid hydration is contraindicated, e.g., due to pre-existing pulmonary, cardiac, or renal impairment, will not be eligible to participate in the clinical trial.**	Clarification, changed to align with the 003A1 study
Table 3: Guidelines for Non-hematologic Treatment Emergent Toxicities in Carfilzomib Patients	N/A	Add: Serum creatinine **clearance** < 15 mL/min (or CrCl decreases to ≤ 50% of baseline), or need for dialysis	Clarification

8.3.2 Excluded Concomitant Medication	Additionally, no alternative anticancer therapy including Chinese herbal medicine with curative intent (other than that administered in the study), or other investigational agents are allowed prior to treatment discontinuation.	Additionally, alternative anticancer therapy including Chinese herbal medicine with curative intent (other than that administered in the study), or other investigational agents are **not** allowed prior to **confirmed progressive disease (PD)**.	Clarification
8.4.4 Thrombocytopenia and Neutropenia	N/A	Delete: ~~Refer to the CCSI for detailed information~~.	Clarification
8.4.6 Gastrointestinal Events	N/A	Delete: ~~Refer to the CCSI for detailed information~~.	Clarification

<table>
<tr>
<td>8.4.6 Gastrointestinal Events, Table 6 Dose Modifications During Carfilzomib Treatment</td>
<td>N/A</td>
<td>Add:
Table 6: Dose Modifications During Carfilzomib Treatment
<table>
<tr><th>Haematologic toxicity</th><th>Recommended action</th></tr>
<tr><td>• Absolute neutrophil count < 0.5 x 10^9/L</td><td>• Stop dose
- If recovered to ≥ 0.5 x 10^9/L, continue at same dose level
• For subsequent drops to < 0.5 x 10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting</td></tr>
<tr><td>• Febrile neutropenia
• Absolute neutrophil count < 0.5 x 10^9/L and an oral temperature > 38.5°C or two consecutive readings of > 38.0°C for 2 hours</td><td>• Stop dose
• If absolute neutrophil count returns to baseline grade and fever resolves, resume at the same dose level</td></tr>
<tr><td>• Platelet count < 10 x 10^9/L or evidence of bleeding with thrombocytopenia</td><td>• Stop dose
- If recovered to ≥ 10 x 10^9/L and/or bleeding is controlled continue at same dose level
• For subsequent drops to < 10 x 10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting carfilzomib</td></tr>
<tr><th>Non-haematologic toxicity (renal)</th><th>Recommended action</th></tr>
<tr><td>• Serum creatinine equal to or greater than 2 × baseline; or
• Creatinine clearance < 15 mL/min (or creatinine clearance decreases to ≤ 50% of baseline) or need for dialysis</td><td>• Stop dose and continue monitoring renal function (serum creatinine or creatinine clearance)
- Carfilzomib should be resumed when renal function has recovered to within 25% of baseline; consider resuming at 1 dose level reduction[a]
• For patients on dialysis receiving carfilzomib, the dose is to be administered after the dialysis</td></tr>
<tr><th>Other non-haematologic toxicity</th><th>Recommended action</th></tr>
<tr><td>• All other grade 3 or 4 non-haematologic toxicities</td><td>• Stop until resolved or returned to baseline
• Consider restarting the next scheduled treatment at 1 dose level reduction</td></tr>
</table></td>
<td>Added dose modification schedule to reflect current carfilzomib SmPC</td>
</tr>
<tr>
<td>8.4.9 Posterior Reversible Encephalopathy Syndrome</td>
<td>N/A</td>
<td>Add:
8.4.9 Posterior reversible encephalopathy syndrome
Cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving carilzomib. Posterior reversible encephalopathy syndrome is a rare, neurological disorder, which can present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension, and the diagnosis is confirmed by neuro-radiological imaging. Carfilzomib should be discontinued if PRES is suspected.</td>
<td>Added info on AE to reflect current CFZ SmPC</td>
</tr>
</table>

