

CLINICAL STUDY PROTOCOL

Protocol Number: PX-171-010

Study Title: An Open-Label, Single-Arm, Phase 2 Study of Extended Carfilzomib Therapy in Subjects Previously Enrolled in Carfilzomib Treatment Protocols

Investigational Product: Carfilzomib for Injection

Investigational New Drug: IND 71,057

Sponsor: Onyx Therapeutics, Inc.
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South San Francisco, CA 94080
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Original Protocol Date: 24 February 2009

Amendment 1: 11 June 2009

Amendment 2: 09 April 2010

Amendment 3: 25 March 2011

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SIGNATURE PAGE

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Approved By:

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APPROVALS STATEMENT

This document is signed with electronic signatures at Onyx Therapeutics, Inc. (a wholly owned subsidiary of Onyx Pharmaceuticals, Inc.). Electronic signatures made by our employees, agents, or representatives, located anywhere in the world, are the legally binding equivalent of traditional handwritten signatures.

PROTOCOL ACCEPTANCE PAGE

PROTOCOL NUMBER: PX-171-010

PROTOCOL TITLE: An Open-Label, Single Arm Phase 2 Study of Extended Carfilzomib Therapy in Subjects Previously Enrolled in Carfilzomib Treatment Protocols

PROTOCOL DATE: 24 February 2009

AMENDMENT 1: 11 June 2009

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AMENDMENT 3: 25 March 2011

By signing this protocol acceptance page, I confirm I have read, understood, and agree to conduct the study in accordance with the current protocol.

Principal Investigator Name (Printed)

Principal Investigator Signature

Date

Please return original form to Onyx Therapeutics, Inc. or designee. Please retain a copy for your study files.

This study is to be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, Title 21 of the Code of Federal Regulations §§ 50, 56, and 312, the International Conference on Harmonization E6, and any applicable regulatory requirements.

The study protocol and any amendments are to be reviewed by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) before implementation.

Written informed consent is to be obtained from each study subject prior to the conduct of any study procedures which exceed or differ from standard practice at the study site.

Confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Onyx Therapeutics.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
BSA	body surface area
CBC	complete blood count
CFR	Code of Federal Regulations
CHF	congestive heart failure
CR	complete response
CRu	unconfirmed complete response
CRO	clinical research organization
CrCl	creatinine clearance
CRF	case report form(s)
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	curricula vitae
DLT	dose-limiting toxicity
ECOG	Eastern Cooperative Oncology Group
FAS	full analysis set
FCBP	females of childbearing potential
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IV	intravenous
MM	multiple myeloma
MR	minimal response
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PR	partial response
QDx2	consecutive day dosing

Abbreviation	Definition
QDx5	daily dosing for 5 consecutive days
QIU	Qualified Investigator Undertaking Form
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
sCR	stringent complete response
SD	stable disease
TLS	tumor lysis syndrome
TTP	time to tumor progression
US	United States
VGPR	very good partial response

PROTOCOL SYNOPSIS: PX-171-010

TITLE	An Open-Label, Single-Arm Phase 2 Study of Extended Carfilzomib Therapy in Subjects Previously Enrolled in Carfilzomib Treatment Protocols
OBJECTIVE	To evaluate the safety and efficacy of long-term or continuing carfilzomib treatment in subjects who have completed a previous carfilzomib treatment study.
STUDY DESIGN	<p>This is a multi-center, open-label, Phase 2 study of carfilzomib to monitor the safety and efficacy of long-term or continuing carfilzomib therapy for subjects who previously completed a primary carfilzomib treatment study. Only subjects who have adequately completed a prior carfilzomib study will be eligible for the current study.</p> <p>Safety endpoints will consist of the following: (1) all reported Grades 3 and 4 adverse events (AEs), (2) all reported peripheral neuropathy AEs (Grades 1–4), (3) all serious adverse events (SAEs), and (4) Grades 1–4 AEs leading to either a missed carfilzomib dose, carfilzomib dose reduction, or discontinuation. In the event of a toxicity leading to a dose reduction or discontinuation, pertinent laboratory measurements and concomitant medications will be collected and monitored as unscheduled visits.</p> <p>Efficacy endpoints will include time to tumor progression (TTP), progression-free survival (PFS), and overall survival (OS). Data on the first subsequent treatment regimen following carfilzomib study discontinuation will also be collected.</p>
STUDY POPULATION	Approximately 100 subjects from approximately 50 sites in the United States and Canada will be eligible for participation in the extended carfilzomib therapy study. Additional subjects may be enrolled should the number of eligible subjects exceed 100.
INCLUSION CRITERIA	<p>Subjects must meet all of the following inclusion criteria to be eligible to enroll in this study:</p> <p><i>Disease Related</i></p> <ol style="list-style-type: none">1. Previous completion of a carfilzomib study within 90 days prior to first dose of study drug for Protocol PX-171-010.2. Disease Assessments performed within 30 days prior to first dose of study drug for Protocol PX-171-010. <p><i>Ethical/Other</i></p> <ol style="list-style-type: none">3. Written informed consent in accordance with federal, local, and institutional guidelines.4. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test, with a sensitivity of at least 50 mIU/mL, within 3 days prior to first dose of study drug for Protocol PX-171-010.

	<p>5. Subjects must agree to adhere to the study visit schedule and other study requirements and receive outpatient treatment and laboratory monitoring at the institution that administers the drug.</p>
EXCLUSION CRITERIA	<p>Subjects who meet any of the following exclusion criteria are not eligible to be enrolled in this study:</p> <p><i>Disease Related</i></p> <ol style="list-style-type: none">1. Administration of an intervening chemotherapy between the time of previous carfilzomib study termination and first dose of study drug for Protocol PX-171-010. <p><i>Concurrent Conditions</i></p> <ol style="list-style-type: none">2. Pregnant or lactating females.3. Diagnosis of a new malignancy of a different tumor type.
PROCEDURES	<p>After screening, eligibility determination, and enrollment; subjects will receive carfilzomib according to the doses and schedules as summarized in the Study Treatment section of the Synopsis. Standard monitoring for hematologic and non-hematologic toxicity is outlined in Section 6.2. Subjects may continue carfilzomib treatment until disease progression and discussion with Onyx Medical Monitor, diagnosis of new malignancy, unacceptable toxicity, Investigator discretion, voluntary withdrawal, or commercial availability of carfilzomib.</p> <p>Safety Measures. A complete blood count (CBC) including platelets and basic metabolic chemistry panel (eg, Chem 7 or 8) will be performed on Day 1 of each cycle. Other general safety monitoring (eg, physical examinations, imaging, specialty tests, etc.) shall be in accordance with institutional guidelines and as clinically indicated. These data will not be routinely collected.</p> <p>Efficacy Measures. Tumor measurements and efficacy assessments will be in accordance with the methods employed in the subject's prior carfilzomib study. For subjects participating in a carfilzomib trial without prior tumor measurements and efficacy assessments (eg, PX-171-008), tumor assessments employing standard institutional methods will be conducted at the time of screening for the current study. Disease assessments (eg, extent of disease measurements and objective response category) will occur within 30 days prior to enrollment to determine eligibility, at least every 3 months throughout study participation, and at end of study. Refer to Appendix D–E for Response Criteria.</p> <p>For subjects with multiple myeloma (MM) entering the extended study with a partial response (PR), minimal response (MR), or stable disease (SD); bone marrow biopsies for cytogenetic and fluorescence <i>in situ</i> hybridization (FISH) evaluation will be optional at screening. A bone marrow biopsy in these subjects will also be optional at end of study for cytogenetic and FISH evaluation if the reason for study</p>

	<p>discontinuation is disease progression. For subjects with MM entering the extended study with stringent complete response (sCR), complete response (CR), or very good partial response (VGPR), a bone marrow biopsy for cytogenetic and FISH analyses will also be optional upon the establishment of disease progression.</p>
STUDY TREATMENT	<p>Carfilzomib will be administered intravenously (IV), using the same method, dose level and frequency as administered in the last cycle of the subject's previous carfilzomib study; carfilzomib doses will be administered on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle (or the same dose level and frequency as administered at the last visit of the prior carfilzomib study) until disease progression and discussion with the Onyx Medical Monitor, diagnosis of new malignancy, unacceptable toxicity, Investigator discretion, voluntary withdrawal, or commercial availability of carfilzomib. Each dose will consist of Carfilzomib for Injection administered on a mg/m² basis. Subjects with a body surface area (BSA) > 2.2 m² will receive a dose based upon a 2.2 m² BSA. Dosing will be continued or modified based upon clinical and laboratory findings.</p> <p>Decreased carfilzomib dosing frequency to include dosing on Days 1, 2, 15 and 16 (eg, every other week dosing schedule), will be permitted at the discretion of the Investigator; the Onyx Therapeutics Medical Monitor may be consulted as needed. Carfilzomib dose reductions for toxicity, to a minimum dose of 11 mg/m², will be permitted following discussion with the Medical Monitor, as needed. Missed doses of carfilzomib will not be made up.</p> <p>Dose escalations above the original dose level are permitted.</p> <p>For subjects with evidence of disease progression, the Onyx Medical Monitor must be consulted prior to the dose escalation or termination from study.</p> <p>Acyclovir or valacyclovir should be given to all subjects with a history of herpes simplex or zoster, per institutional prophylaxis guidelines, unless contraindicated.</p>
PRIMARY ENDPOINT	<ul style="list-style-type: none">• Safety
SECONDARY ENDPOINTS	<ul style="list-style-type: none">• Overall Survival (OS)• Progression Free Survival (PFS)• Time to Progression (TTP)

