CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202714Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

NDA 202714 for Carfilzomib was submitted on 9/27/201.The sponsor is seeking FDA approval to use Carfilzomib 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.

	Information		Information
NDA/BLA Number	202714	**Brand Name**	Kyprolis
OCP Division (I, II, III, IV, V)	5	**Generic Name**	Carfilzomib
Medical Division	Oncology	**Drug Class**	Oncology
OCP Reviewer	Bahru A Habtemariam, Pharm.D	**Indication(s)**	Carfilzomib indicated 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
OCP Team Leader	Julie Bullock, Pharm.D	**Dosage Form**	solution
Pharmacometrics Reviewer	Bahru A. Habtemariam, Pharm.D.	**Dosing Regimen**	20/27 mg/m2 IV (Cycle 1/Cycle ≥ 2) over 2 to 10 minutes, twice weekly on consecutive days for 3 weeks (Days 1, 2,8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28).
Date of Submission	9/27/2011	**Route of Administration**	Intravenous
Estimated Due Date of OCP Review	May 28, 2012	**Sponsor**	Onyx
Medical Division Due Date	June 15, 2012	**Priority Classification**	Standard
PDUFA Due Date	July 27, 2012		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	9	9	The sponsor submitted a total of 9 studies. One of the studies is the pivotal phase 2 study which is intended to suppor the main indication. In addition, the sponsor has submitted results of renal, DDI, and QT studies.
Tabular Listing of All Human Studies	X	9	9	
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X	1	1	
Pharmacokinetics (e.g., Phase I) -	X	7	7	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	X	1	1	This is a very small study (n=7) of which 6 and 1 patients had Child Pugh classification classes B and C, respectively
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X	2	2	
Data sparse:	X	3	3	
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:		**2**	**2**	
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X	244	-	
Total Number of Studies	X	9	9	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		X		
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

Bahru A. Habtemariam, Pharm.D.	November 8, 2011
Reviewing Clinical Pharmacologist	Date
Julie Bullock, Pharm.D.	November 8, 2011
Team Leader/Supervisor	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BAHRU A HABTEMARIAM
06/14/2012

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	202-714
Submission Date(s):	9/27/2012: \\CDSESUB1\EVSPROD\NDA202714\0001\
Brand Name:	Kyprolis
Generic Name:	Carfilzomib
Submission Type; Code:	NME NDA; Standard review
PUDFA Date:	07/27/2012
Sponsor:	Onyx Pharmaceuticals
Relevant IND(s):	IND 71,057
Formulation; Strength(s):	Intravenous, 60 mg/vial
Proposed Indication:	Relapsed and refractory multiple myeloma
OND Division:	DHP
OCP Division:	DCP5
Primary Reviewer:	Bahru A. Habtemariam, Pharm.D.
Team Leader:	Julie M. Bullock, Pharm.D.
Pharmacometric Reviewer:	Bahru Habtemariam, Pharm.D.
Pharmacometric Team Leader:	Christine Garnett, Pharm.D.

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1 EXECUTIVE SUMMARY

Kyprolis (Carfilomib) is a second generation proteasome inhibitor being developed for the treatment of patients with refractory and relapsed multiple myeloma. The proposed dosing regimen is 20 mg/m^2 during cycle 1 and 27 mg/m^2 for cycles 2 and beyond given as a 2-10 minute intravenous infusion twice weekly on days 1, 2, 8, 9, 15 and 16 of a 28-day treatment cycle.

To support the proposed indication, the sponsor conducted a single arm trial in 266 patients using the proposed dosing regimen described above. The primary endpoint was overall response rate (ORR) which is a composite endpoint of complete response, very good partial response, and partial response. In this pivotal phase 2 trial, 22.9% of patients achieved the primary endpoint of ORR. One of the most important adverse events was liver enzyme elevation, with 6.4% of treated patients experiencing grade 3 or more ALT elevations. Exposure-response relationship was not evident for efficacy or safety.

Preclinical and clinical studies were conducted to characterize the disposition and drug-drug interaction potentials of carfilzomib. *In vitro* studies showed carfilzomib is metabolized in plasma by protein peptidase and epoxide hydrolysis. In total, these studies show the exposure to carfilzomib will not be influenced by other drugs and carfilzomib will not influence exposure to other drugs.

The ADME characteristics of carfilzomib were not conducted in humans; ADME data were available from a rat study. The rat ADME study showed 30.5% of the administered drug undergoes biliary elimination while about 26% of the administered drug is eliminated by the kidneys. A renal impairment study in cancer patients showed the Cmax and AUC of carfilzomib were similar across all renal function categories including patients with normal renal function and those with mild, moderate, and severe renal impairment, and those patients on chronic dialysis.

The proportion of the administered drug that undergoes biliary elimination has not been evaluated in humans. In addition, the occurrence of grade 3/4 ALT elevations in 6.4% of patients in the pivotal phase 2 study suggests those patients with pre-existing hepatic impairment maybe at an increased risk of liver toxicity when treated with carfilzomib. In order to characterize the influence of hepatic function on the safety and pharmacokinetics of carfilzomib, a post marketing study in patients with hepatic impairment will be requested.

1.1 Recommendation

This NDA is acceptable from a clinical pharmacology perspective provided that the applicant and the agency come to an agreement regarding the labeling language and the identified clinical studies under the post marketing requirements (PMRs).

1.2 Post Marketing Requirements

1. Conduct a clinical trial in patients with hepatic impairment. The number of patients enrolled in the study should be sufficient to detect PK differences that would warrant dosage adjustment recommendations in the label. The duration of the study should be sufficient 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.

   Conduct the hepatic impairment trial according to the following schedule:

Final Protocol Submission Date: 31 January 2013
Trial Completion Date: 30 September 2015
Final Report Submission: 31 March 2016

2. Since PK assessment in the renal impairment study was conducted following carfilzomib doses of 15/20 mg/m^2 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^2 using the 30 minute infusion as planned in your upcoming phase 3 trial Protocol number 2011-003. Collect PK samples following carfilzomib doses of 56 mg/m^2 or highest clinical dose in the protocol. Conduct your renal impairment evaluation using either of the following two options or propose an alternative option for our review and concurrence:
    - Amend the planned Phase 3 trial (Protocol number 2011-003) to include patients with varying degrees of renal impairment and those on chronic dialysis.

