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*APPLICATION NUMBER:*

**202714Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type NDA  
Application Number 202714  
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Reviewer Name Thomas M. Herndon, MD  
Review Completion Date June 1, 2012

Established Name Carfilzomib  
Proposed Trade Name Kyprolis™  
Therapeutic Class Proteasome Inhibitor (PI)  
Applicant Onyx Pharmaceuticals

Formulation Lyophilized Powder (60 mg)  
Dosing Regimen Intravenous administration on Days 1, 2, 8, 9,  
15, and 16 at 20 mg/m<sup>2</sup> for Cycle 1 and at 27  
mg/m<sup>2</sup> for Cycles ≥ 2  
Indication Multiple Myeloma (MM)  
Intended Population Patients with relapsed and refractory MM who  
received ≥ 2 prior lines of therapy including a  
PI and an immunomodulatory agent

Template Version: March 6, 2009

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Table of Abbreviations

AE	Adverse Event
CMC	Chemistry Manufacturing Control
CTCAE	Common Toxicity Criteria
DHP	Division of Hematology Products
DLT	Dose Limiting Toxicities
DOR	Duration of Response
ECG	Electrocardiogram
eCTD	Electronic Common Technical Document
ISS	Integrated Safety Summary
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MTD	Maximum Tolerated Dose
ND	Not Done
NDA	New Drug Application
NOAEL	No Observed Adverse Effect Level
NR	No Response
OS	Overall Survival
PFS	Progression Free Survival
PMC	Post Marketing Commitment
PMR	Post Marketing Requirement
RV	Right Ventricular
SAE	Serious Adverse Advent
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal

## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

The recommendation of the clinical reviewer is accelerated approval (Subpart H) with the post-marketing requirements outlined below.

### 1.2 Risk Benefit Assessment

#### Efficacy as Measured by the Primary Endpoint

The overall response rate to carfilzomib in 266 patients with relapsed multiple myeloma was 22.9%, whether analyzed by the Applicant or by the FDA.

#### Safety

Cardiac, respiratory, and hepatic adverse events were the most concerning events observed in the safety population. Cardiac adverse events contributed to on-study deaths, other serious adverse events, and discontinuations of carfilzomib. Cardiac adverse events and adverse events associated with the respiratory organ system class and to, a lesser extent, the hepatobiliary system and those associated with carfilzomib infusion require further characterization. As these safety signals were identified using data from a single arm study, it is not possible to differentiate their association with carfilzomib, multiple myeloma, or the treatment history of the heavily pretreated patients enrolled in these studies.

#### Benefit Risk Assessment:

The benefit of the overall response rate of 22.9% observed in the primary efficacy study in a heavily pretreated population of patients, 89% of whom were resistant to bortezomib, the only available proteasome inhibitor, outweighs the adverse events, some of which may be life threatening, that occurred at low frequency in a heavily pretreated population of patients with a universally fatal disease.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<b>Summary of evidence:</b> Multiple myeloma is a fatal disease.	<b>Conclusions (implications for decision):</b> Patients with multiple myeloma require additional therapies.
Unmet Medical Need	<b>Summary of evidence:</b> There is no proven effective therapy available for patients with multiple myeloma who have received all approved therapies.	<b>Conclusions (implications for decision):</b> Patients with multiple myeloma require additional therapies as many of the approved therapies are not well tolerated or ineffective.

<b>Clinical Benefit</b>	<b>Summary of evidence:</b> A single arm trial was performed in patients with relapsed or refractory multiple myeloma. The overall response rate to carfilzomib was 22.9%. The duration of response was 7.8 months.	<b>Conclusions (implications for decision):</b> This overall response rate is acceptable for a new therapy for multiple myeloma based on response rates of current therapies in heavily pretreated patients with multiple myeloma.
<b>Risk</b>	<b>Summary of evidence:</b> The safety data base was 526 patients enrolled in single arm studies. Adverse events associated with cardiac, respiratory, and hepatic adverse events including deaths.	<b>Conclusions (implications for decision):</b> The concerning adverse events occurred at a low frequencies in a relapsed/ refractory population with no additional approved therapies available to them.
<b>Risk Management</b>	<b>Summary of evidence:</b> Benefit risk is favorable for the heavily pretreated population of patients with multiple myeloma enrolled in the submitted studies.	<b>Conclusions (implications for decision):</b> PMR needed to further characterize cardiac and respiratory adverse events in a randomized controlled trial.

**Benefit-Risk Summary and Assessment**

The benefit of the overall response rate of 22.9% observed in the primary efficacy study in a heavily pretreated population of patients, 89% of whom were resistant to bortezomib, the only available proteasome inhibitor, outweighs the adverse events, some of which may be life threatening, that occurred at low frequency in a heavily pretreated population of patients with a universally fatal disease.

**1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

None.

**1.4 Recommendations for Postmarket Requirements (PMR) and Commitments**

**PMR 1: Requirement under subpart H to verify clinical benefit**

To verify and describe the clinical benefit of carfilzomib, the Applicant agrees to conduct one or more randomized controlled trials.

The Applicant will conduct a randomized controlled trial per Protocol 2011-003, as finalized, to compare carfilzomib plus dexamethasone with bortezomib plus dexamethasone in a population of patients with multiple myeloma, whose disease has relapsed after at least 1 but not more than 3 prior therapies, to assess the efficacy and safety of carfilzomib. The estimated sample size is 900, and will balance known important prognostic factors, to test for superiority of carfilzomib on the basis of the primary endpoint of progression free survival as determined by an independent review committee blinded to the treatment given.

### **PMR 2: Cardiac Safety Trial**

Cardiac dysfunction is common in heavily pretreated multiple myeloma patients. Adverse events associated with cardiac dysfunction have been observed with carfilzomib, and the safety of carfilzomib in the relapsed multiple myeloma population is not well characterized.

Therefore, the Applicant will conduct a randomized clinical trial in patients receiving carfilzomib to identify and characterize the cardiac events associated with carfilzomib. FDA suggests that the Applicant consider doing this study as a sub-study within the proposed Protocol 2011-003, or the Applicant may propose a separate trial with this safety objective. The primary objective is to compare changes in cardiac function between the group receiving carfilzomib and a control group not receiving carfilzomib, in a parallel group trial.

If the Applicant chooses to add this sub-study to the proposed protocol, the study protocol must require a resting ECG and a baseline transthoracic ECHO to assess LVEF on all patients. If transthoracic ECHO is not available at some sites, MUGA will be acceptable for baseline screening of LVEF evaluation. A subset of patients from both study treatment arms should be assessed for LVEF and right ventricular function with transthoracic ECHO periodically throughout study treatment and at the time of the End-of-Treatment visit, using similar test procedures and equipment to allow serial intra-patient comparisons. This subset of patients must include a minimum of 100 patients and a maximum of 300 patients (50 to 150 patients per treatment arm). Specific details regarding the interpretation of LVEF changes in the subset of patients must be pre-specified and outlined in the SAP for this sub-study. Readers of the ECHOs must be blinded to the treatment arm.

In addition, any patient who has a cardiac adverse event that is considered a clinically significant adverse event must have an ECHO performed to assess left ventricular (LV) and right ventricular (RV) function as part of the evaluation of that adverse event; this applies to all patients enrolled in the study.

### **PMR 3: Pulmonary Safety Trial**

Pulmonary toxicities have been observed with carfilzomib but they are not well characterized.

Therefore, the Applicant will conduct a randomized clinical trial in patients receiving carfilzomib to identify and characterize the pulmonary toxicities associated with carfilzomib. The primary objective is to compare pulmonary toxicities between the group receiving carfilzomib and a control group not receiving carfilzomib, in a parallel group trial. This could be done within the proposed Protocol 2011-003 as a sub-study or as a separate study. If performed as a sub-study of protocol 2011-003, this baseline exam must be obtained on all patients enrolled in that trial, during screening, and to serve as the baseline ECHO for later comparisons on all patients. This study must include a baseline transthoracic ECHO to estimate the pulmonary artery pressures and to assess right ventricular size, thickness, and function. Subsequently, a subset of patients from both treatment arms should be assessed periodically for pulmonary artery pressures and right ventricular function with repeat transthoracic ECHO throughout study treatment and at the time of the End-of-Treatment visit, using similar test procedures and equipment to allow serial intra-patient comparisons. Emergent pulmonary toxicities must be further characterized in all patients receiving carfilzomib, to include time course of onset and resolution, oximetry and/or blood gases, and consultation with a pulmonary specialist when available to provide further documentation of the nature of the emergent condition. The Applicant must document the response to oxygen supplementation and other treatment measures.

A minimum of 100 patients and a maximum of 300 patients are necessary (50 to 150 patients per treatment arm). The Applicant must pre-specify how comparisons will be performed for changes between the two groups for outcomes related to pulmonary hypertension, right ventricular function, and clinical pulmonary safety events. Additionally, any patient who has a cardiac or pulmonary adverse that is considered a clinically significant adverse event, must have a follow up ECHO at the time of the event to assess LV, RV, and pulmonary artery function. This evaluation is for all patients enrolled in the study.

### **Clinical Pharmacology PMRs**

#### **Clinical Pharmacology PMR 1: Hepatic Impairment Study**

The Applicant must conduct a clinical trial in patients with hepatic impairment to assess safety and pharmacokinetic (PK) characteristics of carfilzomib. The number of patients enrolled in the study should be sufficient to detect PK differences that would warrant dosage adjustment recommendations in the labeling. The duration of the study should be sufficient (several cycles) to reasonably characterize potential safety issues. The PK sampling scheme should be optimal to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol.

## Clinical Pharmacology PMR 2: Renal Impairment Study

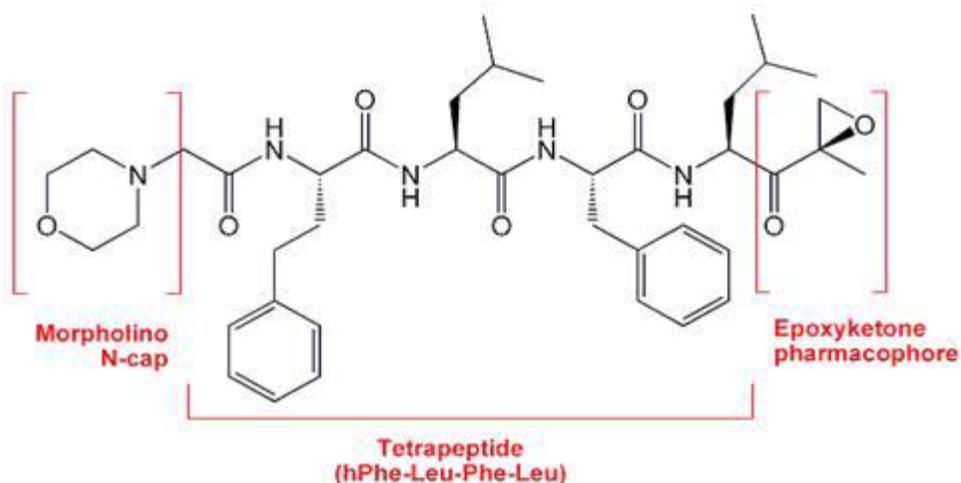
Since the renal impairment study was conducted using carfilzomib doses of 15/20 mg/m<sup>2</sup> given intravenously over 2 – 10 minutes and since this dosing regimen may not necessarily produce clinical responses at the level that would be seen with higher doses, evaluate the PK, safety, and efficacy of carfilzomib in patients with varying degrees of renal impairment following the administration of carfilzomib when given as a 30 minute intravenous infusion at a sufficient dose level that will likely produce comparable exposure and clinical response to those patients without renal impairment that receive carfilzomib doses of 20/56 mg/m<sup>2</sup> using the 30 minute infusion as planned in the upcoming phase 3 trial Protocol number 2011-003. The Applicant must collect PK samples following carfilzomib doses of 56 mg/m<sup>2</sup> or the highest clinical dose in the protocol.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Carfilzomib is a tetrapeptide epoxyketone (Figure 1) that is a potent, long-acting and selective second-generation proteasome inhibitor. The chemical name is (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbonyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide. The molecular formula is C<sub>40</sub>H<sub>57</sub>N<sub>5</sub>O<sub>7</sub> and the molecular weight is 719.91. Carfilzomib specifically functions as an inhibitor of the chymotrypsin-like activity of the 20s proteasome leading to the accumulation of protein substrates within the cell and induction of apoptosis.

Figure 1. Structure of carfilzomib (excerpted from the NDA submission)



Two drug product dosage forms (frozen solution and lyophilized drug product) were supplied for Study PX-171-003. Carfilzomib drug product was provided as a sterile frozen liquid (prior to Amendment 1) or lyophilized powder (after Amendment 1) containing carfilzomib for administration intravenously over 2 to 10 minutes. Both the frozen and reconstituted lyophilized presentations consisted of 2 mg/ml solution of carfilzomib Free Base in 2 mg/ml (b) (4)

The established drug name is carfilzomib and the proposed commercial name is Kyprolis™. Carfilzomib has also been known as PX-171.

## 2.2 Currently Available Treatments for Proposed Indications

The proposed indication is “for the treatment of patients with relapsed and refractory multiple myeloma who have received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent”.

The agents that are commonly utilized in the treatment of patients with multiple myeloma at this time are summarized in Table 1.