STATISTICAL METHODS	<p>Safety Analyses: Safety data analysis will be conducted on all subjects receiving at least 1 dose of study treatment. Analyses will consist of data summaries for reported AEs. The number and percentage of subjects experiencing 1 or more AEs will be summarized by dose, relationship to study drug, and severity.</p> <p>Disease Response Analyses: Response to treatment will be tabulated using the criteria employed in the subject's prior carfilzomib treatment study.</p> <p>For subjects participating in a carfilzomib trial without explicit tumor measurements and defined response criteria (eg, PX-171-008), response to treatment will be tabulated using the appropriate method (eg, RECIST criteria for solid tumors). Response to treatment will be based on the tumor assessment conducted at the time of screening for the current study.</p> <p>The distribution of subjects by response category will be made by disease cohort. Time-to-event endpoints will be evaluated with the use of the Kaplan-Meier method and plots will be provided. Analysis of time-to-event outcomes will be performed by disease cohort.</p>
STUDY DURATION	<p>An individual subject is considered to have completed the study 30 days after the last administered dose of carfilzomib to allow for safety follow up.</p> <p>Treatment with carfilzomib will continue until the earliest of the following:</p> <ul style="list-style-type: none">• Confirmation of disease progression, and discussion with Medical Monitor- OR -• Diagnosis of a new malignancy- OR -• Unacceptable toxicity- OR -• Investigator discretion- OR -• Voluntary withdrawal- OR -• Commercial availability of carfilzomib

1 INTRODUCTION

1.1 CARFILZOMIB BACKGROUND

Carfilzomib (PR-171) is a tetrapeptide ketoepoxide-based selective inhibitor of the chymotrypsin-like activity of the 20S proteasome ([Demo 2005](#)). Carfilzomib is structurally and mechanistically different from the dipeptide boronic acid proteasome inhibitor bortezomib, which is currently approved for use in the treatment of patients with multiple myeloma ([Demo 2005](#), [Velcade 2008](#)). In preclinical studies, carfilzomib demonstrates potent anti-tumor activity in a variety of tumor models, including multiple myeloma (MM) ([Demo 2007](#), [Ivancsits 2006](#), [Kuhn 2007](#)).

1.2 PHASE 1 AND 2 EXPERIENCE WITH CARFILZOMIB IN HEMATOLOGIC MALIGNANCIES ([Carfilzomib IB 2010](#), [Stewart 2007](#), [Onyx Data on File](#))

Phase 1 clinical trials of carfilzomib have been conducted in subjects with hematological tumors, including MM, Waldenström's macroglobulinemia, non-Hodgkin's lymphoma (NHL), and Hodgkin's lymphoma. In a completed study (PX-171-001), carfilzomib dosing ranged from 1.2 mg/m² to 20 mg/m² daily for 5 consecutive days (QDx5) followed by 9 days' rest, in cycles repeated every 14 days. Dose-limiting toxicities (DLTs) associated with the highest dose (20 mg/m²) were Grade 4 thrombocytopenia and Grade 3 febrile neutropenia, and the maximum tolerated dose (MTD) was established at 15 mg/m².

In a completed Phase 1 Study PX-171-002, doses ranging from 1.2 mg/m² to 27 mg/m² are administered on consecutive day dosing (QDx2) twice weekly for 3 weeks, followed by 12 days rest, in cycles repeated every 28 days. DLTs observed at the highest dose (27 mg/m²) included thrombocytopenia and hypoxia, therefore the MTD was established at 20 mg/m². Observations of fever, chills, and rigors, and an elevated creatinine (Grade 2) observed on Day 2 of the 27 mg/m² cohort prior to dosing in this part of the study, led to the development of a stepped-up dosing regimen wherein carfilzomib administration is initiated with a dose at 20 mg/m² followed by escalation to 27 mg/m² after the first cycle.

The most common non-hematologic toxicity events reported from the Phase 1 studies are generally mild, low-grade nausea, diarrhea, dyspnea, headache, and constipation. A Grade 3

or 4–thrombocytopenia may occur in subjects with preexisting low platelets, with recovery occurring between treatments. Grade 3 or higher neutropenia and anemia have also been reported, but less frequently than thrombocytopenia.

Objective responses including partial responses (PRs) (50%–90% decreases in M-protein) and minimal responses (MRs) (25%–49% decreases in M-protein) were seen in several subjects with plasma cell dyscrasias in both studies. The responses have been durable with PRs on average of 9 months. In addition, both MM and NHL subjects have had stable disease (SD), exceeding 1 year in some cases. Carfilzomib has also shown activity against refractory MM, solid tumors, and 1 mantle cell lymphoma subject with gastrointestinal lymphoma involvement that achieved an unconfirmed complete response (CRu).

The use of carfilzomib in combination with lenalidomide and dexamethasone is being evaluated in a Phase 1b dose escalation Study PX-171-006 in relapsed MM subjects. The study will evaluate the MTD of this combination regimen.

Two Phase 2 studies are ongoing, one for relapsed refractory MM and another in MM subjects relapsed following 1–3 prior therapies. In these studies, tumor lysis syndrome (TLS) has been observed in 4 of 77 subjects treated at the 20 mg/m² dose. Guidelines for the investigator were subsequently implemented for the prevention and management of TLS in ongoing studies.

In May 2009, a MM arm was added to the PX-171-007 study to explore carfilzomib given as a 30-minute infusion. MM subjects receiving carfilzomib administered over 30 minutes have dose escalated to 20/36 mg/m² (4 subjects) and 20/45 mg/m² (3 subjects) without dose-limiting toxicities.

1.3 PHASE 1 AND 2 EXPERIENCE WITH CARFILZOMIB IN SOLID TUMORS ([Carfilzomib IB 2010, Stewart 2007, Onyx Data on File](#))

Carfilzomib is also being studied as a single agent in a Phase 1b/2 Study PX-171-007 in advanced stage solid tumor subjects who have failed available therapies. Subjects are treated with carfilzomib on the QDx2 schedules using the stepped-up dosing regimen previously described. A Phase 1b dose escalation portion has been completed, demonstrating that

administration of 20 mg/m² on Days 1 and 2 followed by 36 mg/m² on subsequent days is well tolerated.

A Simon 2-stage open label study of 70 patients with 5 cohorts was initiated as the Phase 2 portion in April 2008. The cohorts were stratified according to solid tumor disease type. The objective of this portion of the trial was to estimate overall response to 4 cycles of carfilzomib. This portion would only proceed to stage 2 if 1 PR or better occurred after 16 weeks in a cohort.

Seventy-nine patients had been enrolled on study through May 2009 in the Phase 1 (14 patients) and Phase 2 (65 patients) parts. The median number of carfilzomib cycles given was 2 (range 1-12). Of the 1064 doses administered ~68% were at the 36 mg/m² dose level. One PR was observed in a renal cell patient; 11 patients achieved stable disease. The most common AEs included fatigue, headache, diarrhea, nausea, and constipation. There was a low incidence of peripheral neuropathy and severe hematologic toxicity.

Dose escalation to evaluate and determine an MTD with a 30-minute infusion of carfilzomib is ongoing in patients with solid tumors and multiple myeloma. At this time, there is limited safety data available to comment on differences, if any, associated with a 30-minute infusion versus a 10-minute infusion of carfilzomib.

A drug-drug interaction Study PX-171-008 has been initiated where 15 subjects with advanced solid tumors will be assessed to determine the effect of carfilzomib on the pharmacokinetics of midazolam, a sensitive substrate for human CYP3A4. In addition, renal and biliary excretions will be assessed in this study.

The safety data from the solid tumor study indicate that the non-hematologic toxicities are similar to those seen in the Phase 1 studies. The most common events reported regardless of relationship to study drug are fatigue, diarrhea, and headache.

Further information about the Phase 1 and 2 studies is presented in the Investigator's Brochure (IB).

1.4 EXTENDED CARFILZOMIB TREATMENT STUDY RATIONALE

For all of the aforementioned primary carfilzomib treatment studies, the maximum duration of treatment ranges from 1 to 18 cycles. The purpose of the extended carfilzomib treatment study is to evaluate the safety and efficacy of long-term carfilzomib treatment for patients who have completed a carfilzomib study.

1.5 DOSE RATIONALE

Carfilzomib will be administered intravenously (IV) using the same method, dose level and frequency as administered in the last cycle of the subject's previous carfilzomib study.

A carfilzomib dosing schedule on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle (or the same dose level and frequency as administered at the last visit of the prior carfilzomib study) will be employed and evaluated for long-term safety and efficacy. Subjects will remain at the same dose level and frequency as their previous study because the dose has been shown to be tolerable in the individual subject.

The option will be available to reduce the dosing frequency to Days 1, 2, 15, and 16 of a 28-day cycle (eg, twice a week, every other week). Reductions in dosing frequency will be made at the discretion of the Investigator in consultation with the Medical Monitor.

Dose escalations beyond the original dose level up to the maximum tolerated dose established in primary carfilzomib studies may be permitted following discussion with the Medical Monitor for subjects whose disease progresses on the extended carfilzomib treatment regimen.

2 STUDY OBJECTIVES

2.1 OBJECTIVE

To evaluate the safety and efficacy of long-term or continuing carfilzomib dosing in subjects who have completed a previous carfilzomib treatment study.

3 EXPERIMENTAL PLAN

3.1 STUDY DESIGN

This is a multicenter, open-label, Phase 2 study of carfilzomib to monitor the safety and efficacy of long-term or continuing carfilzomib therapy for subjects who previously completed a primary carfilzomib treatment study. Only subjects who have completed a prior carfilzomib treatment study will be eligible for the current study.

Safety endpoints will consist of the following: (1) all reported Grades 3 and 4 adverse events (AEs), (2) all reported peripheral neuropathy AEs (Grades 1–4), (3) all serious adverse events (SAEs), and (4) Grades 1–4 AEs leading to either a missed carfilzomib dose, carfilzomib dose reduction, or discontinuation. In the event of a toxicity leading to a dose reduction or discontinuation, pertinent laboratory measurements and concomitant medications will be collected and monitored as unscheduled visits.

Efficacy endpoints will include time to tumor progression (TTP), progression-free survival (PFS), and overall survival (OS). Data on the first subsequent treatment regimen following extended carfilzomib therapy study discontinuation will also be collected.