    OR
    - Conduct a stand-alone renal impairment study in patients with varying degrees of renal impairment including patients with mild, moderate, severe renal function and those on chronic dialysis. Conduct the study for sufficient duration in order to detect and assess safety and efficacy signals. If you choose to do a stand-alone renal impairment trial, submit a complete study protocol for review and concurrence by the Agency.

    Final Protocol Submission Date: 31 January 2013
    Trial Completion Date: 30 September 2015
    Final Report Submission: 31 March 2016

Signatures:

Reviewer: Bahru A. Habtemariam, Pharm.D. Division of Clinical Pharmacology 5 Christine Garnett, Pharm.D. Pharmacometrics Team Leader	Team Leader: Julie Bullock, Pharm.D. Division of Clinical Pharmacology 5

Cc: DDOP: CSO - **K Bengtson ;** MTL - **A Deisseroth**; MO - **T Herndon**
DCP-5: Reviewers - **B Habtemariam**, TL - **J Bullock**, PM TL - **C Garnett**,
DDD - **B Booth;** DD - **A Rahman**

1.3 Summary of Important Clinical Pharmacology Findings

Carfilzomib is a tetrapeptide epoxyketone compound designed to be an irreversible proteasome inhibitor with a primary potency for the chymotrypsin-like (CT-L) activity. The sponsor is seeking the approval of carfilzomib for the treatment of relapsed and refractory multiple myeloma (MM). The drug is formulated for intravenous infusion.

In order to determine the safety and clinical activity of carfilzomib, the sponsor conducted two phase 1 dose escalation trials in patients with advanced hematological malignancies. The first phase 1 trial evaluated carfilzomib doses of 1.2 to 20 mg/m^2 given 5 times per week (daily x5) every two weeks. This trial found that when using the daily x 5 dosing schedule, the maximum tolerated dose of carfilzomib was 15 mg/m^2. A second phase 1 trial evaluated carfilzomib doses of 1.2 to 20 mg/m^2 given twice weekly on days 1, 2, 8, 9, 15, and 16, of a 28-day treatment cycle. This study was amended to evaluate a 20/27 carfilzomib regimen where 20 mg/m^2 of carfilzomib was given in the first cycle and doses of 27 mg/m^2 were given in cycles 2 and beyond. The carfilzomib dosing regimen of 20/27 mg/m^2 was selected for the pivotal phase 2 trial based on efficacy results. The MTD was not determined in the second phase 1 study.

The pivotal phase 2 trial was conducted in patients with multiple myeloma using the 20/27 mg/m^2 dosing regimen that was selected in the dose escalation trial. The primary endpoint of the trial was overall response rate (ORR), which is a composite endpoint of partial response, very good partial response, and complete response. The primary endpoint of ORR was achieved by 22.9% of the carfilzomib treated patients. In terms of safety, the most severe and frequent adverse event was liver toxicity, where 6.4% of patients experienced grade 3 or 4 ALT elevations. Exposure response analyses for efficacy (ORR) and safety (ALT elevation) found that at the proposed dose, exposure response was not evident for safety and efficacy. It should be noted that the exposure-toxicity analysis for liver toxicity was not conclusive because only 5 patients with grade 3 or 4 ALT elevation had PK data.

The sponsor conducted several preclinical studies to characterize the disposition of carfilzomib. *In vitro* studies showed carfilzomib is metabolized in plasma via protein peptidase and epoxide hydrolysis. In addition, the sponsor showed that the presence of various P450 enzyme inhibitors did not influence the *in vitro* biotransformation rate of carfilzomib.

The sponsor did not conduct a human ADME study; instead, excretion data were available from a rat study. The rat excretion study showed that most of the administered drug, approximately 30.5%, undergoes biliary elimination while about 26% of the administered drug is eliminated by the kidneys. Only 1% of the administered parent drug was observed in the urine, while the rest of the administered drug was eliminated after degradation in plasma.

The sponsor conducted a renal impairment study where the PK and safety of carfilzomib were evaluated in patients with normal renal function and those with mild, moderate, severe renal function and patients on chronic dialysis. The Cmax and AUC of carfilzomib were similar across all renal function categories. The safety profile of carfilzomib was also similar across all renal function categories.

An *in vitro* study showed carfilzomib to be a moderate and time dependent CYP3A4 inhibitor. To confirm the *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 over three periods, each period separated by one week. The Cmax and AUC of midazolam were similar across all three periods, indicating carfilzomib does not influence the PK of CYP3A4 substrates.

An issue that is not addressed in this NDA package is issue of hepatic impairment. The sponsor did not conduct human ADME study and the rat excretion study showed 30.5% of the administered drug undergoes

biliary elimination. In addition, in the pivotal phase 2 study, the most important adverse effect was liver enzyme (ALT/AST) elevations. Based on these findings, patients with baseline hepatic impairment maybe at an increased risk of liver toxicity, therefore a post marketing hepatic impairment study will be requested.

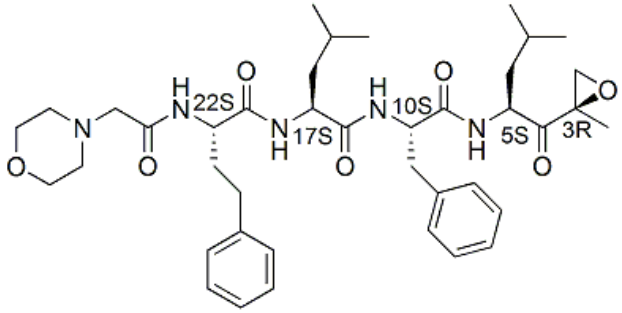
2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Carfilzomib has the following physical and chemical characteristics:

- Established name: Carfilzomib
- Molecular Formula: $C_{40}H_{57}N_5O_7$
- Molecular Weight: 719.9 g/mol
- Chemical Name (CAS)**:** (α*S*)-α-[(4-morpholinylacetyl)amino]benzenebutanoyl-L-leucyl-N-[(1*S*)-3-methyl-1-[[(2R)-2-methyloxiranyl]carbonyl]butyl]-L-phenylalaninamide
- Structural formula:



Carfilzomib for Injection is a lyophilized dosage form contained within a single-use vial, which is reconstituted with sterile water for injection prior to administration.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Carfilzomib is a tetrapeptide epoxyketone, which is an irreversible proteasome inhibitor with a primary potency for the chymotrypsin-like (CT-L) activity. *In vitro*, carfilzomib demonstrated CT-L inhibition potency comparable with bortezomib. Carfilzomib induces proteasome inhibition and, *in vitro*, it is cytotoxic to tumor cells (IC_{50} < 100 nM), including cells made resistant to bortezomib.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The recommended carfilzomib dose is 20 mg/m^2 during cycle 1 and 27 mg/m^2 for cycles 2 and beyond. Carfilzomib is administered by intravenous infusion over 2 to 10 minutes, twice weekly on consecutive days for 3 weeks on days 1, 2, 8, 9, 15, and 16 followed by a 12-day rest period (Days 17 to 28).

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Seven trials in refractory hematologic patients were completed to support the clinical pharmacology and biopharmaceutics portion of the NDA (**Table 1**). Two studies (PX-171-001 and PX-171-002) were dose

escalation studies used to assess dose limiting toxicities and clinical activity. These two studies assessed alternative dosing regimens:

- PX-171-001 used a daily x 5 dosing regimen
- PX-171-002 use a twice weekly dosing regimen

The twice weekly dosing regimen was found more tolerable and adapted for the pivotal phase 2 clinical trials and all other studies thereafter, including the clinical pharmacology studies (**Table 1**).

To demonstrate clinical efficacy, the sponsor conducted an open-label, single-arm, multicenter Phase 2 trial (PX-171-003 – Part 2) designed to evaluate monotherapy with carfilzomib in patients with relapsed and refractory multiple myeloma previously treated with bortezomib and either thalidomide or lenalidomide. Carfilzomib was administered at 20 mg/m^2 for up to 10 minutes in cycle 1, with escalation to 27 mg/m^2 thereafter as tolerated, on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle for up to 12 cycles. Patients completing 12 cycles were eligible to enter extension Study PX-171-010. Long-term follow-up for disease progression, subsequent myeloma treatment, and survival was performed every 3 months after treatment discontinuation for the first year and every 6 months thereafter, for up to 3 years.

Table 1: Clinical Pharmacology and Clinical trials conducted to support marketing approval of carfilzomib

Study No (N)	Type of Study	Dosing Regimen Evaluate	PK Subset
PX-171-001 (29)	Phase 1, dose escalation in patients with refractory HM*	1.2 to 20 mg/m^2; IV, 1–2 min, 14d cycle, QDx5 with 9d rest	27
PX-171-002 (48)	Phase 1, dose escalation in patients with refractory HM*	1.2 to 27 mg/ m^2; IV, 1–2 min, 28d cycle, QDx2 for 3w with 12d rest	29
PX-171-003 (312)	Single arm, phase 2, supportive (Part 1) and Pivotal (Part 2) trial in patients with refractory MM**	Part 1: 20 mg/ m^2 IV, 2 min, 28d cycle, QDx2 for 3w with 12d rest Part 2: 20/27c mg/ m^2 IV, up to 10 min, 28d cycle, QDx2 for 3w with 12d rest	96
PX-171-004 (164)	Phase 2, supportive trial in patients with refractory MM**	Part 1: 20/27c mg/m^2 IV, 2 min, 28d cycle, QDx2 for 3w with 12d rest Part 2: 20/27c mg/m^2 IV, up to 10 min, 28d cycle, QDx2 for 3w with 12d rest	40
PX-171-005 (50)	Phase 2 renal impairment trial in MM patients	15/20/27d mg/m^2 IV, ~10 mL/min, 28d cycle, QDx2 for 3w with 12d rest	43
PX-171-007 (79)	Phase 1b/2, dose escalation trial MM patients in combination with lenalidomide and low-dose dexamethasone	15, 20, 20/27, 20/36 mg/m^2 IV over 2–10 min; or 20/36, 20/45, 20/56, 20/70 mg/m^2 IV over 30 min; 28d cycle, QDx2 for 3w with 12d rest	30
PX-171-008 (18)	Phase 1b, DDI vs. midazolam	27 mg/m^2 IV, ~10 mL/min, 28d cycle, QDx2 for 3w with 12d rest Midazolam, oral;2 mg	17

The sponsor had also conducted population PK analysis using data from five studies as described in **Table 2** below. The sponsor collected carfilzomib plasma collection data following single and multiple doses of carfilzomib. It is not clear, however, as to why the two phase 1 dose escalation trials (studies PX-171-001 and PX-171-002) were not included in the population PK analysis.

Table 2: Trials contributing to population pharmacokinetics

Study (Phase)	Dosing Regimen	PK Sampling	PK Samples (N)
PX-171-003 (2)	28-day treatment cycles (3-weeks ON / 1-week OFF). Up to 12 cycles. Dose escalation following cycle 1. 20 mg/m^2: Cycle 1, D1, 2, 8, 9, 15 & 16. 27 mg/m^2: Other Cycles, D1, 2, 8, 9, 15, & 16.	C1D1(predose, ~15 min post dose); C1D8 (~30 min post dose); C2D15 (30–60 min post dose)	264
PX-171-004 (2)	28-day treatment cycles (3-weeks ON / 1-week OFF). Up to 12 cycles. 20 mg/m^2: D1, 2, 8, 9, 15, and 16	C1D1 (predose, ~15 min post dose); C1D8 (~30 min post dose); C2D15 (30-60 min post dose)	104
PX-171-005 (2)	28-day treatment cycles (3-weeks ON / 1-week OFF). Up to 12 cycles. D1, 2, 8, 9, 15, and 16 Cycle 1: 15 mg/m^2 Cycle 2: Escalation to 20 mg/m^2 Cycle 3 and beyond: 27 mg/m^2	C1D1, C1D15, C2D15 (predose, EOI, 5, 15 and 30 min, 1.0, 1.5, 2, 4, 6, and 24 hr postdose 24-hour samples to be drawn prior to next scheduled dose.	1296
PX-171-006 (1b)	28-day treatment cycles: 3-weeks ON / 1-week OFF. Cycles 1- 8: D1, 2, 8, 9, 15, and 16. Cycles 9–16: D1, 2, 15, and 16. Cohorts 1–3: 15 mg/m^2 Cohorts 4a-5: 20 mg/m^2	C1D1, C1D8, C2D15 (predose,~15 min post dose and 15 min to 3hr post dose)	126
PX-171-007 (1b/2)	28-day treatment cycles. Up to 12 cycles. Three treatment cohorts: 20 mg/m^2: All doses 20/27 mg/m^2: 20 D1 and 2, 27 rest treatment 20/36 mg/m^2: 20 D1 and 2, 36 rest treatment.	C1D1, C1D16, C3D1, C3D16, C5D1, C5D16 (predose, EOI, 5,15 and 30 min, 1, 2 and 4 hr post dose)	1440