**Table 1. Most common agents used as treatments for patients with multiple myeloma**

Agent	Indication	Approval	NCCN Guideline Recommendation (Version 1.2012, MYEL-D)
<b>Proteasome Inhibitor</b>			
Bortezomib	VELCADE® (bortezomib for injection) is indicated for the treatment of patients with multiple myeloma.	Regular	All lines of therapy
<b>IMiD</b>			
Lenalidomide	REVLIMID® (lenalidomide tablets) in combination with dexamethasone is indicated for the treatment of patients with multiple myeloma (MM) who have received at least one prior therapy.	Regular Under Subpart H with restricted distribution	All lines of therapy
Thalidomide	THALOMID® (thalidomide tablets) in combination with dexamethasone is indicated for the treatment of patients with newly diagnosed multiple myeloma. The effectiveness of THALOMID® (thalidomide) is based on response rates.	Accelerated Approval Under Subpart H with restricted distribution	All lines of therapy

Agent	Indication	Approval	NCCN Guideline Recommendation (Version 1.2012, MYEL-D)
<b>Alkylator</b>			
Mephalan	ALKERAN® (melphalan tablets) is indicated for the palliative treatment of multiple myeloma.	Regular	Non-transplant candidates
	ALKERAN® (melphalan for injection) is indicated for the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.	Regular	Primary therapy for non-transplant candidates
Cyclophosphamide	CYTOXAN® (cyclophosphamide for injection) is indicated for treatment of multiple myeloma.	Regular	Primary therapy for transplant candidates, salvage therapy
<b>Anthracycline</b>			
Doxorubicin	DOXIL® (doxorubicin liposome injection) in combination with bortezomib is indicated for the treatment of patients with multiple myeloma who have not previously received bortezomib and have received at least one prior therapy.	Regular	For patients with ≥1 prior therapy who are bortezomib naive
	Doxorubicin HCl – no label	None	All lines of therapy except maintenance
<b>Nitrosurea</b>			
BiCNU (carmustine)	BiCNU® (carmustine for injection) is indicated as palliative therapy as a single agent or in established combination therapy with other approved chemotherapeutic agents in the following: Multiple myeloma—in combination with prednisone.	Regular	Approved for use in combination with prednisone but not included in 2012 NCCN Guidelines
<b>Corticosteroids</b>			
Dexamethasone	Dexamethasone - no label	Approved for hematological malignancies	All lines
Prednisone	Prednisone - no label	None	Primary therapy for non-transplant candidates

Table 1 contains only the most commonly used agents for the treatment of patients with multiple myeloma. There are numerous additional non-FDA approved and experimental therapies available for treating patients with multiple myeloma.

There are currently seven agents in six different drug classes approved by the FDA for the treatment of MM. These are bortezomib, a proteasome inhibitor, lenalidomide, an immunomodulatory drug (IMiD), thalidomide an IMiD, melphalan and cyclophosphamide, both alkylators, Doxil®, an anthracycline, and carmustine, a nitrosurea. Dexamethasone is approved for the treatment of hematologic malignancies.

### 2.3 Availability of Proposed Active Ingredient in the United States

Carfilzomib is a NME and does not contain an active moiety that has been marketed in the United States or in any other country.

### 2.4 Important Safety Issues With Consideration to Related Drugs

Bortezomib is the only approved agent in the same drug class (PI) as carfilzomib. Bortezomib is a dipeptide boronate reversible inhibitor of the peptidase activity of the 20S proteasome in mammalian cells currently approved for the treatment of multiple myeloma and mantle cell lymphoma. Bortezomib is administered as an intravenous (IV) bolus on Days 1, 4, 8, and 11 of a 28-day cycle at 1.3 mg/m<sup>2</sup>/dose. At the 1.3 mg/m<sup>2</sup> dose, the mean maximum plasma concentration is in the range of 89 to 120 ng/ml with a mean elimination half life ranging from 76 to 108 hours, and an observed inhibition of 20S proteasome activity at 1 hour of 65%–71%.

Regarding adverse events (AEs) in the relapsed MM population, asthenic conditions (61%), gastrointestinal events (diarrhea [57%], nausea [57%], vomiting [35%], constipation [42%]), and peripheral neuropathy [36%]) were among the most common non-hematological adverse events accounting for the most commonly reported drug-related events leading to discontinuation.

### 2.5 Summary of Presubmission Regulatory Activity Related to Submission

The regulatory history of carfilzomib is outlined in Table 2.

**Table 2. Regulatory history of carfilzomib**

Date	Event
2005 (JUN 13)	IND 71,057 submitted
2007 (MAR 07)	EOP1 Meeting
2008 (JAN 18)	Orphan Drug Designation granted for MM
2008 (NOV 06)	EOP2 Meeting
2009 (AUG 03)	EOP2 CMC Meeting
2010 (JAN 15)	Special Protocol Agreement reached
2010 (AUG 05)	Pre-NDA Clinical Meeting
2010 (SEP 28)	Pre-NDA CMC Meeting
2011 (JAN 06)	Fast Track Designation Granted
2011 (SEP 27)	NDA 202714 submitted

## 2.6 Other Relevant Background Information

Orphan drug status was given to carfilzomib under FDA Act 526 for MM. There will be no requirement for a pediatric waiver request (see CFR316(d) Exemption for Orphan Drugs).

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

NDA 202714 was submitted as an electronic Common Technical Document (eCTD) and is organized following the FDA Guidance for Industry. The submission is acceptable for review.

OSI inspections for data audits were performed for the sites as outlined in Table 3. No major discrepancies were noted during the inspections.

Table 3. OSI Audit Sites

Protocol ID	Site Number	Investigator / Institution	Location	Number of Subjects
PX-171-003	11	Sagar Lonial / Winship Cancer Institute of Emory University	Atlanta, GA	14
PX-171-003	15	David Siegel / Cancer Center of the Hackensack University Medical Center	Hackensack, NJ	33
PX-171-003	18	Ravi Vij / Siteman Cancer Center Washington University in St Louis	St Louis, MO	15

### 3.2 Compliance with Good Clinical Practices

This study was conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonization and laws and regulatory requirements of all countries in which the trial was carried out.

### **3.3 Financial Disclosures**

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. These arrangements do not raise questions about the integrity of the data.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

None.

### **4.2 Clinical Microbiology**

None.

### **4.3 Preclinical Pharmacology/Toxicology**

Significant cardiac, gastrointestinal, renal and pulmonary toxicities were observed in rats and monkeys receiving a 20 second intravenous bolus injection of carfilzomib. Monkeys administered a single intravenous bolus dose of carfilzomib at 3 mg/kg (approximately 1.3 times the recommended dose in humans of 27 mg/m<sup>2</sup> based on total body surface area) experienced hypotension, increased heart rate, and increased serum levels of troponin-T. The repeated intravenous bolus administration of carfilzomib at  $\geq 2$  mg/kg/dose in rats and 2 mg/kg/dose in monkeys using dosing schedules similar to those used clinically, resulted in mortalities that were due to toxicities occurring in the following systems:

- Cardiovascular (cardiac failure, cardiac fibrosis, pericardial fluid accumulation, cardiac hemorrhage/degeneration),
- Gastrointestinal (necrosis/hemorrhage),
- Renal (glomerulonephropathy, tubular necrosis, dysfunction), and
- Pulmonary (hemorrhage/inflammation).

Following repeated bolus intravenous administration in monkeys at  $\geq 1$  mg/kg/dose, cardiovascular toxicities included myocardial degeneration, myocyte hypertrophy and inflammation. Other toxicities noted in rats included thrombocytopenia and an acute phase response. Many of these toxicities observed in non-clinical studies were the same ones observed in clinical studies.

The dose of 2 mg/kg/dose in rats resulted in systemic exposures (AUCs) approximately 40% of those observed in patients who received 27 mg/m<sup>2</sup> of carfilzomib twice weekly for two weeks.

The non-clinical safety studies in rats and monkeys were conducted with bolus intravenous injections of carfilzomib (usually over 20 seconds), while in the Applicant's primary efficacy study (Study 3), carfilzomib was administered as an intravenous bolus injection over 2 to 10 minutes. In an attempt to further reduce the toxicities observed in rats with the twice weekly bolus administration (dosing was on consecutive days; i.e., days 1, 2, 8, 9, 15, 16, etc.), a series of studies was conducted in rats comparing the pharmacodynamics, pharmacokinetics and toxicities of intravenous carfilzomib administered as a bolus injection, a 10-minute infusion or a 30-minute infusion in order to investigate the potential for reducing drug-related toxicities by reducing the peak serum concentrations. The C<sub>max</sub> and significant toxicities in rats, including death, pre-renal azotemia (elevated blood urea nitrogen and creatinine), lethargy, and dyspnea observed following a single bolus (over 20 seconds) injection of 8 mg/kg carfilzomib were reduced when the same dose was administered as a 30-minute infusion, while a similar level of proteasome inhibition was maintained.

#### 4.4 Clinical Pharmacology

The Applicant did not conduct a human Absorption, Distribution, Metabolism, Excretion (ADME) study; instead, excretion data were available from a rat study. The rat excretion study showed that 30.5% of the administered drug undergoes biliary elimination while about 26% of the administered drug is eliminated by the kidneys.

The Applicant conducted a renal impairment study where the pharmacokinetic (PK) and safety of carfilzomib were evaluated in patients with normal renal function and those with mild, moderate, and severe renal function and patients on chronic dialysis following carfilzomib doses of 15 mg/m<sup>2</sup> during Cycle 1, 20 mg/m<sup>2</sup> during Cycle 2, and 27 mg/m<sup>2</sup> during Cycles 3 and beyond. The C<sub>max</sub> and AUC of carfilzomib were similar across all renal function categories following carfilzomib doses of 15 and 20 mg/m<sup>2</sup>. PK data were not available for the proposed 27 mg/m<sup>2</sup> dose. The mean treatment duration for all renal function categories was 5.5 months. The safety profile of carfilzomib was similar across all renal function categories.

Pharmacokinetic data were available from 85 patients who took part in the primary efficacy Phase 2 trial in patients with multiple myeloma. Exposure-response analyses for efficacy showed that increasing doses did not result in increased efficacy. There were not sufficient data to conduct exposure-response analysis for liver toxicity.

An *in vitro* study showed carfilzomib to be a moderate CYP3A4 inhibitor. To confirm these *in vitro* PK findings, a human PK study was conducted in cancer patients following the administration of the CYP3A4 substrate midazolam in the absence and presence of

carfilzomib. The  $C_{max}$  and AUC of midazolam were similar across all three time periods, indicating that carfilzomib does not influence the PK of CYP3A4 substrates.

A Clinical Pharmacology issue that is not addressed in this NDA package is that of hepatic impairment. The sponsor did not conduct a human ADME study and the rat excretion study showed 30.5% of the administered drug undergoes biliary elimination. In the primary efficacy Phase 2 study (Study 3), one of the most important adverse effects was liver enzyme elevations, where 42.1% exhibited a Grade 1-2 elevation of alanine aminotransferase (ALT) from baseline and 3.6% experienced Grade 3 ALT elevations. These findings indicate patients with baseline hepatic impairment might be at an increased risk of liver toxicity.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

The efficacy of carfilzomib is based primarily on the results from Study PX-171-003 – Part 2 (A1). This is a single arm, open label clinical trial of carfilzomib in patients with relapsed and refractory multiple myeloma.

The application contains efficacy results from 266 patients with relapsed and/or refractory multiple myeloma enrolled in Study PX-171-003, the primary efficacy study.

The safety analysis of carfilzomib is based on data from 768 patients treated with carfilzomib in nine Phase 1 and Phase 2 clinical studies, which are presented in 12 clinical study reports.

Table 4 provides an overview of the numbers of patients from Onyx-sponsored studies contributing to the database in each Phase 1 and Phase 2 trial. Of these 768 patients, the majority (612 or 80%) had multiple myeloma, while 156 patients had a variety of solid tumors or other hematologic malignancies. Of the 612 patients with multiple myeloma, a total of 336 patients (55%) were exposed to carfilzomib at the proposed to-be-marketed dose and schedule. A number of these patients have enrolled in an ongoing long-term safety study during which they continue to receive carfilzomib treatments for extended durations.

**Table 4. Clinical trials and diseases included in ISS**

<b>Trial Number</b>	<b>Trial Phase</b>	<b>Number of Patients Total / MM</b>	<b>Disease</b>
PX-171-001	1	29 / 10	Hematologic Malignancies
PX-171-002	1	48 / 28	Hematologic Malignancies
PX-171-003 Part 1	2	46 / 46	MM
PX-171-003 Part 2	2	266 / 266	MM

Trial Number	Trial Phase	Number of Patients Total / MM	Disease
PX-171-004 Part 1	2	35 / 35	MM
PX-171-004 Part 2	2	129 / 129	MM
PX-171-005	2	50 / 50	MM
PX-171-006	1b	40 / 40	MM
PX-171-007	1b/2	108 / 8	Solid Tumors, Lymphoma, MM
PX-171-008	1b	17 / 0	Solid Tumors
		<b>Sum: 768 / 612</b>	

## 5.2 Review Strategy

The review of the efficacy data focused on the results of Study PX-171-003 A1 as this was the primary efficacy study contained in the submission. The applicant requested approval for carfilzomib under the accelerated approval pathway and Study PX-171-003 A1 was the most pertinent to this approval pathway. Other studies were reviewed in support of this study.

All of the safety data was included in the safety review. The safety analysis focused on the 526 patients with MM who were enrolled in Phase 2 trials. Only 52.9% of the 526 patients received carfilzomib at 20 mg/m<sup>2</sup> during Cycle 1 and 27 mg/m<sup>2</sup> during Cycle 2 and thereafter, as proposed for the requested indication (this will be referred to as the “20/27 regimen” or the “step-up program”). For this reason, emphasis was also placed on the 266 patients in the primary efficacy study, all of whom received carfilzomib at 20 mg/m<sup>2</sup> during Cycle 1 and 27 mg/m<sup>2</sup> during Cycle 2 and beyond.