3.2 NUMBER OF CENTERS

Approximately 50 study centers in the United States (US) and Canada will be eligible for participation in the current study. Additional study sites selected to participate in future studies may also be included.

3.3 NUMBER OF SUBJECTS

Approximately 100 subjects will be eligible for enrollment in this open-label multicenter study. Additional subjects from future studies may also be enrolled to further establish long-term safety of carfilzomib.

3.4 ESTIMATED STUDY DURATION

An individual subject is considered to have completed the study 30 days after the last administered dose of study drug in order to allow for safety follow up. Treatment with carfilzomib will continue until the earliest of the following:

- Confirmation of disease progression, and discussion with Medical Monitor
 - OR -
- Diagnosis of a new malignancy
 - OR -
- Unacceptable toxicity
 - OR -
- Investigator discretion
 - OR -
- Voluntary withdrawal
 - OR -
- Commercial availability of carfilzomib

4 SUBJECT SELECTION

4.1 INCLUSION CRITERIA

Subjects must meet all of the following inclusion criteria to be eligible to enroll in this study:

1. Previous completion of a carfilzomib study within 90 days prior to first dose of study drug for Protocol PX-171-010.
2. Disease Assessments performed within 30 days prior to first dose of study drug for Protocol PX-171-010.

Ethical/Other

3. Written informed consent in accordance with federal, local, and institutional guidelines
4. Females of childbearing potential (FCBP)* must have a negative serum or urine pregnancy test, with a sensitivity of at least 50 mIU/mL, within 3 days prior to first dose of extended carfilzomib therapy study drug.

5. Subjects must agree to adhere to the study visit schedule and other study requirements and receive outpatient treatment and laboratory monitoring at the institution that administers the drug.

* Females of childbearing potential (FCBP): Defined as sexually mature females who have not undergone a hysterectomy or who have not been postmenopausal for at least 24 consecutive months (ie, who have had menses at some time in the preceding 24 consecutive months), or had a bilateral oophorectomy are considered to be females of childbearing potential.

4.2 EXCLUSION CRITERIA

Subjects who meet any of the following exclusion criteria are not eligible to be enrolled in this study:

1. Administration of an intervening chemotherapy between the time of previous carfilzomib study termination and first dose of study drug for Protocol PX-171-010.

Concurrent Conditions

2. Pregnant or lactating females.
3. Diagnosis of a new malignancy of a different tumor type.

5 SUBJECT ENROLLMENT

The screening period for a particular subject commences at the point which the subject signs the informed consent. Consent must be signed before any study-specific tests may be performed.

Subject demographics, including previous carfilzomib study unique identifier, will be captured in a study enrollment form. Tumor measurements and efficacy assessments (eg, extent of disease measurements and objective response category) relevant to the subject's tumor type will be collected in accordance to the method(s) employed in the subject's previous carfilzomib study protocol. Refer to [Appendix D–E](#) for Response Criteria. For subjects participating in a carfilzomib trial without explicit tumor measurements and defined response criteria (eg, PX-171-008), response to treatment will be tabulated using the appropriate method (eg, RECIST criteria for solid tumors). Response to treatment will be based on the tumor assessment conducted at the time of screening for the current study. Disease assessments will be required within 30 days prior to study enrollment, at least every 3 months throughout the extended treatment period (Day 1), and at end of study visit.

After a subject has been screened and has successfully fulfilled all eligibility criteria, the site representative will fax the inclusion/exclusion checklist and all other required documentation to Onyx Therapeutics.

Subjects will retain their study-specific number from the previous study. This number will be used to identify the subject throughout the study and must be used on all study documentation related to that subject.

The number of subjects may be expanded to include eligible subjects from future studies, to further establish safety and efficacy, if needed.

6 TREATMENT PROCEDURES

6.1 DRUG PREPARATION AND ADMINISTRATION

6.1.1 CARFILZOMIB DRUG ADMINISTRATION

Carfilzomib for Injection is supplied as a lyophilized parenteral product in single-use vials which, when reconstituted with an appropriate volume of Water for Injection, contains 2 mg/mL of carfilzomib. The product is supplied in labeled carton(s) and is shipped and stored between 2°C–8°C (36°F–46°F). Details of the description, formulation, preparation, storage, and accountability of Carfilzomib for Injection may be found in a separate Pharmacy Manual.

Carfilzomib will be administered IV, using the same method, frequency, and at the same dose level as administered in the last cycle of the subject's previous carfilzomib study; in this study, carfilzomib doses will be administered on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle (or the same dose level and frequency as administered at the last visit of the prior carfilzomib study) until disease progression or unacceptable toxicity. Each dose will consist of Carfilzomib for Injection administered on an mg/m² basis. Subjects with a body surface area (BSA) > 2.2 m² will receive a dose based upon a 2.2 m² BSA.

Dosing will be continued or modified based upon clinical and laboratory findings.

The dose will be administered at a facility capable of managing hypersensitivity reactions. If a carfilzomib dose is delayed by more than 1 day, it will not be made up.

Subjects should be well hydrated prior to dosing with carfilzomib. Blood chemistries, including creatinine, complete blood counts (CBC), and platelet count must be obtained and reviewed by the Principal Investigator or qualified designee prior to carfilzomib dosing for all treatment cycles, and the values must meet the guidelines below for retreatment.

Electrolyte abnormalities that are clinically significant should be corrected prior to dosing.

Subjects should have a dedicated line for drug administration. Before and after carfilzomib administration, the line must be flushed with 20 mL of normal saline. If a dedicated line is not possible, the existing line must be flushed with a minimum of 20 mL of normal saline before and after carfilzomib administration.

6.2 DOSE MODIFICATION GUIDELINES

6.2.1 DOSE FREQUENCY AND DOSE LEVEL REDUCTIONS

Subjects enrolled in this protocol will begin treatment at the same carfilzomib dose level, frequency and method as the last dose received on their previous study. Dose levels are as follows:

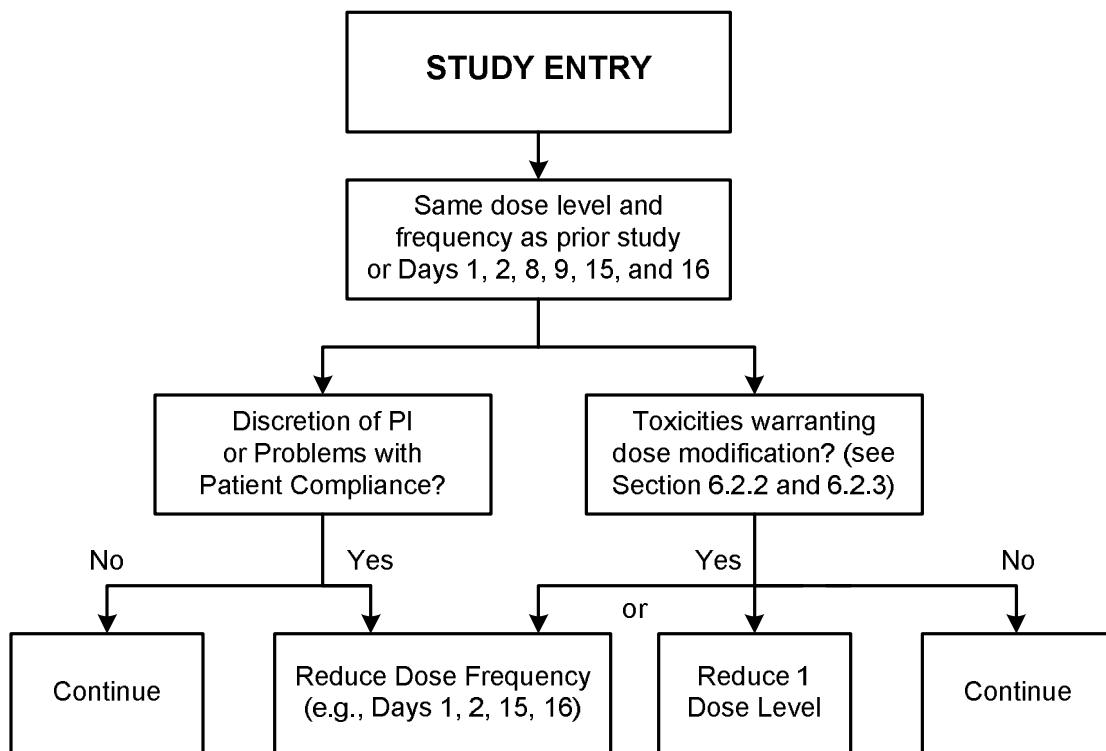
Table 1: Carfilzomib for Injection Dose Levels

Carfilzomib Dose Levels
11 mg/m ²
15 mg/m ²
20 mg/m ²
27 mg/m ²
36 mg/m ² *
45 mg/m ² *
56 mg/m ² *

* Dose level for 30-minute infusion

Dose frequency reductions will be allowed at the discretion of the Investigator in consultation with the Medical Monitor. The dose frequency can be reduced to carfilzomib administration on Days 1, 2, 15, and 16 (eg, every other week dosing) of a 28-day cycle, and continued until conditions in section 3.4 are met.

Dose level reductions, to a minimum dose of $11 \text{ mg}/\text{m}^2$, for toxicity will also be permitted; the Medical Monitor may be consulted as needed. Missed doses of carfilzomib will not be made up. Doses of carfilzomib may be rescheduled by up to 48 hours if the scheduled administration falls upon a holiday. Anticipated delays of a scheduled carfilzomib dose by more than 1 day should be discussed beforehand with the Medical Monitor. A dose reduction guideline diagram is as follows:



6.2.2 DOSE MODIFICATIONS FOR HEMATOLOGIC TOXICITIES

Study drug will be withheld from subjects with:

- Grade 3 neutropenia ($\text{ANC} < 1000/\text{mm}^3$)
- Grade 4 thrombocytopenia with active bleeding

Grade 4 anemia and thrombocytopenia (without active bleeding) do not require the carfilzomib dose to be withheld. However, subjects should receive supportive measures in accordance with institutional guidelines. *For patients with Grade 4 thrombocytopenia without evidence of bleeding, study drug dosing may occur following consultation with the Medical Monitor.*

Subjects with reversible and manageable hematologic toxicity (eg, effects have diminished to baseline or better at the time of the next scheduled treatment) will continue to receive carfilzomib at the same dose level. For the purposes of this study, ‘baseline’ refers to the subject’s status at the start of this Protocol (PX-171-010).