8.4.10 Thrombotic Microangiopathy 8.4.11 Venous Thrombosis		***8..4.10 Thrombotic microangiopathy*** **Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome (TTP/HUS) have been reported in patients who received carfilzomib. Some of these events have been fatal. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, treatment should be interrupted. If diagnosis of TTP/HUS is excluded, carfilzomib can be restarted.** ***8.4.11 Venous thrombosis*** **Cases of venous thromboembolic events, including deep vein thrombosis and pulmonary embolism with fatal outcomes, have been reported in patients who received carfilzomib. Patients with known risk factors for thromboembolism, including prior thrombosis, should be closely monitored. Action should be taken to try to minimise all modifiable risk factors (e.g., smoking, hypertension, and hyperlipidaemia). Caution should be used in the concomitant administration of other agents that may increase the risk of thrombosis (e.g., erythropoietic agents or hormone replacement therapy). Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, haemoptysis, arm or leg swelling or pain. Thromboprophylaxis should be considered based on an individual benefit/risk assessment.**	
9.1.9 Pregnancy Evaluation and Contraception Considerations	For FCBPs, a serum pregnancy test that is confirmed negative is required for eligibility. This protocol defines a FCBP as a sexually mature woman who: 1) has not undergone a hysterectomy, bilateral oophorectomy, or bilateral salpingectomy, or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).	For FCBPs, a serum pregnancy test that is confirmed negative is required for eligibility. This protocol defines a FCBP as a sexually mature woman who: 1) has not undergone a hysterectomy, bilateral oophorectomy, or bilateral salpingectomy, or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding **24** consecutive months).	Clarification

9.1.10.1 Plasmacytoma Evaluations	N/A	Delete: The baseline plasmacytoma evaluation may consist of palpation, ultrasound, ~~x-ray,~~ computed tomography (CT) scan, magnetic resonance imaging (MRI), or positron emission tomography with diagnostic CT (PET/CT).	X-ray not an appropriate method to evaluate plasmacytoma
9.1.10.3 Bone Marrow Aspirate and/or Biopsy	9.1.10.3 Bone Marrow Aspirate and Biopsy All subjects will have a baseline bone marrow aspirate and biopsy done and evaluated locally for percent plasma cell involvement and by multiple myeloma-specific interphase fluorescent in situ hybridization (FISH) testing. Percent plasma cells and percentage positivity for chromosome 1 abnormalities, t (4;14), t(6;14), t (11;14), t(14; 20), del(13) and del(17p) will be reported. A bone marrow aspirate and biopsy, evaluated locally, is required to confirm a response of CR or sCR.	9.1.10.3 Bone Marrow Aspirate and**/or** Biopsy All subjects will have a baseline bone marrow aspirate and**/or** biopsy done and evaluated locally for percent plasma cell involvement**.** **M**ultiple myeloma-specific interphase **F**luorescent **I**n **S**itu **H**ybridization (FISH) testing **is optional**. A bone marrow aspirate and**/or** biopsy, evaluated locally, is required to confirm a response of CR or sCR.	FISH made optional since not all sites can perform it
9.1.10.4 Disease Response and Progression Assessments	N/A	Add: Subjects will be evaluated by the investigator for disease response according to the IMWG-URC assessment parameters as outlined in Appendix E on Day 1 of Cycles 2 and higher through to EOT **and during Active Follow-up** (Durie, 2006; Rajkumar, 2011).	Clarification
9.1.10.4.2 Laboratory Assessments of Disease – During Treatment Period and Active Follow-Up	• Urine M-protein: Subjects with urine positive for M-protein levels measured by UPEP (> 200mg/24 hr at baseline) – must have 24 hour urine for UPEP and UIFE done on day 1 of each cycle (± 3 days) from Cycle 2 and beyond, at EOT, and	• Urine M-protein: **All s**ubjects must have 24 hour urine for UPEP and UIFE done on day 1 of each cycle (± 3 days) from Cycle 2 and beyond, at EOT, and during active follow-up. UPEP and UIFE will be performed at the central laboratory.	Clarification