## 5.3 Discussion of Individual Studies/Clinical Trials

The clinical trials of carfilzomib that were included in the application are summarized in Table 5.

Table 5. Overview of clinical trials

Trial Number	Description	Study Design / Control	Product / Schedule	Number of Patients Enrolled	Status
<b>Phase 1</b>					
PX-171-001	Dose Escalation/ PK Study	Open label, dose escalation / No control	CFZ, frozen / 1.2 to 20 mg/m <sup>2</sup> ; IV, 1–2 min, 14d cycle, QDx5 with 9d rest	29	Complete

<b>Trial Number</b>	<b>Description</b>	<b>Study Design / Control</b>	<b>Product / Schedule</b>	<b>Number of Patients Enrolled</b>	<b>Status</b>
PX-171-002 Part 1	Dose Escalation/ PK Study	Open label, dose escalation / No control	CFZ, frozen / 1.2 to 27 mg/m <sup>2</sup> ; IV, 1–2 min, 28d cycle, QDx2 for 3w with 12d rest	37	Complete
PX-171-002 Part 2	Dose Expansion	Open label, dose expansion / No control	CFZ, frozen or lyophilized / 20/27 mg/m <sup>2</sup> ; IV, up to 10 min, 28d cycle, QDx2 for 3w with 12d rest.	11	Complete
<b>Phase 1b and Phase 2</b>					
PX-171-003 Part 1	Supportive	Open label / No control	CFZ, frozen or lyophilized / 20 mg/m <sup>2</sup> IV, 2 min, 28d cycle, QDx2 for 3w with 12d rest.	46	Complete
PX-171-003 Part 2	Efficacy	Open label, dose escalation / No control	CFZ, frozen or lyophilized / 20/27 mg/m <sup>2</sup> IV, up to 10 min, 28d cycle, QDx2 for 3w with 12d rest	266	Complete
PX-171-004 Part 1	Supportive	Open label, dose escalation / No control	CFZ, frozen or lyophilized / 20/27 mg/m <sup>2</sup> IV, 2 min, 28d cycle, QDx2 for 3w with 12d rest.	35	Ongoing
PX-171-004 Part 2	Supportive	Open label, dose escalation /	CFZ, frozen or lyophilized /	129	Ongoing

Trial Number	Description	Study Design / Control	Product / Schedule	Number of Patients Enrolled	Status
		No control	20/27 mg/m <sup>2</sup> IV, up to 10 min, 28d cycle, QDx2 for 3w with 12d rest.		
PX-171-005	Supportive	Open label / No control	CFZ, lyophilized / 15/20/27 mg/m <sup>2</sup> IV, ~10 mL/min, 28d cycle, QDx2 for 3w with 12d rest.	50	Ongoing
PX-171-006	Renal Impairment	Open label, dose escalation (carfilzomib plus lenalidomide and dexamethasone / No control	CFZ, frozen or lyophilized / 15, 20, or 20/27 mg/m <sup>2</sup> IV over 10 min, 28d cycle, QDx2 for 3w with 12d rest. LEN; 15 or 20 mg; oral DEX; 40 mg; oral	84	Ongoing
PX-171-007	Dose Escalation/ Expansion Study	Open label, dose escalation / No control	CFZ, frozen or lyophilized / 15, 20, 20/27, 20/36 mg/m <sup>2</sup> IV over 2–10 min; or 20/36, 20/45, 20/56, 20/70 mg/m <sup>2</sup> IV over 30 min; 28d cycle, QDx2 for 3w with 12d rest	153	Ongoing
PX-171-008	Drug-Drug Interaction	Open label / No control	CFZ, lyophilized /	17	Complete

Trial Number	Description	Study Design / Control	Product / Schedule	Number of Patients Enrolled	Status
			27 mg/m <sup>2</sup> IV, ~10 mL/min, 28d cycle, QDx2 for 3w with 12d rest Midazolam, oral;2 mg		
<b>Extension Study</b>					
PX-171-010	Extension Study	Open label extension	CFZ, lyophilized / administered as in previous studies.	9	Ongoing
<b>Phase 3</b>					
PX-171-009	Confirmatory: C, LEN, and DEX vs. LEN and DEX	Randomized, open-label Rd vs. CRd	CFZ, / 20mg/m <sup>2</sup> IV on Days 1 and 2 of Cycle 1, escalating to 27 mg/m <sup>2</sup> IV on Days 8, 9, 15, and 16 of Cycle 1 and continuing on Days 1, 2, 8, 9, 15, and 16 of Cycles 2 through Cycle 9. Cycles 10 and beyond will receive 27 mg/m <sup>2</sup> IV on Days 1,2,15, and 16	268	Ongoing
PX-171-011	Confirmatory: CFZ vs BSC	Randomized, open label / Best supportive care vs. C	CFZ, / 20mg/m <sup>2</sup> IV on Days 1 and 2 of Cycle 1, escalating to 27 mg/m <sup>2</sup> IV	90	Ongoing

Trial Number	Description	Study Design / Control	Product / Schedule	Number of Patients Enrolled	Status
			on Days 8, 9, 15, and 16 of Cycle 1 and continuing on Days 1, 2, 8, 9, 15, and 16 of Cycles 2 through Cycle 9. Cycles 10 and beyond will receive 27 mg/m <sup>2</sup> IV on Days 1,2,15, and 16		

Abbreviations: CFZ = carfilzomib; QD = daily; d = days; w = weeks; min = minutes; DEX=dexamethasone; L=liter.

### Phase 1 Studies

#### PX-171-001

PX-171-001 was an open-label, dose-escalation safety trial with the primary objective of characterizing dose limiting toxicities (DLTs) and identifying the maximum tolerated dose (MTD) of carfilzomib given daily for 5 days in a 14-day cycle in subjects with previously treated hematologic malignancies. Carfilzomib dose assignment was based on consecutive enrollment using a Fibonacci multiple scheme. According to the Clinical Study Report (CSR) all 29 treated subjects experienced 1 or more adverse events (AEs). The most common AEs regardless of grade or causality were nausea, fatigue (each in 48.3% of subjects), and diarrhea (34.5%). At the 20 mg/m<sup>2</sup> dose level, 2 subjects experienced DLTs: Grade 4 thrombocytopenia and Grade 3 febrile neutropenia and chills—all considered possibly related to carfilzomib. Consequently, 15 mg/m<sup>2</sup> was considered the MTD of carfilzomib when administered daily for 5 consecutive days.

#### PX-171-002

PX-171-002 was an open-label Phase 1 study of escalating dose levels of carfilzomib administered twice per week (Days 1, 2, 8, 9, 15, and 16) for 3 weeks, followed by 1 week of rest, in 4-week cycles. Up to 86 subjects with various hematologic malignancies were planned. The study was divided into a sequential Dose Escalation phase (Part 1), followed by a Dose Expansion period (Part 2) consisting of: A) a carfilzomib-only cohort and B) a carfilzomib-plus Dexamethasone cohort Studies PX-171-002 Part 1 and PX-171-002 Part 2 are presented in separate CSRs. According to the CSR, objective responses were observed at carfilzomib doses ranging from 15 to 27 mg/m<sup>2</sup> and were seen only in subjects with MM. The minimally effective dose on this schedule appeared

to be carfilzomib 15 mg/m<sup>2</sup> given in a regimen of once-daily x 2 for 3 weeks in a 4-week cycle. The MTD for carfilzomib was not reached.

#### Part 2

Eleven patients entered the dose expansion phase of Study PX-171-002: 7 patients were treated with a starting dose of 20/27 mg/m<sup>2</sup>, and 4 were treated with a starting dose of 20/27 mg/m<sup>2</sup> with dexamethasone. On the basis of this trial, a dose of 20 mg/m<sup>2</sup> followed by a dose of 27 mg/m<sup>2</sup> (“the step up program”) was recommended for future studies in patients with advanced hematologic malignancies to reduce adverse events associated with carfilzomib infusion.

No additional efficacy was observed with addition of low-dose dexamethasone (40 mg/week; 120 mg/28-day cycle), either upon examination of the patients who received carfilzomib + dexamethasone beginning with the first dose in Cycle 1 Day 1 or of the 1 patient with stable disease in whom dexamethasone was added on Cycle 3 Day 1. One patient (2-01-027) out of 4 receiving carfilzomib + dexamethasone experienced a drug-related serious adverse events (SAE) (hypoxia) as well as 3 AEs that were considered to be dose limiting toxicities (DLTs); these consisted of Grade 3 elevations in alkaline phosphatase and liver transaminases (ALT and AST). No patient receiving single-agent carfilzomib experienced an adverse event (AE) considered to be a DLT.

### **Phase 1b and Phase 2 Studies**

#### **Study PX-171-003**

Study PX-171-003 contains the primary efficacy study of carfilzomib in patients with relapsed and refractory multiple myeloma who had received prior bortezomib and an IMiD agent. Study PX-171-003 was an open-label, multi-center study (PX-171-003) of the safety and efficacy of carfilzomib that was presented in 2 clinical study reports (CSRs).

PX-171-003 – Part 1 (A0) (46 patients) describes the completed initial portion of this protocol prior to Amendment I, and CSR PX-171-003 – Part 2 (A1) (266 patients) describes the post Amendment 1 key portion of the study that provides the key data. These 2 study reports include similar patient populations: patients with multiple myeloma who had received at least 2 prior therapies (including bortezomib and a thalidomide/thalidomide analog), and demonstrated no response or disease progression on or within 60 days of their most recent therapy. Carfilzomib was administered as an IV bolus infusion over 2 to 10 minutes twice weekly for 3 weeks followed by a 12-day rest period (28-day treatment cycle) for a maximum of 12 cycles.

In Study Report PX-171-003 A0, carfilzomib was administered in doses of 20 mg/m<sup>2</sup> throughout (although 3 patients were permitted to dose escalate to 27 mg/m<sup>2</sup> in later cycles). In Study Report PX-171-003, carfilzomib was administered in what has been referred to as the “step-up” program or the 20/27 regimen, in which carfilzomib was given at 20 mg/m<sup>2</sup> in Cycle 1 and then at 27 mg/m<sup>2</sup> for subsequent cycles.

The primary endpoint of Study Report PX-171-003 A1 was over all response rate (ORR), as determined by an Independent Review Committee (IRC), in the Response Evaluable Population. The study was pre-specified to be successful if the lower boundary of the 2-sided 95% confidence intervals (CI) of the ORR was > 10%.

#### **Study PX-171-004**

Study PX-171-004 was a multicenter, open-label, single-arm trial in patients with multiple myeloma who had relapsed or refractory disease after at least 1, but no more than 3 prior therapeutic treatments or regimens. Study PX-171-004 is described in 2 CSRs. PX-171-004 – Part 1 describes results of carfilzomib treatment in bortezomib treated patients (N=35) and CSR PX-171-004 – Part 2 describes results of carfilzomib treatment in bortezomib-naïve patients (N=127). The primary endpoint of the study was ORR, as determined by IRC assessment, in the Response Evaluable Subset.

#### **Study PX-171-005**

Study PX-171-005 was designed to further characterize the safety and dosing of carfilzomib in patients with multiple myeloma who had baseline renal impairment. Study PX-171-005 was initiated in 5 cohorts of patients: one cohort consisting of patients with decreased creatinine clearance (CrCl), 1 cohort consisting of patients with normal CrCl, and 1 cohort of patients on hemodialysis. Carfilzomib was administered using a dose of 15 mg/m<sup>2</sup> on the once a day (QD) x 2 schedule, with an option for dose escalation to 20 mg/m<sup>2</sup> or 27 mg/m<sup>2</sup> in subsequent cycles as tolerated.

PX-171-005 is an ongoing Phase 2, open-label, single-arm, multicenter study designed to assess the influence of renal impairment on the PK of carfilzomib in patients with multiple myeloma who had relapsed or progressive disease (PD) after at least 1 (original protocol) or 2 (following protocol Amendment 1) prior therapeutic treatments or regimens. Five groups of multiple myeloma patients, representing different levels of renal function based on the Cockcroft-Gault formula, were evaluated, as follows:

- Group 1: Patients with CrCl > 80 mL/minute (Normal)
- Group 2: Patients with CrCl between 50–80 mL/minute (Mild impairment)
- Group 3: Patients with CrCl between 30–49 mL/minute (Moderate impairment)
- Group 4: Patients with CrCl < 30 mL/minute (Severe impairment)
- Group 5: Patients undergoing chronic hemodialysis (Dialysis)

Although the study is ongoing, the PK, pharmacodynamic (PDn), metabolite, protein binding, and electrocardiogram (ECG) analyses have been completed.

The primary endpoint of the study was the slope of the regression of clearance against CrCl at Cycle 1, Day 1 and Day 15. Additionally, ORR, clinical benefit rate CBR, duration of response DOR, progression-free survival (PFS), time to progression TTP and OS were analyzed in the Response Evaluable Population.

### **Study PX-171-006**

Study PX-171-006, initiated in May 2008, is an ongoing Phase 1b trial to assess safety and preliminary efficacy of the combination of carfilzomib, lenalidomide, and low-dose dexamethasone (40 mg/week) (CRd), with both carfilzomib (given at 15, 20, or 20/27 mg/m<sup>2</sup>) and lenalidomide escalated in sequential cohorts in patients with relapsed multiple myeloma. The primary endpoint is to evaluate safety and the MTD and/or a protocol-defined dose below the MTD of carfilzomib with lenalidomide and dexamethasone if an MTD is not determined in patients with relapsed multiple myeloma. The secondary efficacy endpoints include ORR, DOR, PFS, and TTP.