If required by continued or worsening toxicity, dose level and/or frequency reductions will be permitted after discussion with the Medical Monitor. The minimum dose level will be 11 mg/m². Dose reductions below 11 mg/m² will not be permitted. The minimum dose frequency will be carfilzomib administration on Days 1, 2, 15 and 16 (eg, every other week). Less frequent dosing will not be permitted. If toxicity continues, the subject should be removed from the study.

For subjects whose dose level/frequency is reduced due to study drug-related hematologic toxicity, dose level/frequency re-escalation may be considered if the subject tolerates the reduced dose and at the Investigator’s discretion in consultation with the Medical Monitor.

If there is no resolution of toxicity after 2 weeks of withholding treatment (up to 3 weeks for infection treatment), the subject will be withdrawn from the study.

6.2.3 DOSE MODIFICATIONS FOR NON-HEMATOLOGIC TOXICITIES

Study drug should be held for drug-related \geq Grade 3 events until resolution to \leq Grade 1 or return to baseline status. For the purposes of this study, ‘baseline’ refers to the subject’s status at the start of this Protocol (PX-171-010).

After resolution to \leq Grade 1 or return to baseline status of the event, subsequent treatment with carfilzomib may resume at full dose at the Investigator’s discretion.

If required by continued or worsening toxicity, dose level and/or frequency reductions will be permitted after discussion with the Medical Monitor. The minimum dose level will be 11 mg/m². Dose reductions below 11 mg/m² will not be permitted. The minimum dose frequency will be carfilzomib administration on Days 1, 2, 15, and 16 (eg, every other week). Less frequent dosing will not be permitted. If the toxicity continues, the subject should be removed from the study.

For subjects whose dose level/frequency is reduced due to study drug-related toxicity, dose level/frequency re-escalation may be considered if the subject tolerates the reduced regimen and at the Investigator's discretion in consultation with the Medical Monitor.

If there is no resolution of toxicity after 2 weeks of withholding treatment (up to 3 weeks for infection treatment), the subject will be withdrawn from the study.

6.2.3.1 Decreased Creatinine Clearance

Carfilzomib should be held for calculated creatinine clearance (CrCl) < 15 mL/min.

For subjects who enter this study with a CrCl < 15 mL/min, study drug should be held if CrCl drops $\geq 50\%$ from baseline. When the CrCl returns to baseline, carfilzomib treatment should resume at 1 dose level reduction (ie, from 27 to 20 mg/m², from 20 to 15 mg/m², or from 15 to 11 mg/m²). If the CrCl is still $\geq 50\%$ below baseline after 2 weeks the subject should be withdrawn from the study.

Subjects on routine hemodialysis may receive carfilzomib at the same dose as the previous carfilzomib study.

The Cockcroft and Gault formula will be used to calculate the CrCl as follows: Creatinine Clearance = $\{[(140 - \text{age}) \times \text{Mass (kg)}] / [\text{Creatinine (mg/dL)} \times 72]\} \times 0.85$ if female.

Table 2: Dose Adjustment Guideline for Renal Dysfunction

Renal Dysfunction	Recommended Action
Normal to Mild (CrCl > 50 mL/min)	Full dose
Moderate to Severe (CrCl 15–50 mL/min)	Full dose
Upon study entry, CrCl < 15 mL/min and CrCl drops below 50% of baseline	Hold carfilzomib until CrCl returns to baseline; restart at 1 level dose reduction

6.2.3.2 Infections

Subjects with active or suspected infections should have treatment withheld until the infection has resolved and anti-infective treatment has been completed. After the infection has resolved and anti-infective treatment has been completed, treatment may continue at the

original dose. If there is no resolution of the infection after 3 weeks, the subject will be withdrawn from the study.

6.2.3.3 Congestive Heart Failure

Any subject with symptoms of new or worsening congestive heart failure (CHF), whether or not drug related, must have the dose held until resolution of the CHF. After the CHF has resolved or returned to baseline, treatment may continue at a reduced dose with the approval of the Medical Monitor, or the subject may be withdrawn from the study. If there is no resolution of CHF after 2 weeks, the subject will be withdrawn from the study.

6.2.3.4 Conditions Not Requiring Dose Reduction

The following conditions are exceptions to the above guidelines. Carfilzomib does not need to be held in the following cases:

- Grade 3 nausea, vomiting, or diarrhea (unless persisting > 3 days with adequate treatment of anti-emetics or anti-diarrheals)
- Grade 3 fatigue (unless persisting for > 14 days)
- Alopecia
- \geq Grade 3 hyperglycemia attributed to dexamethasone

Other exceptions may be discussed with the Medical Monitor on a case-by-case basis.

6.2.4 *MISSED DOSES*

Missed doses will not be replaced during a cycle. If a subject misses greater than 2 doses of any cycle for reasons other than toxicity, the subject will be discontinued.

6.2.5 *CHANGES IN BODY SURFACE AREA*

Dose adjustments do not need to be made for weight gains/losses of $\leq 20\%$. Subjects with a BSA of $> 2.2 \text{ m}^2$ will receive carfilzomib based on 2.2 m^2 BSA.

6.2.6 *OTHER DOSING MODIFICATIONS*

Dose modifications and delays different from those stated in the protocol, for management of toxicities, may be permitted but must be decided jointly by the Principal Investigator and the Medical Monitor or designee.

6.2.7 DOSE ESCALATION RULES

Dose escalations beyond the original dose level up to the maximum tolerated dose established in primary carfilzomib studies may be permitted following discussion with the Medical Monitor.

6.3 SAFETY GUIDANCE FOR INVESTIGATORS

6.3.1 SAFETY GUIDANCE

Based upon the experience in Phase 1 studies with carfilzomib, the following observations must be noted:

Physicians administering carfilzomib in subjects with compromised renal function should hydrate appropriately and treat according to calculated CrCl, not on serum creatinine. It is recommended that electrolyte abnormalities judged as clinically significant by the Principal Investigator (or qualified designee) be corrected to \leq Grade 1 or baseline. Renal function and serum creatinine should be monitored prior to dosing. Carfilzomib must be held if a subject presents with a CrCl < 15 mL/min with the following exception: for subjects with CrCl < 15 mL/min at study entry, study drug must be held if CrCl drops $\geq 50\%$ from baseline. Subjects who develop an active infection requiring systemic treatment should not be dosed with carfilzomib until the infection has resolved and the treatment course has been completed. Subjects with \geq Grade 3 neutropenia should not be treated with carfilzomib.

Carfilzomib dosing must be held for Grade 4 thrombocytopenia with bleeding. If platelet counts do not recover, the dose of carfilzomib may be reduced or held according to the Dose Reductions/Adjustments rules outlined in [Section 6.2.2](#). For Grade 4 thrombocytopenia without evidence of active bleeding, platelet transfusions may be used per study site policies and at the discretion of the Investigator or treating physician.

Carfilzomib treatment can cause nausea, vomiting, diarrhea, or constipation, sometimes requiring the use of antiemetics or antidiarrheals. Fluid and electrolyte replacement should be administered to prevent dehydration.

6.4 CONCOMITANT MEDICATIONS

Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements.

6.4.1 REQUIRED CONCOMITANT MEDICATION

All subjects with a history of herpes viral infection should receive acyclovir or valacyclovir prophylaxis according to institutional guidelines and the investigator's discretion.

6.4.2 ALLOWED CONCOMITANT MEDICATIONS

Commercially available bisphosphonates are permitted. Subjects may receive antiemetics and antidiarrheals as necessary, but these should not be administered unless indicated.

Colony-stimulating factors may be used if neutropenia occurs but should not be given prophylactically.

Subjects may receive platelet transfusions in accordance with institutional guidelines.

Red blood cell (RBC) transfusions or supportive care with erythropoietin or darbepoetin alfa, in accordance with institutional guidelines, is also permitted.

Subjects who received 4 mg dexamethasone prior to carfilzomib dosing on an ongoing basis during their previous carfilzomib treatment protocol may continue to receive 4 mg dexamethasone prior to carfilzomib dosing on the current protocol at the investigator's discretion.

The addition of certain approved agents with known antitumor activity is permitted if there is concern for disease progression and per Investigator discretion in consultation with the Onyx Medical Monitor.

6.4.3 EXCLUDED CONCOMITANT MEDICATIONS

Other investigational agents should not be used during the study.

7 STUDY TESTS AND OBSERVATIONS

Protocol-required tests, observations, and procedures are summarized in the Schedule of Events, [Appendix A](#).

Safety Measures

A CBC including platelets and basic metabolic chemistry panel (eg, Chem 7 or 8) will be performed on Day 1 of each cycle. Other general safety monitoring (eg, physical examinations, imaging, specialty tests, etc.) shall be in accordance with institutional guidelines and as clinically indicated. These data will not be routinely recorded on case report forms (CRFs).

Pregnancy Test

Females of Child Bearing Potential (FCBP) must have a negative serum or urine pregnancy test, with a sensitivity of at least 50 mIU/mL within 3 days prior to dosing. All subjects must be informed that he/ she needs to use a dual effective method of birth control while in this study, such as oral contraceptives plus use of a physical barrier (ie, condom) for the full duration of the study, plus 3 additional months.