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Efficacy Endpoint

The primary endpoint was ORR, as determined by an independent review committee (IRC), in the Response Evaluable Population. The study was to be deemed successful if the lower boundary of the 2-sided 95% CI of the ORR was > 10%. A sample size of 250 patients was selected in order to detect a difference between the null hypothesis proportion of 10% and an anticipated response rate of 16%, with a power of 83% using a one-tailed significance level of 0.025.

The study enrolled 266 patients from 30 sites in the US and Canada between June 2008 and November 2010. Median age was 63.0 years (range: 37, 87 years). Median time from the diagnosis of myeloma was 5.4 years (range: 0.5, 22.3 years). In patients that received at least one carfilzomib dose, the IRC-determined ORR was 22.9% (95% CI: 18.0, 28.5)]. There were 61 responders (CR 1, VGPR 13, and PR 47) and median time to response was 1.9 months (**Table 3**).

Table 3: Summary of efficacy evaluation of carfilzomib.

Characteristic	No. (%) of Patients	
	Response Evaluable Population	Safety Population*
No. of patients (%)	257 (100)	266 (100)
Response category†		
Complete response	1 (0.4)	1 (0.4)
Very good partial response	13 (5.1)	13 (4.9)
Partial response	47 (18.3)	47 (17.7)
Minor response	34 (13.2)	34 (12.8)
Stable disease	81 (31.5)	81 (30.5)
Progressive disease	69 (26.8)	69 (25.9)
Not evaluable	12 (4.7)	21 (7.9)
Overall response	61 (23.7)	61 (22.9)
95% CI‡	(18.7, 29.4)	(18.0, 28.5)
Time to response (months)		
Mean (SD)	1.93 (1.31)	1.93 (1.31)
Median (range)	1.9 (0.3, 5.6)	1.9 (0.3, 5.6)
Clinical benefit response	95 (37.0)	95 (35.7)
95% CI‡	(31.1, 43.2)	(30.0, 41.8)
Time to clinical benefit (months)		
Mean (SD)	1.6 (1.7)	1.6 (1.7)
Median (range)	1.0 (0.3, 10.4)	1.0 (0.3, 10.4)

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

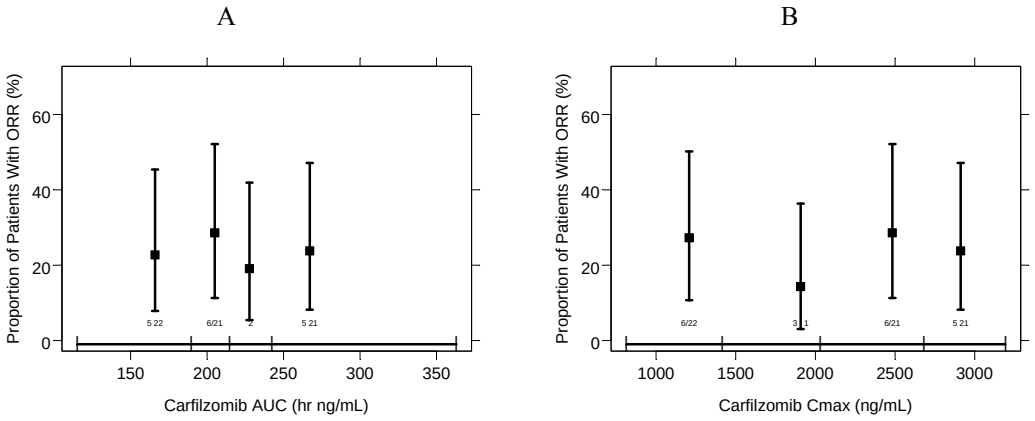
Yes. The sponsor collected PK samples from 7 studies (see **Table 1**).

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Exposure-response relationships were not identified for carfilzomib efficacy based on the available data. Area under the curve (AUC) and Cmax estimates were generated based on the population PK model. Exposure-response analyses were performed to determine whether AUC and Cmax influence the primary efficacy endpoint, ORR, following carfilzomib doses of 20 mg once daily. **Figure 1** below shows that increasing AUC and Cmax carfilzomib do not influence the proportions of patients with ORR.

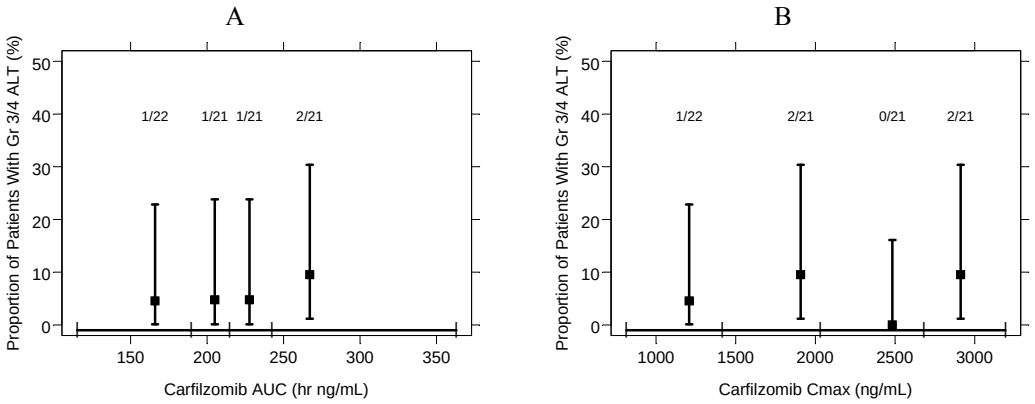
Figure 1. Proportion of objective response rate (ORR) is not influenced by AUC (A) or Cmax (B).