In an interim analysis of 40 patients (of a total of 84 patients enrolled) on 25 February 2011, the MTD had not been reached (Interim CSR for Study PX-171-006). Also, the ORR was 61.5% [95% CI: 44.6, 76.7] and the median DOR in the 24 patients who achieved PR or better was 9.7 months (95% CI: 5.6, 13.8). The CBR was 74.4% (95% CI: 57.9, 87.0).

Based on findings from the dose-escalation phase of Study PX-171-006, pivotal Phase 3 registration trial, Study PX-171-009, was initiated in July 2010 at approximately 200 centers in the US, Canada, the European Union, and Eastern Europe. This trial was a randomized comparison of lenalidomide and dexamethasone with or without carfilzomib.

### **Study PX-171-007**

Study PX-171-007 is an additional study evaluating carfilzomib as monotherapy in patients with multiple myeloma. Study PX-171-007 was initiated in September 2007 and is an ongoing open-label, multicenter study of carfilzomib in patients with relapsed and refractory multiple myeloma, relapsed solid tumors, or refractory lymphoma. This Phase 1b/2 study is an ongoing, open-label, multicenter study in which patients with solid tumors, multiple myeloma (added in Amendment 2), or lymphoma (added in Amendment 3, implemented after the data cutoff date for inclusion in the ISS) whose disease relapsed after conventional therapy. Carfilzomib was assessed as a 2- to 10-minute IV bolus infusion (for doses of carfilzomib up to and including 36 mg/m<sup>2</sup> dose, or as a 30-minute IV infusion (added with Amendment 2) for doses above 36 mg/m<sup>2</sup> per dose.

The primary objectives of this ongoing study are as follows:

- Phase 1b (2- to 10-minute and 30-minute IV injections): to evaluate the safety and tolerability of carfilzomib in patients with relapsed solid tumors, relapsed and/or refractory multiple myeloma, or refractory lymphoma.
- Phase 2 (2- to 10-minute IV injection): to estimate the ORR after 4 cycles of carfilzomib in patients with relapsed solid tumors

A total of 30 patients with multiple myeloma and 120 patients with diseases other than multiple myeloma, were enrolled as of 01 July 2011 in Study PX-171-007. As of 01 July

2011, a total of 153 patients have been enrolled. IV carfilzomib was initially administered over 2–10 minutes; under Amendment 2, the mode of administration was changed to IV administration over 30 minutes for subsequent patients, based on animal studies that showed less toxicity with prolonged administration of higher doses.

Study PX-171-007 also includes an earlier escalation of carfilzomib dose (ie, 20 mg/m<sup>2</sup> on Cycle 1, Days 1 and 2 only, followed by a dose of 27 mg/m<sup>2</sup> for the remainder of treatment). Efficacy endpoints include determination of the MTD, ORR, DOR, PFS, and TTP. The interim CSR for PX-171-007 that is contained within the application includes safety data only for the 79 patients with solid tumors who were treated with IV administration over 2–10 minutes; results in patients receiving IV carfilzomib over 30 minutes will be reported separately. The Applicant intends to further study carfilzomib administration over 30 minutes in future trials, but currently does not seek a label for this regimen.

#### **Study PX-171-008**

Study PX-171-008 is an open-label, Phase 1b, non-randomized, fixed-sequence study in patients with solid tumors. An in vitro study in human liver microsomes indicated that carfilzomib is a direct and time-dependent inhibitor of human CYP3A4. Midazolam, which is metabolized primarily by CYP3A4 to 1-hydroxymidazolam in humans, was used as a probe drug for CYP3A4 in this study. Patients were assessed to determine the effect of carfilzomib on the PK of midazolam, a sensitive substrate of human cytochrome P450 (CYP) 3A4. This study consisted of 2 periods, as follows:

- Period 1, before Carfilzomib Cycle 1: Day –7 (plus up to 3 days) before Cycle 1, patients were administered a single, oral, 2-mg dose of midazolam. The washout period for midazolam was 7 to 10 days. PK blood samples were collected on Day –7 (or up to Day –10).
- Period 2, Cycle 1: The same patients were administered carfilzomib at 27 mg/m<sup>2</sup> IV at the rate of approximately 10 mL/min IV on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle.

Midazolam (2 mg) was administered orally immediately after carfilzomib administration on Days 1 and 16. A total of 17 patients who had diseases other than multiple myeloma received carfilzomib in Study PX-171-008.

#### **Study PX-171-010**

Study PX-171-010 is designed to determine the duration of clinical benefit. Study PX-171-010 was initiated to allow patients who had completed other carfilzomib studies to continue to receive carfilzomib treatment, thus providing information on duration of efficacy and on safety.

PX-171-010 is an ongoing open-label, multicenter, Phase 2 extension study designed to monitor the safety and efficacy of long-term carfilzomib therapy in patients who have completed a primary carfilzomib treatment study within the preceding 90 days, including

Study Reports PX-171-002 – Part 1, PX-171-002 – Part 2, PX-171-003 – Part 2 (A1), PX-171-003 – Part 1 (A0), PX-171-004 – Part 1, and PX-171-004 – Part 2, and Studies PX-171-005, PX-171-006, and PX-171-007, or drug–drug interaction Study PX-171-008. Only patients who have completed a prior carfilzomib treatment study were eligible for Study PX-171-010. Per Amendment 2 (implemented 09 April 2010), an additional anticancer drug could be added to the patient’s regimen. Efficacy endpoints included PFS, TTP, and OS. A total number of 92 patients was enrolled as of 01 July 2011 in Study PX-171-010.

### **Phase 3 Studies**

Two Phase 3 studies of carfilzomib are currently ongoing, including Studies PX-171-009 (considered as the Phase 3 confirmatory trial) and PX-171-011.

#### **Study PX-171-009**

Study PX-171-009 is an ongoing, Phase 3, multicenter, international, randomized, open-label study of lenalidomide with low-dose dexamethasone (Rd) vs. carfilzomib, lenalidomide, and low-dose dexamethasone (CRd) with PFS as the primary endpoint in patients with relapsed or refractory multiple myeloma after 1–3 prior therapies was initiated under a Special Protocol Assessment (SPA) dated 15 January 2010. Patients are being randomized in a 1:1 ratio to receive either the control Rd or CRd, and the estimated sample size is 700 patients. The applicant plans that this study will serve as confirmation of clinical benefit for carfilzomib in patients with relapsed multiple myeloma, in the event that an accelerated approval is granted for the proposed indication. The first patient was enrolled 23 June 2010. A total of 268 multiple myeloma patients were enrolled as of 01 July 2011.

#### **Study PX-171-011**

Study PX-171-011 is an ongoing, Phase 3, randomized, open-label, multicenter study comparing carfilzomib alone (Regimen C) vs best supportive care (Regimen BSC) for patients with multiple myeloma who have no available approved alternative therapies and who would otherwise be offered supportive and/or palliative care. The objective is to compare OS in patients with refractory multiple myeloma relapsed after at least 3 prior regimens and who are randomized to receive either Regimen C or Regimen BSC. Eligible patients are randomized in a 1:1 ratio to Regimen C or Regimen BSC, and the estimated sample size is approximately 300 patients. The first patient was enrolled 24 August 2010. A total number of 90 multiple myeloma patients was enrolled as of 01 July 2011.

## **6 Review of Efficacy**

### **Efficacy Summary**

The overall response rate (ORR) to carfilzomib in the 266 patients enrolled in PX-171-003 A1 (the intent to treat (ITT) population) with relapsed multiple myeloma was 22.9%.

The ORR was 22.9%, whether analyzed by the Applicant or by the FDA. The number of entered patients who had been shown to be unresponsive or intolerant to 5 of the 6 groups of approved agents for multiple myeloma (excluding carmustine) was 69 out of 266 patients. The ORR for this subset of patients was 23.2%. The duration of response was 7.8 months.

## 6.1 Indication

The Applicant's proposed indication is for "the treatment of patients with relapsed and refractory multiple myeloma who have received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent."

### 6.1.1 Methods

This section will describe design issues for Study PX-171-003 A1, hereafter referred to Study 3. For additional details, see Section 5.3.

Study 3 was an open-label, single-arm, multicenter Phase 2 clinical study. Patients received carfilzomib by intravenous (IV) bolus over 2-10 minutes at 20 mg/m<sup>2</sup> on days 1, 2, 8, 9, 15 and 16 of the 28 days of Cycle 1, and by a 2-10 minute IV bolus at 27 mg/m<sup>2</sup> on days 1, 2, 8, 9, 15 and 16 of the 28 days of Cycle 2 and following cycles for up to 12 cycles. The primary endpoint was best ORR as determined by an Independent Response Review Committee (IRC).

Due to the observation of fever, chills, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness and angina during or shortly after the infusion of carfilzomib in early studies in some patients, the Applicant modified the protocol to require that dexamethasone (4 mg orally or intravenously) be administered prior to each carfilzomib administration in Cycles 1 and 2, and thereafter, at the discretion of the investigator in order to reduce the intensity of infusion related reactions to carfilzomib. IV or oral fluids were also given prior to and after each carfilzomib administration. These adverse events associated with carfilzomib administration have been designated as the "first dose effect" by the Applicant, even though it continues to be observed beyond the first two cycles in some patients.

## Safety Monitoring

Patients were evaluated for adverse events at the start of each cycle and prior to the administration of each dose of carfilzomib. Adverse events were scored using the NCI-CTCAE version 3.0 grading scale.

**Dose Modifications**

Hematologic Toxicities

Carfilzomib was to be withheld in the event of Grade 3 neutropenia, Grade 4 thrombocytopenia and Grade 4 lymphopenia persisting for > 14 days that was not pre-existing.

Non-Hematologic Toxicities

Carfilzomib was to be withheld for ≥ Grade 3 events until resolved to ≤ Grade 1 or return to baseline.

The eligibility criteria are contained in Table 6 (Inclusion criteria) and Table 7 (Exclusion criteria).

**Table 6. Inclusion criteria for Study PX-171-003 A1 (Study 3)**

Inclusion Criteria	
Disease Related	
1	Subjects had to have measurable disease, defined as 1 or both of the following: <ul style="list-style-type: none"> <li>• Serum M-protein ≥ 1 g/dl</li> <li>• Urine M-protein ≥ 200 mg/24 hr</li> </ul>
2	Subjects must have been responsive (ie, achieved an MR or better) to at least 1 of their prior treatment regimens
3	Refractory to the most recently received therapy. Refractory disease was defined as ≤ 25% response to, or progression during, therapy or within 60 days after completion of therapy
4	Subjects must have received ≥ 2 prior regimens for relapsed disease. Induction therapy and stem cell transplant (± maintenance) were to be considered as one regimen.
5	Subjects must have received prior treatment with bortezomib, [and] either thalidomide or lenalidomide
6	Subjects must have received an alkylating agent either alone or in combination with other myeloma treatments (history of stem cell transplant was acceptable)
7	Subjects must have received an anthracycline either alone or in combination with other myeloma treatments, unless not clinically indicated
Demographic	
8	Males and females ≥ 18 years of age
9	Life expectancy of more than 3 months
10	ECOG Performance Status of 0–2
Laboratory	
11	Adequate hepatic function, with bilirubin < 2.0 times the upper limit of normal, and AST and ALT < than 3.0 times the upper limit of normal

Inclusion Criteria	
12	Absolute neutrophil count $\geq 1,000/\text{mm}^3$ , hemoglobin $\geq 8.0$ g/dl, and platelet count $\geq 50,000/\text{mm}^3$ <ul style="list-style-type: none"> <li>• Subjects were to be platelet transfusion independent</li> <li>• Screening ANC was to be independent of G-CSF or GM-CSF support for <math>\geq 1</math> week and pegylated G-CSF for <math>\geq 2</math> weeks</li> <li>• Subjects could receive red blood cell (RBC) or platelet transfusions or receive supportive care such as erythropoietin and darbepoetin in accordance with institutional guidelines</li> </ul>
13	Calculated or measured creatinine clearance (CrCl) of $\geq 30$ mL/min.
	Ethical / Other
14	Written informed consent
15	Use adequate contraception and not be pregnant

Abbreviations: dl = deciliter; hr = hour;

**Table 7. Exclusion criteria for Study 3**

Exclusion Criteria	
Disease Related	
1	Multiple Myeloma IgM
2	Subjects who failed to achieve at least a confirmed MR ( $\geq 25\%$ reduction in M-protein for $\geq 6$ weeks) on any of their prior treatment regimens
3	Subjects with non-secretory multiple myeloma, defined as $< 1$ g/dL M-protein in serum and $< 200$ mg/24 hr M-protein in urine
4	Subjects with disease measurable only by serum free light chain (SFLC) analysis
5	Glucocorticoid therapy (prednisone $> 10$ mg/day or equivalent) within the last three weeks
6	POEMS syndrome
7	Plasma cell leukemia
8	Chemotherapy with approved or investigative anticancer therapeutics including steroid therapy within the 3 weeks prior to first dose
9	Radiation therapy or immunotherapy in the previous four weeks; localized radiation therapy within 1 week prior to first dose
10	Participation in an investigational therapeutic study within 3 weeks or within 5 drug half-lives ( $t_{1/2}$ ) prior to first dose, whichever time was greater
11	Prior treatment with carfilzomib
Concurrent Conditions	
12	Major surgery within three weeks before Day 1
13	Congestive heart failure (New York Heart Association class III to IV), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, or myocardial infarction in the previous 6 months
14	Acute active infection requiring systemic antibiotics, antivirals, or antifungals within 2 weeks prior to first dose

Exclusion Criteria	
15	Known or suspected HIV infection or subjects who were HIV seropositive
16	Active hepatitis A, B, or C infection
17	Non-hematologic malignancy within the past 3 years except a) adequately treated basal cell or squamous cell skin cancer, b) carcinoma in situ of the cervix, or c) prostate cancer < Gleason Grade 6 with stable PSA
18	Subjects with treatment-related myelodysplastic syndrome
19	Significant neuropathy (Grade 3, 4, or Grade 2 with pain) at the time of study initiation
20	Subjects in whom the required program of oral and IV fluid hydration was contraindicated
21	Subjects with known or suspected amyloidosis
22	Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis
23	Any clinically significant medical disease or condition that, in the Investigator's opinion, may have interfered with protocol adherence or a subject's ability to give informed consent
	Ethical / Other
24	Female subjects who were pregnant or lactating
25	Use adequate contraception and not be pregnant
26	Serious psychiatric or medical conditions that could have interfered with treatment

Abbreviations: PSA = prostate specific antigen.