7.1 SCREENING (DAYS –30 TO –1)

The following screening assessments must be performed between Days –30 and –1:

1. Obtain written informed consent prior to carrying out any study procedure
2. Obtain previous PX-171 protocol unique identifier (patient study number)
3. Determine eligibility according to Inclusion/Exclusion criteria (see [Section 4](#))
4. Perform Disease Assessments, ie, extent of disease measurements (per method employed in previous protocol); and response category (see [Appendix D–E](#)).
Note: If disease assessments are performed previously within 30 days of first dose of extended carfilzomib therapy study drug, a second disease assessment will not be required.
5. Perform routine physical examination
6. Perform pregnancy test for FCBP
7. Obtain height, weight, and BSA
8. Obtain Eastern Cooperative Oncology Group (ECOG) performance status and neuropathy grade
9. OPTIONAL: Bone marrow aspirate and/or biopsy sample collection for cytogenetic and fluorescent in situ hybridization (FISH) analysis (only for *MM* subjects whose disease status at study entry is PR, MR or SD).
10. Record peripheral neuropathy AEs (all grades)
11. Record Grade 3 and 4 AEs, and all SAEs

12. Record AE (any Grade) leading to a missed carfilzomib dose, carfilzomib dose reduction or discontinuation.
13. Record any concomitant chemotherapy agents

7.2 CYCLE 1 (DAY 1)

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

1. Serum chemistry – basic chemistry panel (Chem 7 or 8), pre-dose. Laboratory values may be obtained within 24 hours prior to treatment for convenience. Results must be reviewed prior to dosing.
2. CBC and platelet count – pre-dose. Laboratory values may be obtained within 24 hours prior to treatment for convenience. Results must be reviewed prior to dosing.
3. *Administer carfilzomib dose IV*
4. Record peripheral neuropathy AEs (all grades)
5. Record Grade 3 and 4 AEs, and all SAEs
6. Record AE (any Grade) leading to a missed carfilzomib dose, carfilzomib dose reduction, or discontinuation. In the event of a toxicity leading to a dose reduction or discontinuation, pertinent laboratory measurements and concomitant medications will be collected and monitored as unscheduled visits
7. Record any concomitant chemotherapy agents

7.3 CYCLE 1 (DAYS 2, 8, 9, 15, AND 16)

The following assessments must be completed on Cycle 1 on Days 2, 8, 9, 15, and 16 (or the same dose level and frequency as administered at the last visit of the prior carfilzomib study):

1. *Administer carfilzomib dose IV*
2. Record peripheral neuropathy AEs (all grades)
3. Record Grade 3 and 4 AEs, and all SAEs
4. Record AE (any Grade) leading to a missed carfilzomib dose, carfilzomib dose reduction, or discontinuation. In the event of a toxicity leading to a dose reduction or discontinuation, pertinent laboratory measurements and concomitant medications will be collected and monitored as unscheduled visits.
5. Record any concomitant chemotherapy agents

7.4 CYCLES 2 AND HIGHER (DAY 1)

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

1. Serum chemistry – basic panel (Chem 7 or 8), pre-dose; laboratory values must be reviewed prior to dosing.
2. CBC and platelet count, pre-dose; laboratory values must be reviewed prior to dosing.

3. Obtain weight and BSA
4. *Administer carfilzomib dose IV*
5. Record peripheral neuropathy AEs (all grades)
6. Record Grade 3 and 4 AEs, and all SAEs
7. Record AE (any Grade) leading to a missed carfilzomib dose, carfilzomib dose reduction, or discontinuation. In the event of a toxicity leading to a dose reduction or discontinuation, pertinent laboratory measurements and concomitant medications will be collected and monitored as unscheduled visits.
8. Record any concomitant chemotherapy agents

7.5 CYCLES 2 AND HIGHER (DAYS 2, 8, 9, 15, AND 16)

The following assessments must be completed on Cycle 2 and higher on Days 2, 8, 9, 15, and 16 (or the same dose level and frequency as administered at the last visit of the prior carfilzomib study):

1. *Administer carfilzomib dose IV*
2. Record peripheral neuropathy AEs (all grades)
3. Record Grade 3 and 4 AEs, and all SAEs
4. Record AE (any Grade) leading to a missed carfilzomib dose, carfilzomib dose reduction, or discontinuation. In the event of a toxicity leading to a dose reduction or discontinuation, pertinent laboratory measurements and concomitant medications will be collected and monitored as unscheduled visits.
5. Record any concomitant chemotherapy agents

7.6 CYCLE 3 AND EVERY 3 CYCLES (DAY 1)

The following assessments must be completed on Cycle 3 and every 3 cycles (Day 1):

1. Serum chemistry – basic panel (Chem 7 or 8), pre-dose; laboratory values must be reviewed prior to dosing.
2. CBC and platelet count, pre-dose; laboratory values must be reviewed prior to dosing.
3. Perform Disease Assessments, ie, extent of disease measurements (per method employed in previous protocol); and response category (see [Appendix D–E](#)).
Note: If disease assessments, per standard institutional practices, occur more frequently than every 3 months (eg every month or every 2 months), the most recent assessment may be reported.
4. *Administer carfilzomib dose IV*
5. Record peripheral neuropathy AEs (all grades)

6. Record Grade 3 and 4 AEs, and all SAEs
7. Record AE (any Grade) leading to a missed carfilzomib dose, carfilzomib dose reduction, or discontinuation. In the event of a toxicity leading to a dose reduction or discontinuation, pertinent laboratory measurements and concomitant medications will be collected and monitored as unscheduled visits.
8. Record any concomitant chemotherapy agents

7.7 END OF STUDY ASSESSMENTS (WITHIN 30 DAYS OF STUDY DISCONTINUATION)

The following assessment must be completed within 30 days of administration of last dose of study drug and prior to initiation of any new therapy:

1. Perform complete physical examination
2. Perform Disease Assessments, ie, extent of disease measurements (per method employed in previous protocol); and response category (see [Appendix D–E](#)).
3. OPTIONAL: Bone marrow aspirate and/or biopsy for cytogenetic and FISH analysis (only required for *MM* subjects whose reason for study discontinuation is PD).
4. Record peripheral neuropathy AEs (all grades)
5. Record Grade 3 and 4 AEs, and all SAEs
6. Record any concomitant chemotherapy agents

7.8 TUMOR RESPONSE ASSESSMENT

Efficacy Measures

Tumor measurements and efficacy assessments will be in accordance with the methods employed in the subject's prior carfilzomib study. For subjects participating in a carfilzomib trial without prior tumor measurements and efficacy assessments (eg, PX-171-008), tumor assessments will be conducted at the time of screening for the current study using the appropriate method (eg, RECIST criteria for solid tumors); these assessments will be used as the subjects' baseline disease assessments for determining response and progression while on the current Protocol (PX-171-010). Disease assessments (eg, Extent of Disease Measurements and objective response category) will occur within 30 days prior to enrollment to determine eligibility, at least every 3 months throughout study participation, and at end of study. Subjects will be evaluated for disease response according to the parameters employed in their previous carfilzomib study. Refer to [Appendix D–E](#) for Response Criteria.

7.9 CORRELATIVE STUDIES

7.9.1 CYTOGENETIC AND FISH STUDIES

A bone marrow biopsy and/or aspirate for determining percent plasma cell involvement, including metaphase cytogenetic and FISH studies are optional for all MM subjects entering with a PR, MR, or SD. Samples for cytogenetic and FISH analysis will also be optional for all MM subjects who discontinue study due to PD. Bone marrow cytogenetic and FISH analyses will be carried out at the site's local laboratory, per standard of practice, or in a Central Reference Laboratory.

8 STUDY DISCONTINUATION

Subjects may withdraw from the study at any time. Subjects who discontinue from the study will be monitored for AEs as described in [Appendix C](#) (NCI-CTCAE Version 3.0).

The Sponsor, Onyx Therapeutics, Inc. may elect to discontinue the study at any time.

The Investigator may remove a subject from the study for the following reasons:

- Noncompliance with study procedures
- Need of treatment with medications not allowed by the study protocol
- Subject no longer consents to participate in the study
- Intercurrent illness that interferes with study assessments
- Incidence or severity of AEs in this study indicates a potential health hazard to the subject
- Confirmation of PD, and discussion with the Medical Monitor

Onyx Therapeutics or designee must be notified within 24 hours if a subject is withdrawn from the study.

If the reason for withdrawal is the occurrence of an AE, the subject will be followed by the Investigator until such events resolve, stabilize, and, according to the Investigator's judgment, there is no need of further follow-up. The reason for withdrawal from the study will be documented in the CRF.

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. The CRFs must have appropriate source

documentation to demonstrate that a subject has progressed. Bone marrow aspirate or biopsy samples for cytogenetic analysis are optional for all MM subjects who discontinue due to PD.

9 ADVERSE EVENTS

9.1 ADVERSE EVENTS DEFINITIONS

An AE is any untoward medical occurrence in a study subject administered an investigational product and that does not necessarily have a causal relationship with this treatment.

An unexpected AE is any adverse drug event, the specificity or severity of which is not consistent with the current Investigator's Brochure or prescribing information for a marketed compound. Also, reports which add significant information on specificity or severity of a known, already documented AE constitute unexpected AEs. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected".

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 treatment-related. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the subject signs a consent form for participation is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

Whenever possible, the CTCAE Version 3.0 (see [Appendix D](#)) should be used to describe the event and for assessing the severity of AEs. Any event representing a change in the CTCAE grade needs to be reported on the AE CRF. This includes any change in a laboratory value.

For AEs not adequately addressed in the CTCAE, the severity table below may be used:

Table 3: Toxicity Grading

GRADE 1 – Mild:	Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
GRADE 2 – Moderate:	Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3 – Severe:	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
GRADE 4 – Life Threatening:	Extreme limitation in activity, significant assistance required; life threatening (immediate risk of death); significant medical intervention/therapy required; hospitalization or hospice care probable.
GRADE 5 – Fatal	Death

Any condition, laboratory abnormality, or physical finding with an onset date prior to the subject signing consent for study participation is considered to be pre-existing in nature and part of the subject's medical history.