	during active follow-up. UPEP and UIFE will be performed at the central laboratory.		
9.1.10.4.3 Response Assessments	N/A	Delete: 9.1.10.4.3 Response Assessments ~~for sCR, CR, VGPR, and PR~~ In addition to the above-described assessments of multiple myeloma disease marker levels in serum and urine, the following response assessments are required to confirm all response categories (PR, VGPR, CR, sCR, MR~~, PD~~): • Two consecutive laboratory assessments of M-protein level (serum and/or urine), made at least 24 hours apart and assessed at the central study lab, drawn at any time before the start of new (off protocol) myeloma therapy ~~or before the start of the next cycle of study treatment.~~	Clarification
9.2.1 Screening Assessments, Bullet 14	• Perform bone marrow biopsy and aspirate, documenting percent plasma cells in the marrow and findings of multiple myeloma FISH study. Note: Studies do not need to be repeated if previously done within 30 days of informed consent.	• Perform bone marrow biopsy and**/or** aspirate, documenting percent plasma cells in the marrow. **Performing** FISH **is preferred but optional**. Note: Studies do not need to be repeated if previously done within 30 days of informed consent.	FISH made optional since not all sites can perform it
9.2.3 Cycle 1 Day 1, Bullet 5, 6, and 8	• Obtain blood sample for chemistry and review results prior to Cycle 1 Day 1 dose • Obtain blood sample for hematology panel and review results prior to Cycle 1 Day 1 dose • In subjects participating in the PK sub-study, obtain serial blood samples. See Section 9.3 and Appendix B for additional details.	• Obtain blood sample for chemistry **up to 1 day prior to Cycle 1 Day 1** and review results prior to **carfilzomib** dose • Obtain blood sample for hematology panel **up to 1 day prior to Cycle 1 Day 1** and review results prior to **carfilzomib** dose • In subjects participating in the PK sub-study, obtain serial blood samples. See Section 9.3 and Appendix B for additional details. • **Administer IV hydration predose**	Window added since not all sites can get lab results on the same day

9.2.4 Cycle 1 Day 2, Bullet 2 and 7	• Obtain blood sample for serum chemistry (review results prior to carfilzomib dosing)	• Obtain **optional** blood sample for serum chemistry • **Administer IV hydration postdose**	Blood samples on day 2 removed due to logistic reasons
9.2.5 Cycle 1 Day 8, Bullet 2, 3, and 8	N/A	Add: • Obtain blood sample for serum chemistry (review results **up to 1 day** prior to carfilzomib dosing) • Obtain blood sample for hematology panel (review results **up to 1 day** prior to carfilzomib dosing) • **Administer IV hydration postdose**	Window added since not all sites can get lab results on the same day
9.2.6 Cycle 1 Day 9, Bullet 2 and 7	• Obtain blood sample for serum chemistry (review results prior to carfilzomib dosing)	• Obtain **optional** blood sample for serum chemistry • **Administer IV hydration postdose**	Blood sample optional due to logistic reasons
9.2.7 Cycle 1 Day 15, Bullet 2, 3, and 8	N/A	Add: • Obtain blood sample for serum chemistry (review results **up to 1 day** prior to carfilzomib dosing) • Obtain blood sample for hematology panel (review results **up to 1 day** prior to carfilzomib dosing) • **Administer IV hydration postdose**	Window added since not all sites can get lab results on the same day
9.2.8 Cycle 1 Day 16, Bullet 2 and 7	• Obtain blood sample for serum chemistry (review results prior to carfilzomib dosing)	• Obtain **optional** blood sample for serum chemistry • **Administer IV hydration postdose**	Blood sample optional due to logistic reasons
9.2.10 Cycle 2 (and higher) Day 1, Bullet 3, 5 and 6	N/A	Add: • Measure blood pressure, heart rate, respiratory rate, and temperature within 1 hour prior to **carfilzomib** dosing • Urine or serum pregnancy test must be confirmed negative prior to start of each cycle of therapy for FCBP	Window added since not all sites can get lab results on the same day