### Statistical Analysis Plan

Summary statistics were to be provided for the primary and secondary efficacy endpoints and for safety endpoints. For continuous variables, descriptive statistics were calculated. For discrete data, the frequency and percent distribution were presented. The primary analysis of efficacy was determined by the IRC.

#### 6.1.2 Demographics

The demographic characteristics of the study subjects in Study 3 are summarized in Table 8.

**Table 8. Demographic characteristics of patients in Study PX-171-003-A1**

	Total Patients N = 266	
	n	(%)
<b>Age (years)</b>		
Mean (SD)	62.9 (9.69)	
Median	63.0	
Range	37, 87	
	n	(%)
<b>Age group (years)</b>		
<65	146	(54.9)
≥65	120	(45.1)
<b>Gender</b>		
Female	111	(41.7)
Male	155	(58.3)
<b>Ethnicity</b>		
Caucasian	190	(71.4)
African American	53	(19.9)
Hispanic	10	( 3.8)
Asian/Pacific Islander	6	( 2.3)
Other	7	( 2.6)
<b>ECOG performance status</b>		
0	69	(25.9)
1	162	(60.9)
2	35	(13.2)

Source: Table 14.1.4 Clinical Study Report: PX-171-003 – Part 2 (A1)

### 6.1.3 Subject Disposition

A total of 266 patients from 30 clinical sites in North America (31 sites screened for patients but 1 site did not enroll any patients) were enrolled from July 2008 to October 2009. Median and mean enrollment per site was 8.8 and 7 patients, respectively (range: 1 to 33 patients). All 266 enrolled patients received at least 1 carfilzomib dose, and the median duration of carfilzomib treatment was 3 months (range: 1 day to 16.9 months). One hundred sixty-nine patients (63.5%) completed the minimum 2 cycles specified in the protocol (Table 9). Forty-two patients (15.8%) completed the maximum 12 cycles of treatment specified in the protocol and 7 patients continued in Study 3 past 12 cycles although none remained on Study 3 at the time of the data cutoff.

**Table 9. Disposition of patients**

	<b>Total Patients N = 266 n (%)</b>
<b>Enrolled</b>	266 (100.0)
<b>Treated</b>	266 (100.0)
<b>Completed 12 cycles</b>	50 ( 15.0)
<b>Number starting cycle:</b>	
1	266 (100.0)
2	215 ( 80.8)
3	169 ( 63.5)
4	146 ( 54.9)
5	120 ( 45.1)
6	97 ( 36.5)
7	83 ( 31.2)
8	73 ( 27.4)
9	65 ( 24.4)
10	58 ( 21.8)
11	50 ( 18.8)
12	42 ( 15.8)
≥13	≥ 13 7 ( 2.6)
<b>Duration of treatment</b>	<b>Days</b>
Mean (SD)	134.3 (121.62)
Median	91.5
Range	1, 514

Source: Table 14.1.1 and Table 14.1.9 Clinical Study Report: PX-171-003 – Part 2 (A1)

Patients who discontinued the study are summarized in Table 10. This includes the number of patients who discontinued study drug for various reasons both before starting cycles 3 (before completing the minimum 2 cycles specified by the protocol) and the maximum 12 cycles specified by protocol.

**Table 10. Reasons for patient discontinuation**

	<b>Prior to Cycle 3 n (%)</b>	<b>Prior to Cycle 12 n (%)</b>
<b>Discontinued study drug</b>	97 ( 36.5)	226 (85.0)
<b>Reason for study drug discontinuation</b>		
Progressive Disease	61 ( 22.9)	157 (59.0)
Adverse event	19 ( 7.1)	33 (12.4)
Withdrew consent	10 ( 3.8)	22 ( 8.3)

	Prior to Cycle 3		Prior to Cycle 12	
	n	(%)	n	(%)
Other (1 death, 5 could not tolerate side effects)	7	( 2.6)	14	( 5.3)

Source: Table 14.1.1 and Table 14.1.9 Clinical Study Report: PX-171-003 – Part 2 (A1)

#### 6.1.4 Analysis of Primary Endpoint

The primary endpoint for this trial was Overall Response Rate (ORR) as assessed by an Independent Review Committee (IRC). ORR was defined as stringent Complete Response (sCR), Complete Response (CR), Very Good Partial Response (VGPR), or Partial Response (PR) according to the International Uniform Response Criteria for Multiple Myeloma assessment criteria.

Response status was assessed on Day 15 of Cycle 1, and Day 1 of Cycles 2-12 using the following tests: serum M-protein, urine M-protein, serum and urine M-protein by SPEP and UPEP, and Serum Free Light Chains (SFLC).

In order to confirm response, the following steps were taken: two consecutive assessments of ORR were made, evaluation of any plasmacytomas present at baseline, and a bone survey for new bony lesions. In addition to the above, to confirm a CR or sCR, the following were required: serum and urine immunofixation showing absence of the M protein, bone marrow biopsy showing < 5% plasma cells, disappearance of any soft tissue plasmacytomas, and an unscheduled SFLC draw.

#### Primary Efficacy Analysis by Applicant

The primary efficacy endpoint was ORR as determined by an IRC which required confirmation on at least 2 consecutive evaluations. As shown in Table 11, the Applicant stated that the ORR was 22.9% when computed on the basis of all treated patients (N=266). All responses were confirmed (by Applicant and FDA).

**Table 11. Applicant's Efficacy Analysis for the Primary Endpoint (ORR)**

Study Population	n/N	%
ORR in ITT* Population	61/266	22.9%

\*ITT=intent to treat population

In the response sub-categories, 1 patient had achieved a CR, 13 patients experienced a VGPR, and 47 patients experienced a PR (Table 12). Patient 3-08-090, was assessed by the IRC as having achieved a CR although both the Investigator and Sponsor "derived" programmatic assessment determined the patient as having achieved a VGPR.

**Table 12. Response categories (IRC determination)**

Response Category	Responders N=266	
	n	(%)
SCR	0	( 0)
CR	1	(<1)
VGPR	13	( 5)
PR	47	(18)
Overall response	61	(23)
95% CI	(8.7, 29.4)	

**Primary Efficacy Analysis by FDA**

Accelerated approval applies to certain new drug products that have been studied for their safety and effectiveness and treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments [e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy (CFR 314.500)].

For this reason, it is important to analyze the prior treatment history of each patient entered onto the primary efficacy Phase 2 study (Study 3), and to determine whether each patient had been documented to be unresponsive to or intolerant of each of the drugs which have been approved by the FDA as therapy for multiple myeloma. The prior exposure of the 266 patients entered onto Study 3 to each of the approved agents for multiple myeloma is shown in Table 13. Of the 266 patients enrolled in the study, 35.7% never received anthracyclines, 34.2% never received cyclophosphamide, 15.4% never received melphalan, and only 1.9% of patients were exposed to carmustine.

**Table 13. Prior Exposure to Approved Agents of Patients Entered onto Study 3**

FDA Approved Product	Exposed Patients N= 66	
	n	(%)
Bortezomib	265	(99.6)
Lenalidomide	249	(93.6)
Thalidomide	199	(74.8)
Anthracycline (any)	171	(64.3)
Cyclophosphamide	175	(65.8)
Melphalan	225	(84.6)
Carmustine	5	( 1.9)

The number of patients entered on the study who had been documented to be unresponsive or intolerant of each of the FDA approved agents is shown in Table 14. Although 86.8% of patients were documented to be unresponsive or intolerant to both bortezomib and lenalidomide, only 56% were documented to be unresponsive or

intolerant to thalidomide, and only a minority of patients had been shown to be unresponsive or intolerant to anthracyclines (36.8%), cyclophosphamide (34.6%), or melphalan (28.9%).

**Table 14. Patients Documented to be Unresponsive /Intolerant to Approved Therapies\***

FDA Approved Product	Exposed Patients N= 66	
	n	(%)
Bortezomib	231	(86.8)
Lenalidomide	231	(86.8)
Thalidomide	148	(56.0)
Anthracycline (any)	98	(36.8)
Cyclophosphamide	92	(34.6)
Melphalan	77	(28.9)
Carmustine	1	(<1 )

\*FDA Analysis of Applicant's Data Sets

As shown in Table 15, the FDA analyzed the ORR among patients documented to be unresponsive or intolerant to bortezomib alone (Group 1), documented to be unresponsive or intolerant to bortezomib and lenalidomide (Group 2), documented to be unresponsive or intolerant to bortezomib, lenalidomide and anthracyclines (Group 3), or documented to be unresponsive or intolerant to bortezomib, lenalidomide, anthracyclines and either melphalan or cyclophosphamide or with a history of hematopoietic stem cell transplant (Group 4). The ORR in these groups was found to be: 20.9%, 20.2%, 22.1%, and 23.2% respectively.

**Table 15. FDA Analysis of Patients Unresponsive to Approved Agents (Based on N=266 Patients)**

Patient Population	n/N	(%)	(95% CI)
Intent to Treat Population	61/266	(22.9)	(18%, 28.5)
Group 1 Unresponsive or Intolerant to: • Bortezomib	48/231	(20.9)	(15.7%, 26.6%)
Group 2 Unresponsive or Intolerant to: • Bortezomib • Lenalidomide	42/208	(20.2)	(15.0%, 26.3%)
Group 3 Unresponsive or Intolerant to: • Bortezomib • Lenalidomide • Anthracycline	17/77	(22.1)	(13.4%, 33.0%)
Group 4 Unresponsive or Intolerant to:	16/69	(23.2)	(13.9%, 34.9%)

Patient Population	n/N	(%)	(95% CI)
<ul style="list-style-type: none"> <li>• Bortezomib</li> <li>• Lenalidomide</li> <li>• Anthracycline</li> <li>• Melphalan, Cyclophosphamide, or history of transplant</li> </ul>			

The Applicant's analysis was compared to the FDA subgroup analysis in Table 16. The patient who obtained a CR by the Applicant's analysis was not documented to be unresponsive or intolerant to bortezomib, any anthracycline, melphalan, cyclophosphamide, or carmustine. This patient did have documentation of a transplant, so the patient was exposed to and unresponsive to an alkylating agent. The only approved agent that this patient was documented to be unresponsive or intolerant to was lenalidomide. As shown by the results of the FDA analysis in Table 16, the total number of responders to carfilzomib can be as low as 16 patients depending on the subgroup.

**Table 16. FDA Analysis of Responders**

Response	Applicant Result	FDA Results			
		Group 1 Unresponsive or Intolerant to: • Bortezomib	Group 2 Unresponsive or Intolerant to: • Bortezomib • Lenalidomide	Group 3 Unresponsive or Intolerant to: • Bortezomib • Lenalidomide • Anthracycline	Group 4 Unresponsive or Intolerant to: • Bortezomib • Lenalidomide • Anthracycline • Melphalan, Cyclophosphamide, or history of transplant
CR	1	0	0	0	0
VGPR	13	10	8	3	3
PR	47	38	34	14	13
Total	61	48	42	17	16
ORR (%)	22.9%	20.9%	20.2%	22.1%	23.2%

### 6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoints included: Duration of response (DOR) per IRC, progression-free survival (PFS), time to progression (TTP), overall survival (OS), clinical benefit (sCR, CR, VGPR, PR, and MR), and safety.

#### Duration of Response (DOR)

The DOR was defined by the Applicant as the time interval between the date of the first evaluation at which a response (sCR, CR, VGPR, or PR) was established, and the date of the evaluation at which progression was established. The Applicant carried out an

analysis of DOR based on this definition and concluded that the median DOR was 7.8 months. FDA analysis of DOR using this definition and the responders defined by the Applicant (61/266) was identical (Table 17).

**Table 17. FDA Analysis of Duration of Response Using Applicant's Definition**

Responders N=61	Median DOR (months)	95% CI (months)
All Responders	7.8	6.5, 9.7

The FDA re-analyzed the data submitted by the Applicant to establish the duration of response as defined by the time interval between the date of the first evaluation on which the response was established, and the date of the last evaluation on which the response persisted, prior to the evaluation on which evidence of progression occurred. The result of these analyses, presented in Table 18, leads to the estimate of a median duration of response of 6.5 months.

**Table 18. Duration of Response Using FDA Definition**

Responders N=61	Median DOR (months)	95% CI (months)
All Responders	6.5	4.6, 8.3

FDA analyzed the duration of response for the various groups of responders based on documented unresponsiveness or intolerance to prior therapies (Table 15) using both the Applicant's method of calculating DOR and the alternate method used by FDA. The results using the Applicant's definition of DOR (see Table 19) ranged from 7.8-8.3 months and the results using the FDA definition of DOR (see Table 20) ranged from 6.5-7.4 months).