9.2 CAUSALITY

Relationship of the AE to the study drug should be defined as follows:

- None
- Unlikely
- Possible
- Probable

9.3 ADVERSE EVENTS REPORTING PROCEDURES

The following AEs will be reported and monitored for this study:

- Peripheral Neuropathy (all grades)
- All Grade 3 and 4 AEs
- Any AEs resulting in a missed dose, dose reduction, or treatment discontinuation
- All SAEs

AEs (eg, any new event or worsening in severity or frequency of a pre-existing condition or laboratory finding) with an onset date after the subject signs consent for study participation must be promptly documented on the AE CRF. Details of the event must include severity, relationship to study drug, duration, action taken, and outcome. SAEs will be recorded on

the AE CRF *and* on the SAE reporting form (see [Section 9.5](#), Serious Adverse Event Reporting and Documentation Requirements).

AEs will be collected from the time the subject signs informed consent through 30 days following the last dose of study drugs, or initiation of a new anti-cancer therapy. In addition, the Investigator should report any AE (per instructions described above) that may occur after this time period that is believed to have a reasonable possibility of being associated with study drug.

All AEs that are considered related to study drug must be followed to resolution or stabilization if improvement is not expected. AEs which completely resolve and then recur should be recorded as a new AE. For subjects who complete the end-of-treatment visit less than 30 days following their last dose of protocol-defined therapy, a follow up of ongoing AEs should be attempted by telephone, and documented in the subject's source file.

AEs continuing at 30 days after the last dose should have a comment in the source by the Investigator that the event has stabilized or is not expected to improve.

The Principal Investigator is responsible for evaluating all AEs, obtaining supporting documents, and determining that documentation of the event is adequate. AEs will be assigned a severity grade using the NCI-CTCAE grading scale Version 3.0. Any laboratory finding requiring a therapeutic intervention should also be considered as an AE and reported accordingly.

The Principal Investigator may delegate these duties to Sub-Investigators and must assure that these Sub-Investigators are qualified to perform these duties under the supervision of the Principal Investigator and that they are listed on the Form FDA 1572 or Canadian Qualified Investigator Undertaking Form (QIU).

9.3.1 DISEASE PROGRESSION

Discontinuation of treatment due to either progression or deterioration due to the primary malignancy should be recorded on the Treatment Discontinuation CRF as "Disease Progression" and not as an AE or an SAE, unless the event meets the SAE reporting criteria described in [Section 9.4](#).

In addition to an increase in M-protein, natural disease progression of multiple myeloma typically displays specific clinical signs and symptoms such as elevated Calcium, Renal insufficiency, Anemia, and Bone disease (known as the “CRAB” features) (Durie 2006). Signs and symptoms clearly associated with progression should not be listed as AEs unless judged by the Investigator to be atypical or accelerated or if the Investigator considers the sign or symptom to be caused by the study drug. If there is any uncertainty regarding causality, the event should be recorded in the CRF as an AE or SAE as appropriate.

All deaths during treatment or within 30 days of the last dose of study drug are to be reported as SAEs (see Section 9.4). The corresponding entry for progression-related deaths on the AE CRF should use the verbatim term “Disease Progression” rather than the specific sign or symptom that may have been the immediate cause of death. Additional details of the event (such as the primary and contributory causes of death) should be reported on the Death CRF.

9.4 SERIOUS ADVERSE EVENTS DEFINITIONS

An SAE is one 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 Investigator, at immediate risk of death at the time of occurrence; ie, it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of an existing hospitalization (except scheduled hospitalizations for non-acute, unrelated cause such as an elective surgery)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in the offspring of an exposed subject
- Important medical events that may not result in death, be life threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, it jeopardizes the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Any death occurring within 30 days of the subject receiving study drug, regardless of the subject having discontinued from the study must be reported to the sponsor as an SAE.

9.5 SERIOUS ADVERSE EVENT REPORTING AND DOCUMENTATION REQUIREMENTS

Onyx Therapeutics, Inc. must be notified by telephone or fax of the occurrence of any SAE within 24 hours of the Investigator, designee, or site personnel knowledge of the event.

To report an SAE, call or fax an SAE form to:

Attn: i3 Research
Fax: (866) 880-9343
SAE hotline: (888) 750-8020
E-mail: i3drugsafetyPV@i3drugsafety.com

Telephone reports must be followed by a written report within 24 hours. Follow-up reports must be submitted in a timely fashion as additional information becomes available.

The Investigator is responsible for notifying the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) in accordance with local regulations, of all SAEs. The sponsor may request additional source documentation pertaining to the SAE sent to Onyx. If a subject is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up SAE report form as well as the Study Discontinuation CRF.

All SAEs occurring from the time that the subject signs consent for study participation or up to 30 days after the last administered dose of study drug will be reported. All SAEs regardless of relationship to study drug must be followed to resolution or to stabilization if improvement or resolution is not expected.

9.6 PREGNANCY

The subject must immediately inform her doctor:

- If she becomes pregnant while taking the drug
- If she misses her menstrual period, or experiences unusual menstrual bleeding
- If she stops using birth control
- If she thinks, FOR ANY REASON, that she may be pregnant
- The subject understands that if her doctor is not available, she can call 1-888-668-2528 for information on emergency contraception

If a subject or spouse or partner of a subject becomes pregnant while enrolled in this clinical trial or up to 3 months following administration of carfilzomib, Onyx must be notified within 24 hours of the Investigator, designee, or site personnel learning of the pregnancy. If the subject is pregnant, carfilzomib and all other study drug(s) must be withheld until the Medical Monitor is notified, and the case is discussed. Subjects, spouses, or partners will be followed through the outcome of the pregnancy. The Investigator will be required to complete a Pregnancy Information Form and fax the information to:

Attn: i3 Research
Fax: (866) 880-9343
SAE hotline: (888) 750-8020
E-mail: i3drugsafetyPV@i3drugsafety.com

10 STATISTICAL CONSIDERATIONS

This section outlines the statistical analysis strategy and procedures for the study. Specific details of the primary and key secondary analyses will be provided in the Statistical Analysis Plan (SAP). If, after the study has begun but prior to the final analysis, changes are made to the protocol that affect principal features of the primary or key secondary analyses, then the protocol and/or SAP will be amended, as required. Any other changes made to the planned analyses after the protocol and SAP have been made final, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) of the study. Post hoc exploratory analyses will be clearly identified in the CSR as such.

10.1 OBJECTIVES/HYPOTHESES

The objectives of the study are stated in [Section 2](#). The present protocol will not test any prespecified hypotheses, but will summarize safety and disease response data so that an assessment of each may be made.

10.2 ANALYSIS ENDPOINTS

The safety and disease response endpoints that will be evaluated are listed below, followed by descriptions of the derivations of selected endpoints.

10.2.1 PRIMARY ENDPOINTS (SAFETY)

- Reported peripheral neuropathy AEs (all Grades)
- Reported Grades 3 and 4 AEs
- SAEs
- Grades 1 through 4 AEs leading to a missed carfilzomib dose or a carfilzomib dose reduction or discontinuation

10.2.2 SECONDARY ENDPOINTS (EFFICACY/DISEASE RESPONSE)

- Overall survival (OS)
- Progression-Free Survival (PFS)
- Time to Progression (TTP)

10.3 ANALYSIS POPULATIONS

10.3.1 SAFETY ANALYSIS

The safety population consists of all enrolled subjects who received at least 1 dose of carfilzomib after enrollment in PX-171-010.

10.3.2 DISEASE RESPONSE ANALYSIS

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of the disease response data in this study. The FAS population is a subset of all enrolled subjects, with subjects excluded for the following reasons:

- No post-baseline endpoint data subsequent to at least 1 dose of study treatment on the PX-171-010 protocol (applicable only to PX-171-008 subjects).
- Lack of baseline data for those analyses that require baseline data

10.4 STATISTICAL METHODS

10.4.1 SAFETY ANALYSIS

Safety and tolerability will be assessed by clinical review of all relevant parameters associated with (1) peripheral neuropathy (all Grades) (2) all reported Grade 3 and 4 AEs, (3) Grades 1–4 AEs resulting in a missed carfilzomib dose, dose delay or discontinuation, and (4) reported SAEs.

Treatment-emergent AEs are defined as AEs that start on or after the first day study treatment is administered and within 30 days of the last administration of study treatment.

AEs will be summarized by the number and percentage of subjects who experienced the event, according to system organ class and preferred term. A subject reporting multiple cases of the same AE will be counted once within each system organ class and similarly counted once within each preferred term. Unless otherwise specified, the denominator for these calculations will be based on the number of subjects in each disease cohort (solid tumor or MM) who receive at least 1 administration of carfilzomib on the extended study, irrespective of the total number of doses or treatment cycles administered. These conventions will be appropriately modified to calculate AE incidence rates separately for each cycle that study therapy is administered. AE incidence rates may also be calculated based on other measures of subject exposure (eg, total number of treatment cycles administered). AEs will also be summarized by NCI-CTCAE Version 3.0 severity grade and by relationship to each study drug. For AEs not adequately addressed by the NCI-CTCAE, the severity grading described in [Section 9.1](#) may be used (see [Table 3](#)). Additional summaries may also be provided for SAEs, and events resulting in the permanent discontinuation of therapy. Summaries will be provided by disease cohort. All AEs will be included in individual subject listings.

10.4.2 DISEASE RESPONSE ANALYSIS

The analysis of disease response will be based on the FAS populations defined in [Section 10.3.2](#). The assessment of disease response will be based on duration of OS, PFS, and TTP. For patients previously enrolled in PX-171-008, response may be first noted in PX-171-010. Durations will be calculated from the date of disease response documented in the subjects' prior carfilzomib protocol, or in PX-171-010 for subjects previously enrolled in PX-171-008, to the first documentation of the endpoint's occurrence in the extended trial.

Depending on the completeness of the available follow-up data, analysis of each endpoint will be performed based on the Kaplan-Meier method. The date of progression will be determined using the progression criteria described in [Appendix D–E](#). The date of censoring for subjects who end the study without documented progression will correspond to the date the last disease assessment was performed. Analysis will be performed separately by disease cohort (MM or solid tumor).