2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

In regards to safety, exposure-response relationships were not identified for carfilzomib based on the available data. Safety data for carfilzomib were available from 266 with relapsed and refractory multiple myeloma patients that took part in pivotal phase 2 trial. During the phase 2 clinical trial, 17 patients (6.4%), had grade 3 or more (Grade 3+) ALT elevations. Out of the 266 patients that were enrolled in the pivotal phase 2 trial, 85 patients had PK samples. Although the data is limited, the proportion of patients with Grade 3+ ALT does not increase with increasing AUC or Cmax of carfilzomib (**Figure 2**). It should be noted that only 5 of the 17 patients with Grade 3+ ALT elevations had PK and this exposure-toxicity analysis can not be conclusive.

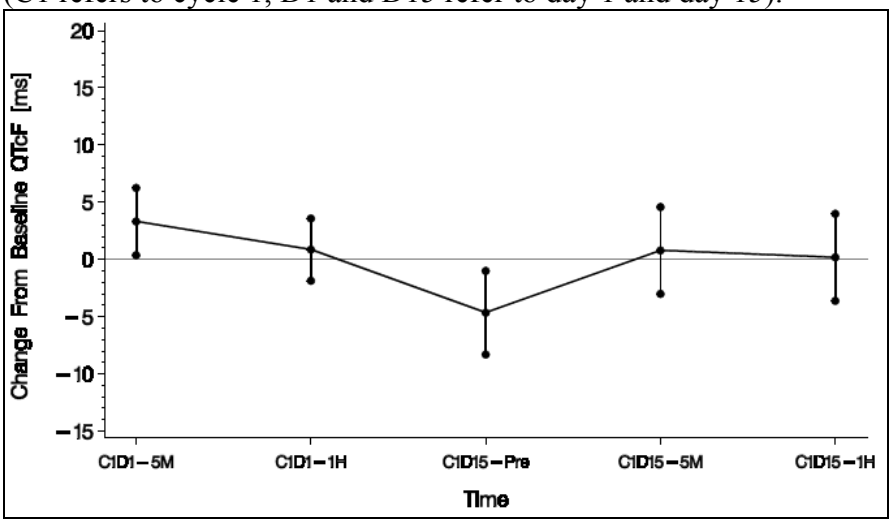
Figure 2. Proportion of patients with Grade 3+ ALT elevation does not increase with increasing AUC total (A) or Cmax (B).



2.2.4.3 *Does this drug prolong the QT or QTc interval?* (You must answer this question, unless this is addressed in the question above.)

The FDA's Interdisciplinary Review Team (IRT) for QT Studies reviewed the results of the QTc study and concluded that there are no detectable prolongations of the QTc-interval. The IRT QTc review is available in DARRTS (J EARP, 03/06/2012). QTc data were collected in study PX-171-007 following carfilzomib doses of 20 and 36 mg/m^2. Patients received 20 mg/mg^2 on days 1 and 2 and 36 mg/m^2 on days 8, 9, 15, and 16 of cycle 1. QTc samples were collected at pre-dose, 5 minuets post dose, and 1 hour post dose.

Figure 3. Change in QTcF vs Time (Study PX-171-007) for the 20/36 mg/m^2 regimen (C1 refers to cycle 1, D1 and D15 refer to day 1 and day 15).



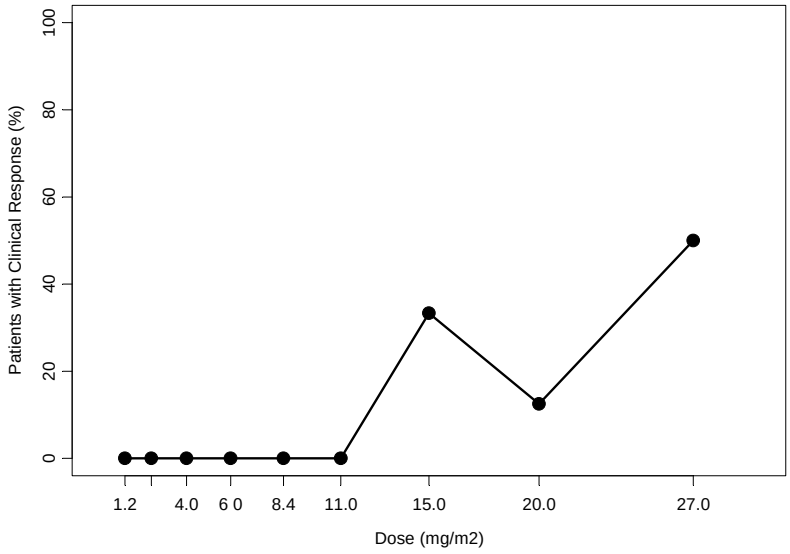
2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The proposed carfilzomib dosing regimen in the draft labeling is as follows:

- Cycle 1: 20 mg/m^2 given on days 1, 2, 8, 9, 15 and 16 of a 28-day treatment cycle.
- Cycles 2 and beyond: 27 mg/m^2 given on days 1, 2, 8, 9, 15 and 16 of a 28-day treatment cycle.

The proposed dosing regimen (20/27 mg/m^2) was selected based on results of a phase 1 dose escalation study (study PX-171-002) that evaluated carfilzomib doses of 1.2, 2.4, 4, 6, 8.4, 11, 15, 20, and 20/27 mg/m^2 given on days 1, 2, 8, 9, 15 and 16 of a 28-day treatment cycle. The 20/27 mg/m^2 dosing regimen was selected based on safety and clinical response. Carfilzomib elicited clinical responses (minimal response, partial response, or complete response) at doses greater than 15 mg/m^2 (**Figure 4**). At the proposed dosing regimen of 20/27 mg/m^2 the clinical response rate was 50%.