**Table 19. FDA Analysis of Applicant's Duration of Response for Patients Unresponsive to Approved Agents**

Responder Group	Median DOR (months)	95% CI (months)
<b>Group 1</b> Unresponsive or Intolerant to: • Bortezomib	7.8	(5.6, 9.2)
<b>Group 2</b> Unresponsive or Intolerant to: • Bortezomib • Lenalidomide	7.4	(5.6, 8.4)
<b>Group 3</b> Unresponsive or Intolerant to: • Bortezomib • Lenalidomide • Anthracycline	8.3	(6.5, 9.2)
<b>Group 4</b> Unresponsive or Intolerant to: • Bortezomib	8.3	(6.7, 9.2)

Responder Group	Median DOR (months)	95% CI (months)
<ul style="list-style-type: none"> <li>• Lenalidomide</li> <li>• Anthracycline</li> <li>• Melphalan, Cyclophosphamide, or with a history of transplant</li> </ul>		

**Table 20. FDA Analysis of FDA Duration of Response for Patients Unresponsive to Agents**

Responder Group	Median DOR (months)	95% CI (months)
<b>Group 1</b> Unresponsive or Intolerant to: <ul style="list-style-type: none"> <li>• Bortezomib</li> </ul>	6.5	(4.6, 8.3)
<b>Group 2</b> Unresponsive or Intolerant to: <ul style="list-style-type: none"> <li>• Bortezomib</li> <li>• Lenalidomide</li> </ul>	6.5	(5.6, 8.3)
<b>Group 3</b> Unresponsive or Intolerant to: <ul style="list-style-type: none"> <li>• Bortezomib</li> <li>• Lenalidomide</li> <li>• Anthracycline</li> </ul>	7.4	(5.6, 8.3)
<b>Group 4</b> Unresponsive or Intolerant to: <ul style="list-style-type: none"> <li>• Bortezomib</li> <li>• Lenalidomide</li> <li>• Anthracycline</li> <li>• Melphalan, Cyclophosphamide, or with a history of transplant</li> </ul>	7.4	(5.8, 8.3)

**Time to Event Analyses (Progression-free Survival, Time to Progression, Overall Survival)**

FDA analysis of other secondary endpoints in Study 3 is presented in Table 21 and Table 22. (For full details see Statistical Review by K. Koti). The outcome of these time to event endpoints are not reliable surrogates of benefit in a single arm trial.

**Table 21. Analysis of Time to Event Endpoints**

Secondary Endpoint	Median Months (95% CI)
Progression-free survival*	3.7 ( 2.8, 4.6)
Overall survival*	15.4 (12.5, 19.0)
Time to progression*	3.9 ( 3.0, 4.8)

\*Time to event endpoints are not interpretable in a single arm trial.

**Clinical Benefit (sCR, CR, VGPR, PR, and MR)**

The clinical benefit response is shown in Table 22. Clinical benefit response is not an accepted endpoint by the FDA.

**Table 22. Clinical Benefit Endpoint**

Secondary Endpoint	N=266		
	n	(%)	(95% CI)
Clinical Benefit Response	9	(36)	(30, 41)

#### 6.1.6 Other Endpoints

Not applicable

#### 6.1.7 Subpopulations

Subgroup analyses by geographic region are not performed as all study sites were in North America.

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The recommended dose based on the data included in this application is the 20/27 regimen (20 mg/m<sup>2</sup> in Cycle 1 and 27 mg/m<sup>2</sup> in Cycle 2 or greater given on Days 1, 2, 7, 8, 15, and 16 of a 28-day cycle).

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable

#### 6.1.10 Additional Efficacy Issues/Analyses

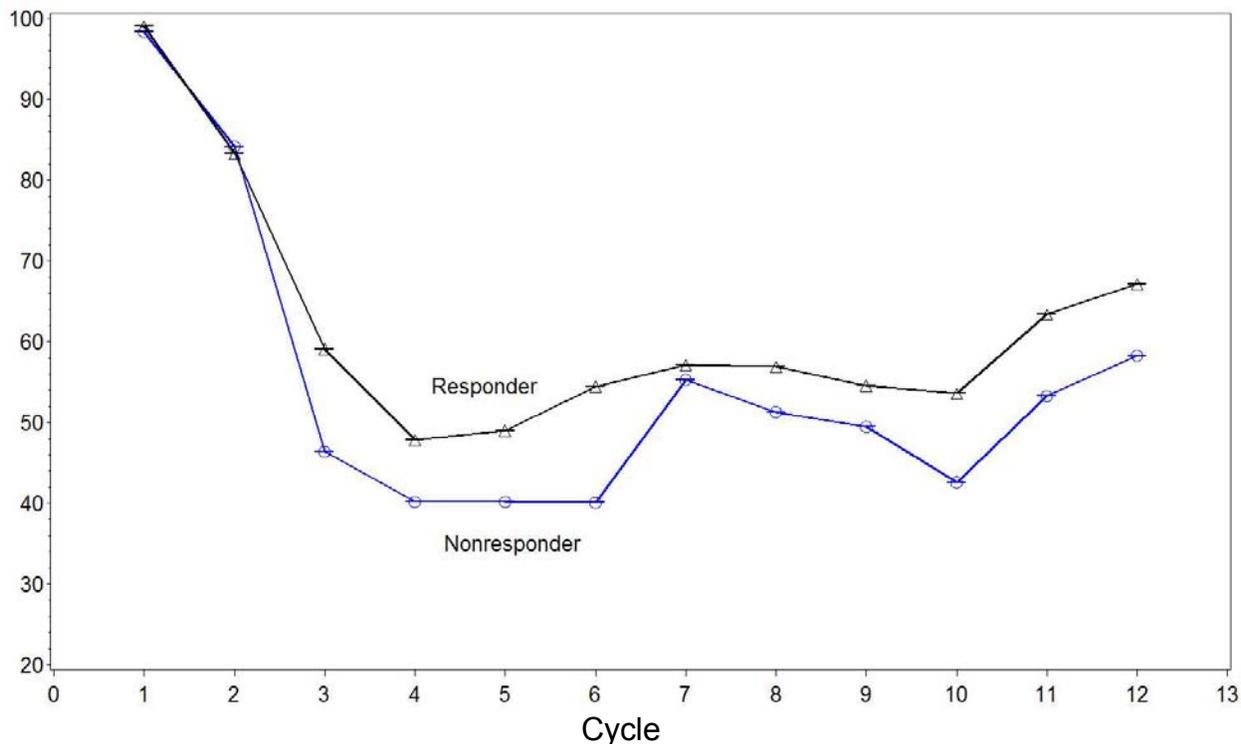
##### **Steroids**

The applicant has reported that dexamethasone was necessary in order to reduce adverse events associated with the carfilzomib infusion. Patients were required to receive dexamethasone (4 mg orally or by IV) prior to all carfilzomib doses during the first cycle and prior to all carfilzomib doses during the first dose escalation (27 mg/m<sup>2</sup>) cycle. After that, dexamethasone use was optional and was restarted in patients with continued toxicities associated with carfilzomib infusion. Dexamethasone is routinely given either alone or with other therapies to treat patients with multiple myeloma. These doses typically are 160 mg/cycle (considered low-dose dexamethasone) to 480 mg/cycle (considered high-dose dexamethasone) range. Since the maximum dose of dexamethasone a patient would receive per cycle in the carfilzomib efficacy study, Study 3, is lower (24 mg/cycle), the contribution of steroids to the responses seen with carfilzomib would appear to be minimal.

FDA examined the amount of dexamethasone given to study patients in the responder group and the non-responder group. Figure 2 shows the mean of the dexamethasone

given per dose of carfilzomib for responders and non-responders for Cycles 1 to 12 in Study 3

**Figure 2. Ratio of Dexamethasone/Carfilzomib Dose per Cycle**



(Graph generated by K. Koti)

In Study 3, since the cumulative dose/cycle is only 24 mg, the FDA does not feel that the actual treatment effect of carfilzomib reported by the Applicant is confounded by the concomitant use of dexamethasone in the pivotal study.

## 7 Review of Safety

### Safety Summary

The safety data suggests that there are a small number of patients with relapsed multiple myeloma who develop life-threatening cardiac toxicities due to carfilzomib. Although cardiac toxicity was prominent among “On Study Deaths”, severe adverse events and adverse events contributing to discontinuation of carfilzomib, the percentage of these adverse events was low. There were in addition significant respiratory, and to a lesser extent hepatic toxicities, but again, the percentages of these were low.

## 7.1 Methods

The entire safety database consists of 768 patients who were exposed to at least one dose of carfilzomib. Some (156) of the 768 patients were patients with solid tumors or hematological diseases besides multiple myeloma (20%) while the majority (612) of patients had multiple myeloma (80%). The data included in the safety data base were from multiple Phase 1 (86 patients) and Phase 2 (526 patients) trials as shown below in Table 23.

**Table 23. Clinical Trials Contained in the Integrated Summary of Safety**

Trial	Phase	Patients (All)	Patients (MM*)
PX-171-001	1	29	10
PX-171-002	1	48	28
PX-171-003 Part 1	2	46	46
PX-171-003 Part 2	2	266	266
PX-171-004 Part 1	2	35	35
PX-171-004 Part 2	2	129	129
PX-171-005	2	50	50
PX-171-006	1b	40	40
PX-171-007	1b/2	108	8
PX-171-008	1b	17	0
<b>Total</b>		<b>768</b>	<b>612</b> <b>(86 P1 + 526 P2)</b>

\*MM = multiple myeloma

For the Safety Analyses, FDA chose to focus on the population of 526 patients with multiple myeloma who were enrolled on Phase 2 studies (Studies PX-171-003 Part 1, PX-171-003 Part 2 (PX-171-003 A1, Study 3), PX-171-004 Part 1, and PX-171-004 Part 2, PX-171-005). Some analyses were performed on the 266 patients who were enrolled on Study 3, the primary efficacy study. The safety outcome for patients entered onto Phase 1 studies was not included since their introduction would have led to a wide range of drug exposures and treatment durations.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The carfilzomib exposure of the safety population used for the FDA review is shown in Table 24. Distribution of Doses of Carfilzomib Administered to Patients with Multiple Myeloma Enrolled in Phase 2 Studies). Only 278 (53%) of the 526 patients with multiple myeloma enrolled in Phase 2 trials received the dose and schedule used in the primary efficacy study (20 mg/mg/m<sup>2</sup> for the first cycle and 27 mg/m<sup>2</sup> for succeeding cycles),

Importantly, 198 (38%) patients received carfilzomib at the 20 mg/m<sup>2</sup> dose only, and 50 (10%) patients were exposed to carfilzomib at the 15/20/27 mg/m<sup>2</sup> dosing regimen. A tabulation of exposure to carfilzomib (as measured by weeks of treatment) is presented in Table 25.

**Table 24. Distribution of Doses of Carfilzomib Administered to Patients with Multiple Myeloma Enrolled in Phase 2 Studies**

Dose (mg/m <sup>2</sup> )	Patients N = 526	
	n	(%)
20/27	278	(53)
20	198	(38)
15/20/27	50	(10)

**Table 25. Exposure to Carfilzomib as Measured by Weeks of Treatment**

	Weeks of treatment
Mean (SD)	21.2 (17.8)
Median	15.1
Min, Max	0, 90

The demographical features of the 526 patients with multiple myeloma entered in Phase 2 trials are presented in Table 26. The median age of the patients with multiple myeloma enrolled in Phase 2 studies was 64 years. Eighty-eight percent of the patients had an ECOG PS of 0-1.

**Table 26. Demographics of Patients with Multiple Myeloma Enrolled in Phase 2 Studies**

	Patients N = 526	
	n	(%)
Age (years)	Mean	63
	Median	64
	Range	37, 87
Age group (years)	<65	279 (53)
	≥65	247 (47)
Gender	Female	224 (43)
	Male	302 (57)
Race	African American	97 (18)
	Asian/Pacific Islander	19 (4)
	Caucasian	381 (72)
	Hispanic	18 (3)
	Other	11 (2)

	Patients	N = 526	
		n	(%)
ECOG PS	0	156	(30)
	1	301	(58)
	2	61	(12)
	ND	2	(<1)

\*ND = Not done

### 7.3 Major Safety Results

#### 7.3.1 Deaths

On study deaths are defined as those deaths occurring during treatment with carfilzomib and within 30 days after the last dose. The on study deaths for patients with multiple myeloma entered on Phase 2 studies (N = 526), and for Study 3 (N = 266) are presented below in Table 27 and Table 28 respectively.

The most frequent type of on study death among the patients with multiple myeloma enrolled in Phase 2 studies was progression of disease. However, the most frequent type of on study death not due to progressive disease was cardiac adverse events. The Applicant identified 5 deaths attributable to cardiac adverse events. The FDA analysis of on study deaths in this population identified an additional 2 patients whose deaths were associated with cardiac adverse events. Patient 3-09-218 was listed by the Applicant as having the cause of death as *Dyspnea* and Patient 3-16-491 was listed by the Applicant as having the cause of death as *Disease Progression with Congestive Cardiac Failure* as an additional significant event. Both of these patients were listed as having Grade 5 cardiac adverse events of death by the FDA. There were an additional 3 cases where cardiac adverse events may have played a role in the death of the patients. This is discussed in greater detail in Section 7.3.5 Primary Safety Concerns.

In addition to the deaths associated with cardiac causes, there were 2 hepatic deaths (Table 27).