10.5 SAMPLE SIZE

The total number of subjects to be enrolled in the study is dependent upon the number of subjects who have completed the primary carfilzomib treatment protocols. It is anticipated that approximately 100 subjects will be enrolled in this study. Formal power calculation was not used to determine the sample size.

10.6 GUIDELINES FOR EARLY STUDY TERMINATION

Safety will be monitored throughout the trial. If any significant safety issues arise, the sponsor will be notified and if necessary, a decision to modify or terminate the study will be made.

11 REGULATORY OBLIGATIONS

11.1 INFORMED CONSENT

No Investigator may involve a human being as a subject in research unless the Investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An Investigator 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.

Onyx Therapeutics or its designated representative will provide the Investigator with a sample consent form. Local and/or institutional requirements may require disclosure of additional information in the informed consent. Any changes to the consent form must be submitted to the Onyx Therapeutics or its designated representative for approval, prior to submission to the IRB/IEC. The IRB/IEC will review the consent form for approval. A copy of the approved form must be submitted to the Onyx or its designated representative prior to initiation of the study.

Before implementing any study procedure, informed consent shall be documented 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

informed consent will be given to the subject or subject's legally authorized representative. The original signed consent must be maintained by the Investigator and available for inspection by Onyx Therapeutics, its designated representative, or regulatory authority at any time.

11.2 COMPLIANCE WITH LAWS AND REGULATIONS

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

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

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

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

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

Onyx Therapeutics will initiate in writing any substantive changes to this protocol as a protocol amendment. The amendment will be submitted to the IRB/IEC, together with a revised informed consent form, if applicable. Written documentation of IRB/IEC approval

must be received before the amendment is implemented. Upon completion of the trial, the Investigator must provide the IRB/IEC with a summary of the trial's outcome.

11.3 PRE-STUDY DOCUMENTATION REQUIREMENTS

Before the start of the study, the following documents must be on file with Onyx Therapeutics or its designated representative:

- An original US Form FDA 1572 or Canadian Qualified Investigator Undertaking Form (QIU) for the site, signed by the Principal Investigator
- Current Curriculum Vitae (CV) for the Principal Investigator and all Sub-Investigators
- Original financial disclosure forms for the Principal Investigator and all Sub-Investigators listed on the US Form FDA 1572 or Canadian QIU
- Current IRB/IEC membership list and/or Department of Health and Human Services number
- Copies of all appropriate laboratory certifications and laboratory normal ranges
- IRB/IEC approval of the protocol
 - The approval letter must identify the Onyx Therapeutics protocol number or title and date of protocol
- IRB/IEC-approved informed consent and approval letter
 - The approval letter must identify the Onyx Therapeutics protocol number or title of protocol and date of the informed consent
 - The informed consent must also be reviewed and approved by Onyx Therapeutics
- IRB/IEC approval of any advertising materials to be used for study recruitment, if applicable
 - Advertising materials must also be approved by Onyx Therapeutics
- Health Insurance Portability and Accountability Act (HIPAA) forms, if required
- Original signed Investigator agreement
- Original signed and dated protocol acceptance form

11.4 SUBJECT CONFIDENTIALITY

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

The Investigator/Institution will permit direct access to source data and documents by Onyx Therapeutics its designee, the FDA, Health Canada, and other applicable regulatory authorities. The access may consist of trial-related monitoring, audits, IRB/IEC reviews, and regulatory authority inspections, including FDA and Health Canada.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 Code of Federal Regulation (CFR) 164.508.

12 ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 PROTOCOL AMENDMENTS AND STUDY TERMINATION

All protocol amendments will be implemented by Onyx Therapeutics and must receive IRB/IEC approval before implementation, except where necessary to eliminate an immediate hazard to subjects. The Investigator or designee must send a copy of the approval letter from the IRB, along with the revised informed consent form, to Onyx Therapeutics.

Both Onyx Therapeutics and the Investigator reserve the right to terminate the study according to the study contract. The Investigator or designee should notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Onyx Therapeutics.

12.2 STUDY DOCUMENTATION AND ARCHIVES

12.2.1 *SOURCE DOCUMENTS*

Source records are original documents, data, and records (eg, medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The Investigator will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical trial. Source records must be adequate to reconstruct all data transcribed onto the CRFs.

12.2.2 CASE REPORT FORM COMPLETION

All required data must be recorded on the CRFs provided by Onyx Therapeutics or its designee. All CRFs must be completed by designated study personnel. The completed CRFs must be reviewed, signed, and dated by the Investigator or designee in a timely fashion.

12.2.3 ARCHIVAL OF RECORDS

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

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

12.3 STUDY MONITORING AND DATA COLLECTION

Following prequalification and initiation of the study site, periodic monitoring visits will be made by Onyx Therapeutics, and/or its designated representative. The Investigator must provide sufficient space and allocate sufficient time for the monitor to inspect subject source records, CRFs, drug accountability records, and regulatory documents.

The purpose of trial monitoring is to verify the following:

- The rights and well-being of human subjects are protected.
- The reported data are accurate, complete, and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol, amendment(s), ICH GCPs, FDA CFR, and any other applicable regulatory requirements.

The monitor shall submit a written report to Onyx Therapeutics after each trial site visit or trial-related communication. Reports shall include a summary of what the monitor reviewed

and significant findings, deviations and deficiencies, conclusions, actions taken or to be taken to ensure site compliance.

The Investigator must also permit trial-related audits, IRB/IEC review, and regulatory inspections providing direct access to data and source documents pertaining to this study if so requested.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Routine study site monitoring
- CRF review against source documents
- Data management quality control checks
- Sponsor medical review

A contract research organization (CRO) will be responsible for the data management of this clinical trial. Onyx Therapeutics or its designee will be responsible for the design and distribution of the CRFs. Onyx Therapeutics or its designee will be responsible for the monitoring of the CRFs. CRFs will be returned to the CRO. The CRO, and/or Onyx Therapeutics, and/or its designee will generate queries in the event of incomplete or inconsistent data to be reconciled by the study site.

13 REFERENCES

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APPENDIX A: SCHEDULE OF EVENTS

Visit	Screening (Day -30 to -1)	Cycle 1	Every Cycle	Cycle 3 and Every 3 Cycles	End of Study (Within 30 days of last dose of study drug)
Written Informed Consent	X				
Inclusion/Exclusion Criteria	X				
Obtain Previous PX-171 Protocol Unique Identifier	X				
Pregnancy Test ¹	X				
Routine Physical Examination	X				X
Height, Weight, and BSA ²	X		Day 1		
ECOG Performance and Neuropathy Grade	X				
Bone Marrow Sample for Cytogenetics and FISH ³	X				X
CBC + Platelet Count and Serum Chemistry ⁶		Day 1	Day 1	Day 1	
Carfilzomib Dosing (the same dose level and frequency as administered at the last visit of the prior Onyx study)		Days 1, 2, 8, 9, 15, 16, or same dose level and frequency as prior study	Days, 1, 2, 8, 9, 15, 16, or same dose level and frequency as prior study	Days, 1, 2, 8, 9, 15, 16, or same dose level and frequency as prior study	
Disease Assessments (Extent of disease measurements and response), per method employed in previous protocol ⁴	X			Day 1	X
Peripheral Neuropathy AEs (all Grades)	X	X	X	X	X
Grade 3 and 4 AEs, SAEs or AEs Resulting in Missed Dose or Dose Reduction (all Grades) ⁵	X	X	X	X	X
Record any concomitant chemotherapy reagent	X	X	X	X	X

1 Females of childbearing potential must have a negative serum or urine pregnancy test, with a sensitivity of at least 50 mIU/mL, within 3 days prior to dosing.

2 Height done at screening visit only; BSA calculated Day 1 of every cycle. However, dose adjustments not needed for weight gains/losses of $\leq 20\%$.

3 Screening bone marrow aspirate or biopsy for cytogenetics and FISH is optional and is for MM subjects whose disease status at study entry is PR or less. A Bone marrow sample is also optional for all MM subjects at the end of study if there is evidence of disease progression.

4 If disease assessments are done previously within 30 days of first dose of extended study drug, they will not be required again at screening. If disease assessments per standard institutional practices occur more frequently than every 3 months (eg, every month or every 2 months), the most recent assessment may be reported.

5 Record all AEs leading to missed dose, dose reduction or discontinuation. Record all Grade 3 and 4 AEs from time of consent through 30 days post last administered dose of study drug or initiation of a new anti-cancer therapy.

6 CBC + Platelet Count and Serum Chemistry data will not be routinely recorded on CRFs.

**Appendix B: ECOG Performance Scale
(Eastern Cooperative Oncology Group)**

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

APPENDIX C: NCI CTCAE VERSION 3.0

Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) Version 3.0

Publish Date: December 12, 2003

<http://ctep.cancer.gov/forms/CTCAEv3.pdf>

APPENDIX D: INTERNATIONAL UNIFORM RESPONSE CRITERIA FOR MULTIPLE MYELOMA

Summary Table	
Response Subcategory	Response Criteria
sCR	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence. ¹
CR	Negative immunofixation on the serum and urine, disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein with urine M-protein level < 100 mg per 24 hours
PR	<p>≥ 50% reduction of serum M-protein and reduction in 24 hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours</p> <p>If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria.</p> <p>If serum and urine M-protein and serum FLC are unmeasurable,² then ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%</p> <p>In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required</p>
SD	Not meeting criteria for CR, VGPR, PR, MR or PD
PD	<p>Progressive Disease requires any one or more of the following:</p> <p>Increase of ≥ 25% from baseline in:</p> <ul style="list-style-type: none"> --- serum M-component and /or (the absolute increase must be ≥ 0.5 g/dL) --- urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h) <p>Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL.</p> <p>Bone marrow plasma cell percentage: the absolute % must be ≥ 10%</p> <p>Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas</p> <p>Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder</p>

Source: Durie BG, Harousseau JL, Miguel JS, Bladé J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia 2006 Sep;20(9): 1467–73. Errata in: Leukemia 2006 Dec;20(12):2220. Leukemia 2007 May;21(5):1134.