		• Obtain blood sample for chemistry panel (review results **up to 1 day** prior to **carfilzomib** dosing)* • Obtain blood sample for hematology panel (review results **up to 1 day** prior to **carfilzomib** dosing)	
9.2.10 Cycle 2 (and higher) Day 1, Bullet 7	• Obtain disease response assessment as outlined in Section 9.1.10.4.2 (± 2-day window, response labs must be drawn prior to administration of Kd)	• Obtain disease response assessment as outlined in Section 9.1.10.4.2 (± **3**-day window, response labs must be drawn prior to administration of Kd)	Clarification
9.2.11 Cycle 2 (and higher) Day 2, Bullet 2 and Footnote	• Obtain blood sample for serum chemistry (review results prior to carfilzomib dosing)	• Obtain **optional** blood sample for serum chemistry***** ***If uric acid was elevated at Cycle 2 (and higher) Day 1, then the recommended IV hydration should be repeated for all of Cycle 2, and, at the investigator's discretion, in conjunction with subsequent cycles**.	Blood sample optional due to logistic reasons
9.2.12 Cycle 2 (and higher) Day 8, Bullet 1, 2, 3 and Footnote	N/A	Add: • Measure blood pressure, heart rate, respiratory rate, and temperature within 1 hour prior to **carfilzomib** dosing • Obtain blood sample for serum chemistry (review results **up to 1 day** prior to **carfilzomib** dosing)***** • Obtain blood sample for hematology panel (review results **up to 1 day** prior to **carfilzomib** dosing) *** If uric acid was elevated at Cycle 2 (and higher) Day 1, then the recommended IV hydration should be repeated for all of Cycle 2, and, at the investigator's discretion, in conjunction with subsequent cycles.**	Window added since not all sites can get lab results on the same day
9.2.13 Cycle 2 (and higher) Day 9, Bullet 1, 2, and Footnote	• Measure blood pressure, heart rate, respiratory rate, and temperature within 1 hour prior to dosing • Obtain blood sample for serum chemistry (review results prior to carfilzomib dosing)	• Measure blood pressure, heart rate, respiratory rate, and temperature within 1 hour prior to **carfilzomib** dosing • Obtain **optional** blood sample for serum chemistry***** ***If uric acid was elevated at Cycle 2 (and higher) Day 1, then the recommended IV hydration should be repeated for all of Cycle 2, and, at the investigator's discretion, in conjunction with subsequent cycles**.	Blood sample optional due to logistic reasons

9.2.14 Cycle 2 (and higher) Day 15, Bullet 2, 3, and Footnote	N/A	Add: • Obtain blood sample for serum chemistry (review results **up to 1 day** prior to carfilzomib dosing)***** • Obtain blood sample for hematology panel (review results **up to 1 day** prior to carfilzomib dosing) ***If uric acid was elevated at Cycle 2 (and higher) Day 1, then the recommended IV hydration should be repeated for all of Cycle 2, and, at the investigator's discretion, in conjunction with subsequent cycles**	Window added since not all sites can get lab results on the same day
9.2.15 Cycle 2 (and higher) Day 16, Bullet 2 and Footnote	• Obtain blood sample for serum chemistry (review results prior to carfilzomib dosing)	• Obtain **optional** blood sample for serum chemistry***** ***If uric acid was elevated at Cycle 2 (and higher) Day 1, then the recommended IV hydration should be repeated for all of Cycle 2, and, at the investigator's discretion, in conjunction with subsequent cycles**.	Blood sample optional due to logistic reasons
9.2.17 End of Treatment Assessment (within 30 days of Treatment discontinuation)	N/A	Delete: Adverse event, pregnancy, withdrawal by subject, ~~physician decision,~~ and progressive disease.	Clarification
11.3.2 Disease Progression	All disease progression-related deaths occurring from the time of the first dose of carfilzomib through 30 days after last dose of study drug(s) must be reported on the AE CRF as a SAE using the verbatim term "Disease Progression" rather than signs and/or symptoms that may have been the immediate cause of death	All disease progression-related deaths occurring from the time of **signing of the ICF** through 30 days after last dose of study drug(s) must be reported on the AE CRF as a SAE using the verbatim term "Disease Progression" rather than signs and/or symptoms that may have been the immediate cause of death.	Adjusted to reflect Amgen standards
11.5 Serious Adverse Event	The investigator is responsible for ensuring that all SAEs observed by	The investigator is responsible for ensuring that all SAEs observed by the investigator or observed by the subject that occur after **signing the**	Adjusted to reflect Amgen standards

Reporting and Documentation Requirements	the investigator or observed by the subject that occur after the first dose of carfilzomib through 30 days after the last dose of carfilzomib are recorded in the subjects' medical record and are reported to the sponsor.	**ICF** through 30 days after the last dose of carfilzomib are recorded in the subjects' medical record and are reported to the sponsor.	
12.2 Determination of Sample Size, Paragraph 4	N/A	Delete: CCI [redacted]	Clarification
12.3 Safety Oversight	N/A	Delete: ~~12.3 Safety Oversight~~ ~~A sponsor Drug Safety review team will conduct periodic analysis of study safety data using standard programmed outputs from the clinical and drug safety databases. Study data will be reviewed regularly, but no less often than quarterly, until study closure. These safety reviews may occur more frequently, or be called ad hoc as needed. Any potential safety signals or concerns identified will be escalated by the study medical monitor or designee and sponsor Drug Safety lead to the appropriate sponsor safety governance teams prior to outcome discussions with study investigators.~~	Deleted as this is not part of the Safety Monitoring Plan
12.4.2 Final Analysis	12.5.2 Primary Completion Final analysis will be performed when all of the enrolled subjects have received 12 cycles of Kd or have discontinued the treatment with Kd.	**12.4.2 Final Analysis** Final analysis will be performed when all of the enrolled subjects have received **at least** 12 cycles of Kd or have discontinued the treatment with Kd. **Study treatments will be administered until disease progression, unacceptable toxicity, or discontinuation of study treatment for any other reason, whichever occurs first. Dose reductions of carfilzomib and dexamethasone will be permitted per protocol guidelines.** **Upon discontinuation of study treatment for reasons other than disease progression, subjects will be followed every 4 weeks until disease progression, or withdrawal of consent.** **After disease progression, each subject will be followed every 3 months (± 2 weeks) for OS for up to 3 years from the start of their**	Clarification