**Table 27. On Study Deaths for Patients with Multiple Myeloma Enrolled in Phase 2 Studies**

Events Associated with Death	Primary Cause of Death (N = 526)	
	n	(%)
Disease Progression	21*	( 4)
Cardiac (Identified by Applicant and FDA)	5	( 1)
Cardiac (Identified by FDA)	2**	(<1)
Cardiac possibly contributory to death (Identified by FDA)	3***	(<1)
Hepatic Failure	2	(<1)
Multi-Organ Failure	1	(<1)

Events Associated with Death	Primary Cause of Death (N = 526)	
	n	(%)
Hemorrhage intracranial	1	(<1)
Pneumonia	1	(<1)
Renal Failure	1	(<1)
Total	37	( 7)

\*Patient 3-16-495: Applicant listed cause of death as *Disease Progression with Cardiac Arrest* as an additional significant event, converted by FDA to *Cardiac Arrest* as primary cause of death

\*\*Patient 3-09-218: Applicant listed cause of death as *Dyspnea*, Patient 3-16-491: Applicant listed cause of death as *Disease Progression with Congestive Cardiac Failure* as an additional significant event.

\*\*\*These 3 cases are comprised of Patient 3-15-432: Applicant listed cause of death as *Sepsis* with a secondary cause of *Cardiac Arrest*, Patient 3-16-495: Applicant listed cause of death as *Disease Progression with Cardiac Arrest* as an additional significant event, Patient 3-16-778: Applicant listed cause of death as *Unknown*

As shown in Table 28, the majority of the on study deaths occurred among patients enrolled in the primary efficacy study (Study 3). Four of the five cardiac deaths identified by both the Applicant and FDA, the 2 additional cardiac deaths attributed by the FDA to primarily cardiac causes, 3 of the 4 deaths associated with cardiac adverse events, and both of the hepatic deaths occurred on Study 3.

**Table 28. On Study Deaths for Study 3**

Adverse Event Associated with Death	Primary Cause of Death (N = 526)	
	n	(%)
Disease Progression	11*	( 5)
Cardiac (Identified by Applicant and FDA)	4	( 2)
Cardiac (Identified by FDA)	2**	(<1)
Cardiac possibly contributory to death (Identified by FDA)	3***	( 1)
Hepatic Failure	2	(<1)
Hemorrhage intracranial	1	(<1)
Pneumonia	1	(<1)

Adverse Event Associated with Death	Primary Cause of Death (N = 526)	
	n	(%)
Total	24	( 9)

\*Patient 3-16-495: Applicant listed cause of death as *Disease Progression with Cardiac Arrest* as an additional significant event, converted by FDA to *Cardiac Arrest* as primary cause of death

\*\*Patient 3-09-218: Applicant listed cause of death as *Dyspnea*, Patient 3-16-491: Applicant listed cause of death as *Disease Progression with Congestive Cardiac Failure* as an additional significant event.

\*\*\*These 3 cases are comprised of Patient 3-15-432: Applicant listed cause of death as *Sepsis* with a secondary cause of *Cardiac Arrest*, Patient 3-16-495: Applicant listed cause of death as *Disease Progression with Cardiac Arrest* as an additional significant event, Patient 3-16-778: Applicant listed cause of death as *Unknown*)

The organ classes associated with on study Grade 5 adverse events are discussed in greater detail in Section 7.3.5 Primary Safety Concerns.

### 7.3.2 Serious Adverse Events

As shown in Table 23 below, pulmonary and cardiac adverse events were prominent among serious adverse events among the 526 patients with multiple myeloma enrolled in Phase 2 studies. There were 42 (8%) patients who experienced a cardiac SAE and 36 (7%) patients experienced a pulmonary toxicity. The majority of these were Grade 3 or 4 adverse events. As with the patients who discontinued carfilzomib due to toxicity, the major SAEs were congestive heart failure and cardiac arrest. Dyspnea was the most frequent pulmonary adverse event leading to discontinuation of carfilzomib and the most frequent pulmonary SAE.

**Table 29. Cardiac, Pulmonary, and Hepatic SAEs for Patients with Multiple Myeloma Enrolled in Phase 2 Studies (N = 526)**

System Organ Class Preferred Term	Grade 1 to 5		Grade 3 or 4	
	n	(%)	n	(%)
<b>Cardiac disorders</b>	<b>42</b>	<b>( 8)</b>	<b>36</b>	<b>( 7)</b>
Cardiac failure congestive	18	( 3)	17	( 3)
Cardiac arrest	5	( 1)	2	(<1)
Atrial fibrillation	4	(<1)	4	(<1)
Myocardial ischemia	3	(<1)	2	(<1)
Atrial flutter	2	(<1)	1	(<1)
Cardiac failure	2	(<1)	2	(<1)
Ventricular dysfunction	2	(<1)	2	(<1)
Acute coronary syndrome	1	(<1)	1	(<1)
Acute myocardial infarction	1	(<1)	1	(<1)
Aortic valve stenosis	1	(<1)	1	(<1)

System Organ Class Preferred Term	Grade 1 to 5		Grade 3 or 4	
	n	(%)	n	(%)
Arrhythmia	1	(<1)	1	(<1)
Cardiac disorder	1	(<1)	0	( 0)
Cardiomyopathy	1	(<1)	1	(<1)
Congestive cardiomyopathy	1	(<1)	1	(<1)
Mitral valve incompetence	1	(<1)	1	(<1)
Right ventricular failure	1	(<1)	1	(<1)
Supraventricular tachycardia	1	(<1)	1	(<1)
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>36</b>	<b>( 7)</b>	<b>21</b>	<b>( 4)</b>
	12	( 2)	10	( 2)
Dyspnea	6	( 1)	5	( 1)
Pulmonary embolism	5	( 1)	4	(<1)
Pulmonary edema	4	(<1)	3	(<1)
Pleural effusion	3	(<1)	3	(<1)
Respiratory failure	2	(<1)	1	(<1)
Hemoptysis	2	(<1)	2	(<1)
Hypoxia	1	(<1)	1	(<1)
Acute pulmonary edema	1	(<1)	1	(<1)
Acute respiratory failure	1	(<1)	0	( 0)
Chronic obstructive pulmonary disease	1	(<1)	0	( 0)
Cough	1	(<1)	1	(<1)
Pneumonia aspiration	1	(<1)	1	(<1)
Pneumonitis	1	(<1)	1	(<1)
Pulmonary alveolar hemorrhage	1	(<1)	1	(<1)
Pulmonary hypertension	1	(<1)	1	(<1)
Respiratory alkalosis	1	(<1)	1	(<1)
<b>Hepatobiliary disorders</b>	<b>3</b>	<b>(&lt;1)</b>	<b>1</b>	<b>(&lt;1)</b>
Hepatic failure	2	(<1)	0	( 0)
Venoocclusive liver disease	1	(<1)	1	(<1)

The patients in Study 3 also experienced cardiac and pulmonary SAEs at similar rates in Study 3 (Table 30), the primary efficacy study as in the larger population of 526 patients with multiple myeloma enrolled in Phase 2 studies.

**Table 30. Cardiac and Respiratory SAEs for Patients with Multiple Myeloma Enrolled in Study 3\***

Organ Class	N = 266	
	n	(%)
Infections and infestations	39	(15)
General disorders and administration site conditions	29	(11)
Cardiac disorders	21	( 8)
Respiratory, thoracic and mediastinal disorders	21	( 8)

Organ Class	N = 266	
	n	(%)
Renal and urinary disorders	15	( 6)
Nervous system disorders	14	( 5)
Metabolism and nutrition disorders	13	( 5)
Musculoskeletal and connective tissue disorders	12	( 5)
Blood and lymphatic system disorders	10	( 4)
Investigations	8	( 3)
Vascular disorders	7	( 3)
Gastrointestinal disorders	6	( 2)
Psychiatric disorders	4	( 2)
Hepatobiliary disorders	2	( 1)
Neoplasms benign, malignant and unspecified	2	( 1)
Endocrine disorders	1	(<1)
Eye disorders	1	(<1)
Immune system disorders	1	(<1)
Injury, poisoning and procedural complications	1	(<1)

\*Patients may be counted in more than 1 organ class.

### 7.3.3 Dropouts and/or Discontinuations

The major reasons for study drug discontinuation for the patients with multiple myeloma enrolled in Phase 2 studies are shown by Organ Class (Table 31) and by Preferred Term (Table 32). In Table 31, the most common class for discontinuations was General Disorders which includes the preferred term for Disease Progression. The two organ class categories that had the most adverse events leading to discontinuation of carfilzomib were Cardiac Disorders 30/526 (6%) and Respiratory Disorders 22/526 (4%).

**Table 31. Discontinuations in Patients with Multiple Myeloma in Phase 2 Studies due to an Adverse Event (Shown in Decreasing Order by Organ Class)**

Organ Class	N =526*	
	n	(%)
General disorders and administration site conditions	42	( 8)
Cardiac disorders	30	( 6)
Respiratory, thoracic and mediastinal disorders	22	( 4)
Infections and infestations	20	( 4)
Nervous system disorders	17	( 3)
Renal and urinary disorders	14	( 3)
Metabolism and nutrition disorders	12	( 2)

Organ Class	N =526*	
	n	(%)
Musculoskeletal and connective tissue disorders	11	( 2)
Blood and lymphatic system disorders	10	( 2)
Investigations	10	( 2)
Psychiatric disorders	7	( 1)
Gastrointestinal disorders	6	( 1)
Skin and subcutaneous tissue disorders	6	( 1)
Hepatobiliary disorders	3	(<1)
Neoplasms benign, malignant and unspecified	3	(<1)
Vascular disorders	3	(<1)
Endocrine disorders	1	(<1)
Eye disorders	1	(<1)
Immune system disorders	1	(<1)
Reproductive system and breast disorders	1	(<1)

\*Patients may be counted in more than 1 organ class

Table 32 lists the most common adverse events leading to discontinuation of carfilzomib. Aside from adverse events due to disease progression, the major adverse events leading to discontinuations of carfilzomib in these categories were dyspnea, pneumonia, congestive heart failure. There were additional patients who discontinued carfilzomib due to a cardiac arrest.

**Table 32. Discontinuations\* in Patients with Multiple Myeloma Enrolled in Phase 2 Studies due to an Adverse Event (Shown in Decreasing Order by Preferred Term, ≥ 1% of Patients)**

Preferred Term	N = 526**	
	n	(%)
Dyspnea	10	(2)
Pneumonia	10	(2)
Cardiac failure congestive	9	(2)
Renal failure acute	9	(2)
Blood creatinine increased	7	(1)
Pyrexia	6	(1)
Cardiac arrest	5	(1)
Thrombocytopenia	5	(1)

\*Excluding terms attributed to progressive multiple myeloma disease (disease progression, hypercalcemia, spinal cord compression)

\*\*Patients may be counted in more than 1 term.

#### 7.3.4 Adverse Events

The frequency of adverse events among the patients with multiple myeloma entered on Phase 2 trials (N=526) is summarized by organ class in Table 33. Seventy percent of

patients experienced a respiratory adverse event. Twenty-three percent of these patients experienced an adverse event associated with cardiac disorders. Among the adverse events, dyspnea occurred in 35% of patients. Significant adverse events are discussed in greater detail in Section 7.3.5 on Specific Primary Safety Concerns.

**Table 33. AEs by Organ Class for 526 Patients with Multiple Myeloma Enrolled in Phase 2 Studies**

System Organ Class	All Grades N=526	
	n	(%)
General disorders and administration site conditions	450	(86)
Gastrointestinal disorders	407	(77)
Blood and lymphatic system disorders	373	(71)
Respiratory, thoracic and mediastinal disorders	370	(70)
Metabolism and nutrition disorders	356	(68)
Musculoskeletal and connective tissue disorders	352	(67)
Investigations	343	(65)
Nervous system disorders	332	(63)
Infections and infestations	332	(63)
Skin and subcutaneous tissue disorders	188	(36)
Psychiatric disorders	179	(34)
Vascular disorders	150	(29)
Cardiac disorders	123	(23)
Renal and urinary disorders	120	(23)
Eye disorders	79	(15)
Injury, poisoning and procedural complications	65	(12)
Reproductive system and breast disorders	33	( 6)
Neoplasms benign, malignant and unspecified	28	( 5)
Ear and labyrinth disorders	24	( 5)
Surgical and medical procedures	17	( 3)
Hepatobiliary disorders	16	( 3)
Immune system disorders	14	( 3)
Endocrine disorders	8	( 2)

### 7.3.5 Submission Specific Primary Safety Concerns

Small single arm studies cannot be used to distinguish whether adverse events were due to the effect of the test drug as opposed to adverse events due to patient factors or to disease related factors. Distinguishing the drug effect from the disease or patient factors is best done through the analysis of data from well designed randomized controlled trials where the drug effect can be isolated. In general, the cause of adverse events from single arm trials where the drug effect is unknown must be assigned to the experimental therapy. Among the safety population of patients with multiple myeloma

enrolled in Phase 2 studies, there are several organ systems in which a higher incidence of adverse events has occurred than would be expected in this population of patients with multiple myeloma including cardiac, pulmonary, and hepatic adverse events, which must be assigned to carfilzomib. In addition to significant life threatening adverse events associated with the heart, lung and liver, a separate and distinct set of adverse events were associated with the infusion of carfilzomib.

### Cardiac Adverse Events

A great variety of cardiac adverse events were reported in Phase 2 studies as shown in Table 34. Cardiac on study deaths occurred in a number that was higher than other organ specific on study deaths (see Table 27 and Table 28). The individual adverse events for the 5 patients whose on study deaths were associated with cardiac adverse events were: acute coronary syndrome (1), cardiac arrest (3), and cardiac disorder (1). In addition, one patient (3-09-218) who had dyspnea listed as the cause of death by the Applicant, may have died from complications of congestive heart failure. Another patient (3-16-491) who was listed by the Applicant as having died primarily of disease progression may have died of congestive heart failure.