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

² Measurable disease: serum M protein ≥ 1 g/dL, urine M-protein > 200 mg/24 h, or serum involved FLC levels > 10 mg/dL with a normal κ/λ ratio.

All response categories require 2 consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

Minimal Response	
Response Subcategory	Response Criteria
MR	<p>25%–49% reduction in the level of serum M-protein or a 50%–89% reduction in 24 hours urinary M-protein, which still exceeds 200 mg/24 h, maintained for a minimum of 6 weeks.</p> <p>For subjects with non-secretory myeloma only, 25%–49% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed, maintained for a minimum of 6 weeks.</p> <p>25%–49% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination)</p>

Source: Bladé J, Samson D, Reece D, Apperley J, Björkstrand B, Gahrton G, et al. Criteria for evaluating disease response and progression in subjects with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol 1998 Sep; 102(5):1115–23.

APPENDIX E: RESPONSE CRITERIA FOR SOLID TUMORS

Evaluation of Target Lesions	
Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
Evaluation of Non-Target Lesions	
Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions ¹

¹ Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete Response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Source: Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–16.

APPENDIX F: SUMMARY OF CHANGES

PROTOCOL PX-171-010, AMENDMENT 3

Revisions have been made to the requirements for subjects with MM to undergo bone marrow aspirate and/or biopsy sample collection (for cytogenetic and fluorescent in situ hybridization [FISH] analysis): These procedures have been changed to optional at all time points, rather than required. An addition has been made to dose levels to accommodate subjects rolled over from previous studies. For clarity, updates to AE recording (in the event of a toxicity leading to a dose reduction or discontinuation), and AE reporting following the last dose of study, have also been made in this document.

Administrative updates, editorial changes, and style and formatting revisions have been made to improve clarity and consistency throughout the document. Specific changes are described in the table below. Changes noted in specific sections were also made in the protocol summary and elsewhere in the document, as applicable. Revised text is presented in bold format.

Section No.	Amendment 2	Amendment 3	Rationale
Synopsis: PROCEDURES <i>Efficacy Measures</i>	For subjects with multiple myeloma (MM) entering the extended study with a partial response (PR), minimal response (MR), or stable disease (SD); bone marrow biopsies for cytogenetic and fluorescence in situ hybridization (FISH) evaluation will be required at screening. A bone marrow biopsy in these subjects will also be required at end of study for cytogenetic and FISH evaluation if the reason for study discontinuation is disease progression.	For subjects with multiple myeloma (MM) entering the extended study with a partial response (PR), minimal response (MR), or stable disease (SD); bone marrow biopsies for cytogenetic and fluorescence in situ hybridization (FISH) evaluation will be optional at screening. A bone marrow biopsy in these subjects will also be optional at end of study for cytogenetic and FISH evaluation if the reason for study discontinuation is disease progression.	Revision. To allow bone marrow biopsies for cytogenetic and fluorescence in situ hybridization (FISH) to be optional, rather than required. To accommodate subjects where bone marrow biopsies are unfeasible or unsafe to obtain.
Synopsis: PROCEDURES <i>Efficacy Measures</i>	For subjects with MM entering the extended study with stringent complete response (sCR), complete response (CR), or very good partial response (VGPR), a bone marrow biopsy for cytogenetic and FISH analyses will only be required upon the establishment of disease progression.	For subjects with MM entering the extended study with stringent complete response (sCR), complete response (CR), or very good partial response (VGPR), a bone marrow biopsy for cytogenetic and FISH analyses will also be optional upon the establishment of disease progression.	Revision. To allow bone marrow biopsies for cytogenetic and fluorescence in situ hybridization (FISH) to be optional, rather than required, upon the establishment of disease progression for subjects with MM. To accommodate subjects where bone marrow biopsies are unfeasible or unsafe to obtain.
Section 6.2.1 Dose Frequency and Dose Level Reductions	Carfilzomib Dose Levels 11 mg/m ² 15 mg/m ² 20 mg/m ² 27 mg/m ² 36 mg/m ² * 45 mg/m ² * * Dose level for 30-minute infusion	Carfilzomib Dose Levels 11 mg/m ² 15 mg/m ² 20 mg/m ² 27 mg/m ² 36 mg/m ² * 45 mg/m ² * 56 mg/m²* * Dose level for 30-minute infusion	Addition. A dose level is added since subjects can escalate up to 56 mg/m ² based on dose levels administered in PX-171-007.
Section 6.4.1 Required Concomitant Medication	A proton-pump inhibitor will be used orally daily to prevent peptic disease.	Deleted	Revision. Proton-pump inhibitors are not a required concomitant medication.

Section No.	Amendment 2	Amendment 3	Rationale
Section 7 Study Tests and Observations	These data will not be routinely collected .	These data will not be routinely recorded on CRFs .	Clarification. These data may be collected, but will not be routinely recorded on CRFs.
Section 7.1 Screening (Days -30 to -1)	Bone marrow aspirate and/or biopsy sample collection for cytogenetic and fluorescent in situ hybridization (FISH) analysis (only for <i>MM</i> subjects whose disease status at study entry is PR, MR or SD).	OPTIONAL: Bone marrow aspirate and/or biopsy sample collection for cytogenetic and fluorescent in situ hybridization (FISH) analysis (only for <i>MM</i> subjects whose disease status at study entry is PR, MR or SD).	Revision. To allow bone marrow biopsies for cytogenetic and fluorescence in situ hybridization (FISH) to be optional at Screening, rather than required, for <i>MM</i> subjects whose disease status at study entry is PR, MR or SD. To accommodate subjects where bone marrow biopsies are unfeasible or unsafe to obtain.
Section 7.1 Screening (Days -30 to -1) Section 7.2 Cycle 1 (Day 1) Section 7.3 Cycle 1 (Days 2, 8, 9, 15, and 16) Section 7.4 Cycles 2 and Higher (Day 1) Section 7.5 Cycles 2 and Higher (Days 2, 8, 9, 15, and 16) Section 7.6 Cycles 3 and Every 3 Cycles (Day 1) Section 7.7 End of Study Assessments	Record Grade 3 and 4 AEs, including SAEs	Record Grade 3 and 4 AEs, and all SAEs	Clarification. All SAEs are to be recorded.

Section No.	Amendment 2	Amendment 3	Rationale
Section 7.2 Cycle 1 (Day 1) Section 7.3 Cycle 1 (Days 2, 8, 9, 15, and 16) Section 7.4 Cycles 2 and Higher (Day 1) Section 7.5 Cycles 2 and Higher (Days 2, 8, 9, 15, and 16) Section 7.6 Cycles 3 and Every 3 Cycles (Day 1)	Record AE (any Grade) leading to a missed carfilzomib dose, carfilzomib dose reduction, or discontinuation.	Record AE (any Grade) leading to a missed carfilzomib dose, carfilzomib dose reduction, or discontinuation. In the event of a toxicity leading to a dose reduction or discontinuation, pertinent laboratory measurements and concomitant medications will be collected and monitored as unscheduled visits.	Addition. To include information/instructions regarding collection of laboratory measurements and concomitant medications in the event of toxicity leading to dose reduction or discontinuation.
Section 7.7 End of Study Assessments Section 8 Study Discontinuation	Bone marrow aspirate and/or biopsy for cytogenetic and FISH analysis (only required for <i>MM</i> subjects whose reason for study discontinuation is PD).	OPTIONAL: Bone marrow aspirate and/or biopsy for cytogenetic and FISH analysis (only required for <i>MM</i> subjects whose reason for study discontinuation is PD).	Revision. To allow bone marrow biopsies for cytogenetic and fluorescence in situ hybridization (FISH) to be optional, rather than required, for <i>MM</i> subjects whose reason for study discontinuation is PD. To accommodate subjects where bone marrow biopsies are unfeasible or unsafe to obtain.
Section 7.9.1 Cytogenetic and FISH Studies Appendix A Footnote	A bone marrow biopsy and/or aspirate for determining percent plasma cell involvement, including metaphase cytogenetic and FISH studies, are mandatory for all <i>MM</i> entering with a PR, MR, or SD. Samples for cytogenetic and FISH analysis will also be required for all <i>MM</i> subjects who discontinue study due to PD.	A bone marrow biopsy and/or aspirate for determining percent plasma cell involvement, including metaphase cytogenetic and FISH studies are optional for all <i>MM</i> subjects entering with a PR, MR, or SD. Samples for cytogenetic and FISH analysis will also be optional for all <i>MM</i> subjects who discontinue study due to PD.	Revision. To allow bone marrow biopsies for cytogenetic and fluorescence in situ hybridization (FISH) to be optional, rather than required, for <i>MM</i> subjects entering with a PR, MR, or SD and for <i>MM</i> subjects who discontinue study due to PD. To accommodate subjects where bone marrow biopsies are unfeasible or unsafe to obtain.

Section No.	Amendment 2	Amendment 3	Rationale
Section 9.3 Adverse Events Reporting Procedures	AEs will be collected from the time the subject signs informed consent through 30 days following the last dose of study drugs.	AEs will be collected from the time the subject signs informed consent through 30 days following the last dose of study drugs, or initiation of a new anti-cancer therapy.	Addition. To include information/instruction regarding collection of AEs. AEs should not continue to be recorded /collected if a subject initiates a new anti-cancer therapy.
Appendix A Footnote	CBC + Platelet Count and Serum Chemistry data will not be routinely collected.	CBC + Platelet Count and Serum Chemistry data will not be routinely recorded on CRFs.	Clarification. These data may be collected, but will not be routinely recorded on CRFs.

Document Title:
PX-171-010 Protocol A3_29Mar11.doc

Workflow Number:
3260856

UserName: PPD
Title: VP, Clinical Development
Date: Sunday, 03 April 2011, 02:31 PM Pacific Daylight Time
Meaning: I have reviewed and approved this document.

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Meaning: I have reviewed and approved this document.