<table>
<tr><td></td><td></td><td>study treatment, or until the subject has withdrawn from further participation, is lost to follow-up, has died, or the sponsor makes a decision to close the study.</td><td></td></tr>
<tr><td>12.5.3 End of Study</td><td>N/A</td><td>Delete:
<s>12.5.3 End of Study</s>
<s>The end of study for each subject is defined as 3 years after Cycle 1 Day 1, the date the subject withdraws full consent from the study, is determined to be lost to follow-up, or dies.</s>

<s>As the subjects will be followed every 3 months for survival for up to 3 years from Cycle 1 Day 1,an OS analysis will be performed at the end of study.</s></td><td>Clarification</td></tr>
<tr><td>12.4.3 Estimated Study Duration</td><td>Patients will be followed until withdrawal of consent, death, loss to follow-up, or 3 years after Cycle 1 Day 1.</td><td>Patients will be followed until withdrawal of consent, death, loss to follow-up, or the sponsor makes a decision to close the study, whichever occurs first.</td><td>Clarification</td></tr>
<tr><td>12.4.4 Independent Review Committee</td><td>N/A</td><td>Delete:
The outcomes determined by the IRC will serve as the primary data source for the primary <s>final</s> analysis for ORR6-IRC.</td><td>Clarification</td></tr>
<tr><td>References</td><td>N/A</td><td>Delete:
<s>Jawed I, Lee CM, Tward JD, et al. Survival outcomes for multiple myeloma over three decades: A Surveillance, Epidemiology, and End Results (SEER) analysis. J Clin Oncol. 2007;25 (No. 18S June 20 Supplement): Abstract 8019.</s></td><td>This reference was deleted from the body of the protocol</td></tr>
<tr><td>References</td><td>N/A</td><td>Add:
Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patient. Leukemia. 2014;28:1122-1128.</td><td>Updated reference added</td></tr>
<tr><td>Appendix A. Schedule of Assessments, Table 14</td><td>N/A</td><td>Add:
<table>
<tr><td></td><td>Day -21 to -1</td><td>Day 1</td><td>Day 2</td><td>Day 8</td><td>Day 9</td><td>Day 15</td><td>Day 16</td></tr>
<tr><td>Chemistry Panel[f]</td><td>x</td><td>x</td><td>(x)</td><td>x</td><td>(x)</td><td>x</td><td>(x)</td></tr>
<tr><td>Adverse Events[o]</td><td>x</td><td>x</td><td>x</td><td>x</td><td>x</td><td></td><td></td></tr>
</table></td><td>Correction to previous version</td></tr>
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		Pharmacokinetic Assessments[p] x	
Appendix A: Schedule of Assessments, Footnoes to Table 14	e. For FCBP, obtain serum pregnancy test within 7 days of first dose of study drug. Urine or serum pregnancy test must be confirmed negative locally on Day 1 of each cycle prior to dosing. f. Obtain chemistry panel (Table 7) prior to each administration of carfilzomib on Days 2, 8, 9, 15, and 16. Results of local laboratory studies must be reviewed and deemed acceptable prior to administration of carfilzomib. g. Obtain hematology panel (Table 8) prior to administration of carfilzomib on Days 8 and 15. Results must be reviewed and deemed acceptable prior to administration of carfilzomib. l. Bone marrow biopsy and aspirate documenting percent marrow involvement and multiple myeloma FISH will be performed at screening. The screening studies do not need to be repeated if previously done within 30 days of consent. o. Record all AEs from time of first administration of carfilzomib through 30 days post-last dose of study drug or initiation of a new anti-cancer therapy.	e. For FCBP, obtain serum pregnancy test within 7 days of first dose of **carfilzomib**. Urine or serum pregnancy test must be confirmed negative locally on Day 1 of each cycle prior to dosing. f. Obtain chemistry panel (Table **7**) **up to 1 day** prior to administration of carfilzomib on Days **1**, 8, **and** 15. **A chemistry panel on Days 2, 9 and 16 is optional.** Results of local laboratory studies must be reviewed and deemed acceptable prior to administration of carfilzomib. g. Obtain hematology panel (Table **8**) **up to 1 day** prior to administration of carfilzomib on Days **1,** 8**,** and 15. Results must be reviewed and deemed acceptable prior to administration of carfilzomib. l. Bone marrow biopsy and/**or** aspirate documenting percent marrow involvement. FISH **is optional** at screening. The screening studies do not need to be repeated if previously done within 30 days of consent. o. Record all AEs from time of first administration of carfilzomib through 30 days post-last dose of study drug or initiation of a new anti-cancer therapy. **Note: All Serious Adverse Events (SAEs) should be collected after signing of the informed consent form (ICF).** **p. Pharmacokinetic (PK) analyses will be characterized in a subset of approximately 15 subjects at selected sites. Subjects who do not provide all required PK assessments at Cycle 1 Day 1 and Cycle 2 Day 1 will be replaced. See Section 9.1.13, Section 9.3, or Appendix B for more details.**	Reflects changes made to body of protocol