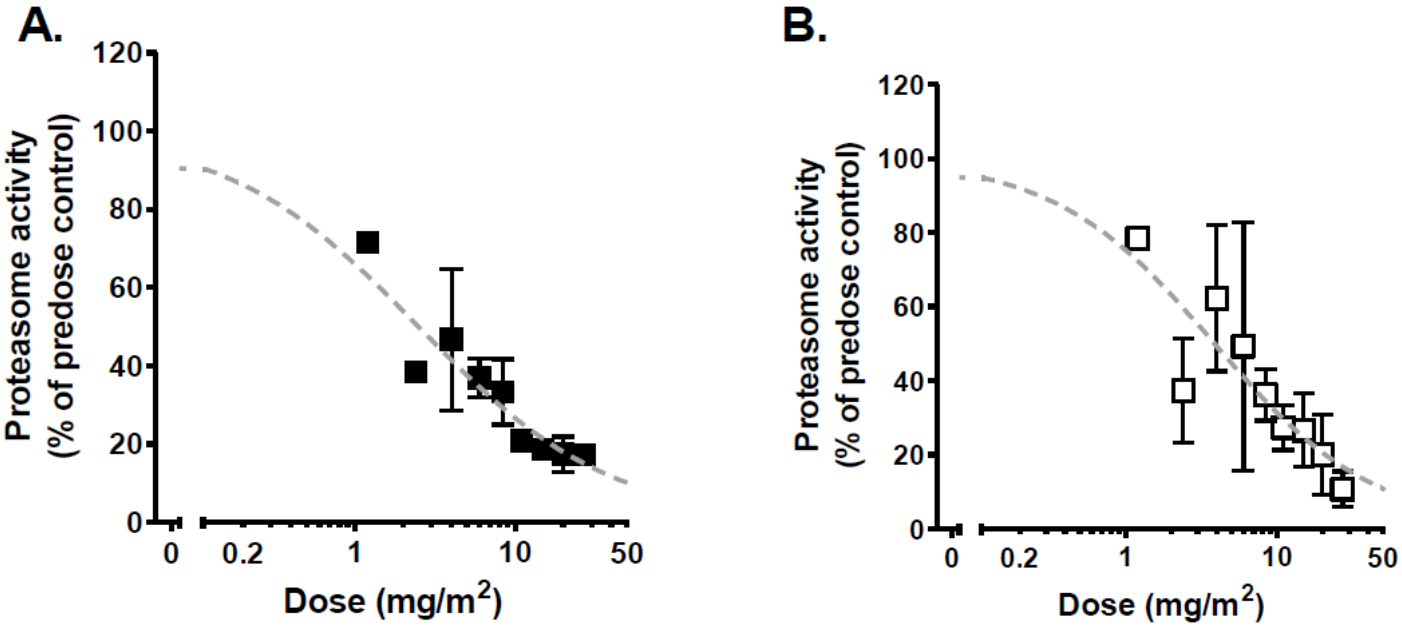
Figure 4. Clinical response rate vs. carfilzomib dose.



Study PX-171-002 also assessed the pharmacodynamic (PD) properties of carfilzomib by characterizing the inhibition of the chymotrypsin-like activity of the proteasome after single and multiple doses. Blood samples were collected for PD analysis before and 1 hour after administration of carfilzomib on days 1, 2, and 8 during cycle 1 and day 1 during cycle 2. Peripheral blood mononuclear cells (PBMCs) were isolated from an aliquot of the blood sample and proteasome specific activity was measured in both whole blood [mainly red blood cells (RBCs)] and PBMCs using a fluorogenic substrate assay specific for the chymotrypsin-like activity of the proteasome.

The PD response measured in subjects on this study showed dose-dependent proteasome inhibition in whole blood and PBMC (**Figure 5**). Dose-dependent inhibition was observed in RBCs and PBMCs after the first dose and appeared to plateau at approximately 75% proteasome inhibition at doses of 11 mg/m^2 and above. Following repeat carfilzomib doses, proteasome inhibition was increased to about 90% in both RBCs and PBMCs.

Figure 5. Proteasome Chymotrypsin-like Activity vs. Carfilomib dose in Whole Blood (A) and PBMCs (B).



2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters?

Most of the submitted human PK studies collected extensive PK data only after single dose administration. The renal impairment study (study PX-171-005) collected extensive PK data on days 1 and 15 in patients with varying degrees of renal impairment. To compare single and multiple dose PK parameters, only data obtained from patients with normal renal function from study PX-171-005 have been used. As shown in **Table 4** below, single and multiple dose AUC and Cmax of carfilzomib were similar. Such a finding is expected because carfilzomib has a very short half life (0.45 to 1 hour), and no drug accumulation is expected following multiple dose drug administration.

Table 4: Summary of single and multiple dose AUC and Cmax of carfilzomib**.**

PK Parameter	Study Day	
	Day 1 (N=8)	Day 15 (N=7)
AUC (hr·ng/mL)	187 (75.3)	159 (186)
Cmax (ng/mL)	2077 (91.4)	1768 (179)
Half Life	0.398 (0.375, 0.626)	0.481 (0.358, 1.73)

AUC/Cmax: geometric mean (geometric CV %); half life: median (minimum, maximum)

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

All of the submitted carfilzomib PK data were collected in cancer patients. Therefore, PK comparison between healthy volunteers and patients can not be conducted.

2.2.5.3 What are the characteristics of drug absorption?

Carfilzomib is formulated for intravenous administration; therefore, the absorption of carfilzomib was not assessed.