The timing of the on study cardiac deaths in relationship to carfilzomib dosing of these 7 patients identified by the FDA as on study cardiac deaths is summarized below in Table 34. Most of these patients died in Cycle 1 or Cycle 2 and three of these patients died within 2 days of the last dose, indicating a direct toxic effect of carfilzomib on the heart in these patients. Patient 3-15-441 had a cardiac arrest within hours of the last dose. There are an additional 3 patients for which cardiac events may have been the cause of death. Patient 3-15-432 had two cardiac arrests in the setting of sepsis, 3 days after the last dose of carfilzomib. Patient 3-16-495 had a cardiac arrest 3 days after the last dose of carfilzomib, and Patient 3-16-778 was found dead at home 6 days after the last dose of carfilzomib.

Nine of these ten patients with on-study deaths that were associated with cardiac adverse events had a history of coronary artery disease or cardiac risk factors (Table 34).

**Table 34. Summary of Cardiac Deaths**

Patient ID	Age (years)	Cardiac History	Death Occurred			Cardiac Syndrome, CHF or Arrest
			Cycle	Days After Last Dose	Total Doses	
3-08-086	50	CAD/CABG DM ↑lipids	1	18	4	Acute Coronary Syndrome
3-09-218*	65	HTN	2	22	12	CHF

Patient ID	Age (years)	Cardiac History	Death Occurred			Cardiac Syndrome, CHF or Arrest
			Cycle	Days After Last Dose	Total Doses	
3-09-220	83	CAD ↑lipids	1	3	2	Arrest
3-11-255	66	HTN	4	1	21	Arrest
3-15-441	53	DM ↑lipids	1	<1**	4	Arrest
3-16-491*	72	HTN	1	8	2	CHF
4-06-156	52	↑lipids	1	2	2	Arrest

\*Attribution of primary cause of death as cardiac made by FDA

\*\*Death occurred within hours of the last dose.

CAD = Coronary artery disease, CABG = Coronary bypass graft, CHF = Congestive heart failure, DM = Diabetes Mellitus, HTN = hypertension, ↑lipids = hyperlipidemia

Carfilzomib was discontinued for cardiac disorders in 5.7% of the 526 patients with multiple myeloma enrolled in Phase 2 studies (Table 31). Among these were discontinuations for congestive heart failure in 9 patients and cardiac arrest in 5 patients (Table 32). In terms of SAEs (Table 30), 42 patients experienced cardiac related SAEs. Among these, 18 patients had a SAE associated with congestive heart failure (preferred terms: cardiac failure congestive and congestive cardiomyopathy), and 5 patients experienced cardiac arrest.

Nearly a quarter of the 526 patients experienced one or more cardiac adverse events as shown Table 33. These adverse events included thirty-seven that were Grade 3 and 10 that were Grade 4 or 5. The most frequently reported cardiac adverse events from Study 3 are summarized in Table 35.

**Table 35. Cardiac Adverse Events from Patients in Study 3**

Preferred Term	All grades N = 266		Grade 3 or greater N = 266	
	n	(%)	n	(%)
Dyspnea	90	(34)	9	( 3)
Hypertension	39	(15)	21	( 8)
Hypotension	21	( 8)	6	( 2)
Cardiac failure congestive	10	( 4)	9	( 3)
Cardiac arrest	4	( 2)	4	( 2)
Atrial fibrillation	5	( 2)	2	(<1)
Deep vein thrombosis	5	( 2)	3	( 1)
Pulmonary edema	5	( 2)	3	( 1)

Preferred Term	All grades N = 266		Grade 3 or greater N = 266	
	n	(%)	n	(%)
Sinus tachycardia	4	( 2)	0	(<1)
Myocardial ischemia	3	( 1)	2	(<1)

### Respiratory Adverse Events

Over 70% of patients enrolled in Phase 2 studies reported adverse events associated with the respiratory system (Table 33). Twenty-two patients discontinued carfilzomib because of a respiratory adverse event (Table 31). Dyspnea and pneumonia were the most frequent pulmonary adverse events leading to carfilzomib discontinuations (see Table 32). There were 36 pulmonary SAEs (Table 29). Reversible SAEs involving the lung were reported in 8 patients, which required hospitalization in 2 patients for stabilization. Two of these events were associated with the clinical diagnosis of pulmonary hypertension (one of which was also associated with veno-occlusive disease and the other with congestive heart failure). Of these 10 patients, carfilzomib was interrupted in 3, the dose was reduced in 1 and carfilzomib was discontinued permanently in 2.

Dyspnea was a common (35%) adverse event in the 526 multiple myeloma patients entered onto Phase 2 trials. The median duration of these events was 8 days. While most of these events were Grade 1 and 2 in severity, 5% were Grade 3 or 4. It is not clear whether dyspnea was associated with pulmonary, cardiac, or infusion reaction associated adverse events because the studies were single arm trials.

Cardiac and pulmonary adverse events were also reported in the pre-clinical toxicity studies of carfilzomib carried out by the Applicant. The pathogenesis of these cardiac and pulmonary events is unknown. Monkeys administered a single bolus intravenous dose of carfilzomib at 3 mg/kg (approximately 1.3 times recommended dose in humans of 27 mg/m<sup>2</sup> based on body surface area) experienced hypotension, increased heart rate, and increased serum levels of troponin-T. (Note that the bolus infusion may have been administered in a shorter time (20 seconds) than was the case in the bolus infusion in human subjects, which was 2-10 minutes). The studies of repeated intravenous bolus administrations of carfilzomib at ≥ 2 mg/kg/dose in rats and 2 mg/kg/dose in monkeys using dosing schedules similar to those used clinically resulted in mortalities that were due to toxicities occurring in the cardiovascular and pulmonary systems. Following repeated bolus intravenous administration in monkeys at ≥ 1 mg/kg/dose, cardiovascular toxicities included myocardial degeneration, myocyte hypertrophy and inflammation. The C<sub>max</sub> and significant toxicities in rats, including death, pre-renal azotemia (elevated blood urea nitrogen and creatinine), lethargy, dyspnea, observed following a single bolus injection of 8 mg/kg carfilzomib were reduced when the same dose was administered as a 30-minute infusion, while a similar level of proteasome inhibition was maintained.

### Hepatic Adverse Events

The distribution of deaths, SAEs and adverse events in patients with multiple myeloma associated with hepatic adverse events is presented in Table 36. Among the 526 patients with multiple myeloma who were entered in Phase 2 trials, and among the 266 patients on Study 3, there were two on-study deaths associated with hepatic failure (Table 27, Table 28, Table 36). Both of these individuals (Patient 3-06-059, Patient 3-34-811) had normal liver function tests before being treated with carfilzomib. There were three other life threatening cases of hepatic failure (Patient 3-08-091, Patient 3-08-086, Patient 3-32-827) which in contrast to the above two cases, were reversible. One of these (Patient 3-08-091) was a 61 year old who experienced Grade 2 hepatic encephalopathy and grade 3 hepatic enzyme elevations from days 47-61 of carfilzomib therapy. One patient (Patient 5-33-069) experienced veno-occlusive disease. There were no Hy's Law cases.

**Table 36. Hepatotoxicity Among Patients with Multiple Myeloma**

Event	Safety Population N=526		Study 3 N=266	
	n	(%)	n	(%)
Deaths	2	(<1)	2	(<1)
SAEs	3	(<1)	2	(<1)
Hepatic failure (Reversible)	3	(<1)	3	( 1)
Veno-occlusive disease	1	(<1)	0	( 0)

**Table 37. Review of Potential Hy's Law Cases**

Patient ID	Hepatic AE Reported	Re-challenged	Explanation	Hy's Law Criteria Met
3-08-090	None	Yes	ALT and TB elevations 9 months apart	No
3-15-434	↑AST and TB	Yes	AST and TB day prior and after unremarkable	No
3-34-811	Hepatic failure	No	Sepsis	No
5-18-012	↑ AST	No	Sepsis	No

### Infusion Reactions Associated with Carfilzomib

During the course of carfilzomib drug development, the Applicant identified symptoms and adverse events which occur within 24 hours of each administration of carfilzomib. These adverse events include: fever, chills, rigors, pyrexia, myalgias, arthralgias, dyspnea, hypotension, hypoxia and flushing. In an attempt to reduce this toxicity, the Applicant modified the clinical protocols by adding premedication with dexamethasone along with the administration of oral and intravenous hydration. In addition, the first carfilzomib dose was always 20 mg/m<sup>2</sup> either for the first cycle or later on for the first two doses of Cycle 1. The etiology for this constellation of symptoms is unknown.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

The adverse events occurring at an incidence of 10% or greater are shown in Table 38. The most frequently occurring are fatigue and cytopenias.

**Table 38. Adverse Events Occurring In Patients with Multiple Myeloma Enrolled in Phase 2 Studies**

Preferred Term	All Grades	All Grades (%)	Grade 3 and 4	Grade 3 and 4 (%)
Fatigue	300	57.0	41	7.8
Anemia	267	50.8	128	24.3
Nausea	244	46.4	8	1.5
Thrombocytopenia	197	37.5	125	23.8
Dyspnea	186	35.4	26	4.9
Diarrhea	179	34.0	5	1.0
Pyrexia	163	31.0	9	1.7
Headache	150	28.5	7	1.3
Upper respiratory tract infection	149	28.3	17	3.2
Cough	140	26.6	1	0.2
Lymphopenia	132	25.1	100	19.0
Blood creatinine increased	132	25.1	14	2.7
Edema peripheral	131	24.9	3	0.6
Vomiting	120	22.8	6	1.1
Neutropenia	118	22.4	59	11.2
Constipation	114	21.7	1	0.2
Back pain	113	21.5	18	3.4
Insomnia	98	18.6	0	0.0
Arthralgia	90	17.1	9	1.7
Chills	84	16.0	1	0.2
Leukopenia	77	14.6	30	5.7
Hypokalemia	77	14.6	21	4.0
Muscle spasms	77	14.6	2	0.4
Hypertension	77	14.6	17	3.2
Asthenia	76	14.4	13	2.5
Hypomagnesaemia	75	14.3	2	0.4
Pain in extremity	74	14.1	7	1.3
Aspartate aminotransferase increased	72	13.7	16	3.0
Pneumonia	69	13.1	57	10.8

Preferred Term	All Grades	All Grades (%)	Grade 3 and 4	Grade 3 and 4 (%)
Hyperglycaemia	66	12.5	19	3.6
Dizziness	66	12.5	6	1.1
Hypoaesthesia	66	12.5	3	0.6
Chest wall pain	65	12.4	3	0.6
Pain	64	12.2	14	2.7
Anorexia	64	12.2	1	0.2
Hypercalcemia	62	11.8	23	4.4
Hyponatremia	59	11.2	37	7.0
Hypophosphatemia	57	10.8	28	5.3

#### 7.4.2 Laboratory Findings

The laboratory findings for hepatic adverse events were discussed above in Section 7.3.5.

#### 7.4.3 Vital Signs

Pulse, blood pressure, temperature, and weight data were reviewed, including means, medians, and shifts from baseline. Summary statistics of baseline, lowest, highest, average, and final values did not reveal any adverse trends in systolic blood pressure, diastolic blood pressure, or temperature in patients in the Phase 2 MM Studies. Patients' pulse fluctuated only slightly through Cycle 13: median change from baseline was not less than -3.0 bpm or greater than 3 bpm on Day 16 of any cycle through Cycle 13 (Applicant Summary, ISS Section 9.1.1). Patients' pulse rates fluctuated slightly more in later cycles. No specific trends in pulse rates were observed within each cycle. The median minimum postbaseline change was -13.0 bpm and the median maximum post baseline change was 21.0 bpm, while the end-of-study median change from baseline was 4.0 bpm (Applicant Summary, ISS Section 9.1.1).

#### 7.4.4 Electrocardiograms (ECGs)

Not applicable.

#### 7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

#### 7.4.6 Immunogenicity

No human immunogenicity data submitted.

## **7.5 Other Safety Explorations**

### 7.5.1 Dose Dependency for Adverse Events

Not applicable.

### 7.5.2 Time Dependency for Adverse Events

Not applicable.

### 7.5.3 Drug-Demographic Interactions

Not applicable.

### 7.5.4 Drug-Disease Interactions

Not applicable.

### 7.5.5 Drug-Drug Interactions

Not applicable.

## **7.6 Additional Safety Evaluations**

### 7.6.1 Human Carcinogenicity

No new cases of leukemias or solid tumors.

### 7.6.2 Human Reproduction and Pregnancy Data

Not applicable.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no abuse potential. The highest dose of carfilzomib, when administered as a 2-10 minute bolus infusion tested in the pivotal clinical study submitted to the NDA was 27 mg/m<sup>2</sup>. Doses up to 70 mg/m<sup>2</sup> are currently being evaluated by the Applicant, but this is using a 30 minute infusion of carfilzomib.

### **7.7 Additional Submissions / Safety Issues**

None

### **8 Postmarket Experience**

None.

## 9 Appendices

### 9.1 Literature Review/References

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## **9.2 Labeling Recommendations**

The label is under development.

## **9.3 Advisory Committee Meeting**

Pending

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/s/  
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THOMAS M HERNDON  
06/18/2012

ALBERT B DEISSEROTH  
06/19/2012





## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	adverse dropouts (and serious adverse events if requested by the Division)?				
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?		X		Orphan Drug status granted in 2008
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

<u>Thomas M. Hearden</u>	<u>2011 November 08</u>
Reviewing Medical Officer	Date
<u>Arthur Dancosky</u>	<u>2011 November 08</u>
Clinical Team Leader	Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THOMAS M HERNDON  
11/09/2011

ALBERT B DEISSEROTH  
11/09/2011