<table>
<tr>
<td>Appendix A: Schedule of Assessments, Table 15</td>
<td>N/A</td>
<td>Add:
<table>
<tr><th>Assessments</th><th>Day 1</th><th>Day 2</th><th>Day 8</th><th>Day 9</th><th>Day 15</th><th>Day 16</th></tr>
<tr><td>Chemistry Panel</td><td>x</td><td>(x)</td><td>x</td><td>(x)</td><td>x</td><td>(x)</td></tr>
<tr><td>IV Hydration</td><td>(x)</td><td>(x)</td><td>(x)</td><td>(x)</td><td>(x)</td><td>(x)</td></tr>
<tr><td>Pharmacokinetic Assessments[n]</td><td>x</td><td></td><td></td><td></td><td></td><td></td></tr>
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<td>Correction to previous version</td>
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<td>Appendix A: Schedule of Assessments, Table 15 Footnotes</td>
<td>d. Obtain chemistry panel (Table 7) prior to each administration of carfilzomib on Days 1, 2, 8, 9, 15, 16, and EOT. Results of laboratory studies must be reviewed and deemed acceptable prior to administration of carfilzomib.</td>
<td>d. Obtain chemistry panel (Table 7) up to 1 day prior to administration of carfilzomib on Days 1, 8, 15, and EOT. Results of laboratory studies must be reviewed and deemed acceptable prior to administration of carfilzomib. A chemistry panel on Days 2, 9, and 16 is optional.</td>
<td>Reflects changes made to body of protocol</td>
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<tr>
<td>Appendix A: Schedule of Assessments, Table 15 Footnotes</td>
<td>N/A</td>
<td>Add:
e. Obtain hematology panel (Table 8) up to 1 day prior to administration of carfilzomib on Days 1, 8, 15, and End of Treatment. Results must be reviewed and deemed acceptable prior to administration of carfilzomib.
k. Record all AEs from first administration of carfilzomib through 30 days post-last dose of carfilzomib or initiation of a new anti-cancer therapy. Note: All Serious Adverse Events (SAEs) should be collected after signing of the informed consent form (ICF).

n. Pharmacokinetic (PK) analyses will be characterized in a subset of approximately 15 subjects at selected sites. Subjects who do not provide all required PK assessments at Cycle 1 Day 1 and Cycle 2 Day 1 will be replaced. See Section 9.1.13, Section 9.3, or Appendix B for more details.</td>
<td>Reflects changes made to body of protocol</td>
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<tr>
<td>Appendix B: Pharmacokinetic Sampling Schedule</td>
<td><table><tr><td>Predose</td><td>5 min Postdose</td></tr></table></td>
<td><table><tr><td>Predose[5]</td><td>5 min Post Start of Infusion</td></tr></table></td>
<td>Clarification</td>
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</table>

Appendix B: Pharmacokinetic Sampling Schedule, Footnote	N/A	Add: *** All timepoints are relative to the start and end of carfilzomib** **15 Within 15 minutes of starting the infusion**	Clarification