2.2.5.4 What are the characteristics of drug distribution?

The plasma protein binding (PPB) of characteristics of carfilzomib was assessed from plasma samples collected in multiple myeloma patients with varying degrees of renal function that took part in the renal impairment study (PX-171-005). The mean PPB was 98.0%, 97.6%, 98.3%, 98.2% and 97.9% in patients with normal renal function, mild, moderate, and severe renal impairment, and dialysis subjects, respectively. These results suggested that renal function does not have a significant impact on PPB of carfilzomib. The PPB values were also similar at different treatment cycles, collection times, and doses levels (15 to 20 mg/m2). In addition, non-compartmental PK analysis showed that the mean steady-state volume of distribution (Vss) of carfilzomib ranged from 11 to 47 L.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

The sponsor did not conduct a human ADME study. The sponsor conducted a renal and biliary excretion study in rats following an intravenous (IV) carfilzomib bolus dose at 2 mg/kg. The study was conducted in three groups of rats (n = 5/group). Rats with and without bile duct cannulation were administrated an IV bolus dose of carfilzomib at 2 mg/kg with blood samples taken at pre-dose and 2, 5, 15, 30, 60, 120, and 240 minutes (min) post-dose (Groups A and B). A third cohort of bile duct-cannulated rats were administrated carfilzomib at 2 mg/kg with blood samples taken at pre-dose, immediately after dosing (0.2–0.3 min) and 1, 2, 5, 15, 30, 60, and 120 min post-dose (Group C). Urine was collected at 0–4, 4–8, and 8–24 hours (hr) post-dose for all groups. Cumulative bile was collected at 0–4 and 4–8 hr post-dose for bile duct-cannulated animals.

In all three groups, carfilzomib plasma concentrations rapidly declined with an average terminal half life ($T_{1/2}$) $\leq$ 12 min (**Table 5**). The observed C_{max} and AUC values for rats with immediate plasma sampling (Group C) were 8.11 ± 0.98 µM and 10.8 ± 1.5 min▪µmol/L, which were at least 2-fold higher than the Cmax and AUC observed in Groups A & B where PK sampling was delaying by 2 minutes. Such a finding indicates that in order to conduct accurate PK characterization of carfilzomib, the PK sampling of carfilzomib should take place immediately after drug infusion.

Table 5: Pharmacokinetic parameters (mean±sd) of carfilzomib following a single IV bolus administration at 2 mg/kg to male sprague dawley rats with different first sampling times.

Group	A	B	C
First sampling time (min)	2	2	0.2–0.3
$T_{1/2}$ (min)	12 ± 6	4 ± 2	4 ± 2
T_{max} (min)	2.60 ± 1.34	2.00 ± 0.00	0.23 ± 0.06
C_{max} (μM)	0.870 ± 0.559	0.733 ± 0.062	8.11 ± 0.98
C_0 (μM)	2.85 ± 0.53	2.12 ± 0.46	11.9 ± 2.0
AUC_{last} (min*μmol/L)	6.39 ± 4.10	4.86 ± 0.42	10.8 ± 1.5
AUC_{inf} (min*μmol/L)	6.44 ± 4.12	4.89 ± 0.43	10.8 ± 1.5
AUC_{inf}/D(min*kg*μmol/L/μmol)	2.32 ± 1.48	1.76 ± 0.15	3.89 ± 0.54
CL (mL/min/kg)	567 ± 275	572 ± 49	261 ± 37
V_{ss} (L/kg)	2.20 ± 1.96	1.28 ± 0.29	0.40 ± 0.10

Less than 1% of the intravenously dosed carfilzomib was excreted intact in urine and bile. PR-389 (M14), a peptide cleavage product was the most abundant metabolite in urine. PR-389 (M14) and PR-413 (M15) were most abundant in bile. PR-519 (M16) was also detected at lower levels. Renal and biliary excretion accounted for 26.2% and 30.5% of the dose, respectively, for a total of 56.7% within 24 hr post-dose for Group C.

2.2.5.6 What are the characteristics of drug metabolism?

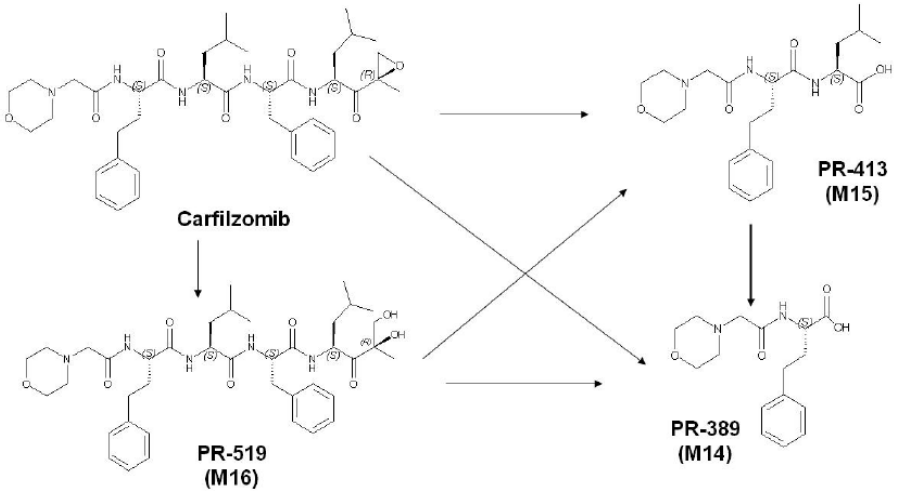
Carfilzomib metabolite identification and characterization was conducted in human plasma and urine following carfilzomib doses of 20 and 27 mg/m^2 in patients (study TR-0077-171). Nine plasma and 13 urine metabolites were identified. Metabolites known as M14, M15, and M16 were the most abundant metabolites detected in human plasma (**Figure 6**). In human urine, the most abundant metabolites were M14, M15, M12, M11, and M10 listed in reverse order of relative abundance. Another *in vivo* study conducted in rats and monkeys showed that M14 and M16 were abundantly present in plasma and M14 was present in urine and bile.

The sponsor conducted several *in vitro* studies to identify enzymatic systems responsible for the biotransformation of carfilzomib (**Table 6**). The *in vitro* studies showed that carfilzomib is not metabolized by any of CYP4540 enzymes; rather it is metabolized by epoxide hydroxylase and peptidases.

Table 6: Summary of *in vitro* study results that characterized carfilzomib metabolism

Study	Study Medium	Findings
TR-0184-171	Rat blood and tissue homogenate	-M14 and M15 are products of peptidase cleavage of -M16 is resulting from epoxide hydrolysis
TR-0040-171	Isolated rat, monkey, and human hepatocytes	-Minor metabolites detected -None of the major metabolites were formed
TR-0212-171	Human Hepatocytes in the presence and absence of chemical P450 enzyme inhibitors	-Metabolites formed as a result of epoxide hydrolysis -Presence of CYP inhibitors did not change the rate of carfilzomib biotransformation

Figure 6: Proposed Major Metabolic Pathways of Carfilzomib



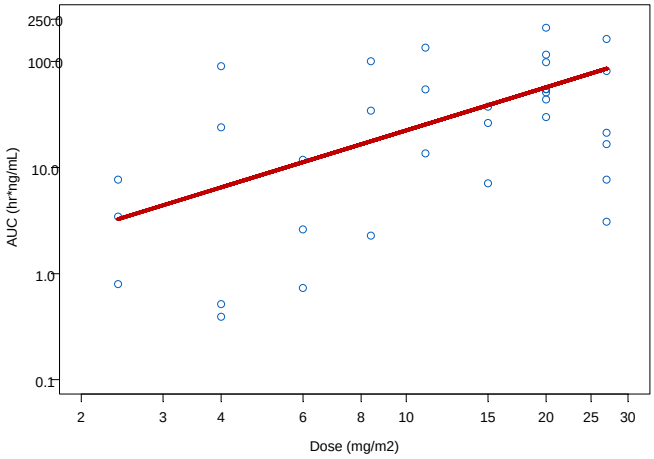
2.2.5.7 What are the characteristics of drug excretion?

Animal studies show that carfilzomib is rapidly converted to inactive metabolites. Those metabolites are excreted by the urine and bile. Human excretion studies were not conducted for carfilzomib.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Overall, the AUC and Cmax of carfilzomib increase in proportion with dose. Intensive single dose PK data were collected in a dose escalation study at all dose levels (study PX-171-002). For patients that received the 20/27 mg/m^2 dosing regimen, PK data were collected following 20 mg/m^2 during the first cycle. Plasma concentrations for the 1.2 mg/m^2 dose level were not detectable. Therefore, AUC and Cmax data were available for the 2.4 to 20 mg/m^2 dose range. As shown in **Figure 7** below, AUC of carfilzomib increased in proportion with dose. It should be noted that the mean AUC of carfilzomib in study PX-171-002 was 2-fold lower than the mean AUCs of carfilzomib in other studies. The sponsor's rationale for this discrepancy is that the sampling time for study PX-171-002 started at 5 minutes post dose, while for other studies sampling time started at the end of infusion. The sponsor's rationale is supported by the rat excretion study where the AUC of carfilzomib was 2-fold higher when sampling time was started at 0.2 minutes (groups C) vs. 2 minutes (groups A and B) as outlined in (**Table 5**).

Figure 7. Dose-proportionality assessment of Carfilzomib using dose escalation study data.



2.2.5.9 How do the PK parameters change with time following chronic dosing?

As described in section 2.2.5.1, the Cmax and AUC of carfilzomib do not change following multiple dosing. Because carfilzomib is metabolized by epoxide hydrolysis and protein peptidases, chronic dosing is not expected to alter the PK parameters of carfilzomib.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Table 7 below summarizes the population PK parameter estimates and associated inter- and intra-individual PK variability. The inter-individual variability of clearance (CL) and volume of distribution (V1) were 25% and 88%, respectively. Residual or intra-individual variability for log transformed carfilzomib concentrations was 0.937. Patients' creatinine clearance was determined to be the main source of inter-individual variability.

Table 7: Summary of carfilzomib PK parameter estimates

Parameter	Estimate	RSE (%)	Interindividual Variability (Exponential)	RSE (%)
Clearance (L/h)	192	6.3	0.25	25
V1 (L)	10.3	9.3		
V2 (L)	6.27	19	0.88	25
Q (L/h)	8.19	12	0.74	23
Proportional decrease in clearance by mL/min CrCl among renally impaired patients	0.00451	24		
σ (additive residual error on log transformed data)	0.937	15		

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The sponsor conducted population PK analysis using data from 236 patients that took part in 5 clinical trials (**Table 8**). To determine the influence of intrinsic factors on the PK of carfilzomib, the population PK analysis evaluated age, weight, height, body mass index, creatinine clearance (CrCL), gender, ethnicity, degree of renal impairment (mild/moderate/severe), and disease type. Population PK analysis revealed that CrCL influences the clearance of carfilzomib. The analysis further revealed that the influence of CrCL is minimal since even in patients with severe renal impairment, the carfilzomib clearance was reduced by no more than 20%. The reviewer agrees that the influence of CrCL on the clearance of carfilzomib is minimal since a separate evaluation of PK data from the dedicated renal impairment trial showed that the AUC and Cmax of carfilzomib were overlapping (**Figure 8**). Other than CrCL, none of the other intrinsic factors influenced the PK of carfilzomib.

Table 8: Summary of patient characteristics that were part of the population pharmacokinetics analysis

	PX-171-003	PX-171-004	PX-171-005	PX-171-006	PX-171-007
*Patient Population	MM	MM	MM	MM	ST
Number Subjects	96	40	35	37	28
Number PK Observations	203	79	636	157	413
Sex (m/f)	57/39	23/17	19/16	20/17	15/13
Mean Age (sd)	61(9.7)	62(9.8)	67(7.8)	61(9.1)	61(11)
Mean Height (sd)	168(9.8)	171(12)	170(11)	168(11)	169(9.3)
Mean Weight (sd)	79(19)	87(20)	84(20)	84(18)	80(21)
Mean BSA (sd)	1.90(0.26)	1.97(0.27)	1.93(0.24)	1.96(0.22)	1.92(0.28)
Mean Baseline CrCl (sd)	80.3(36)	95.5(39)	61.2(34)	93.1(32)	95.7(37)
Mean BMI (sd)	27.7(5.5)	29.3(4.9)	29.0(6.0)	29.9(6.1)	27.8(7.3)
Ethnicity (Asian/African/ Caucasian/Hispanic/Other)	1/18/67/6/4	0/7/32/1/0	2/9/24/0/0	1/6/27/3/0	0/1/22/5/0
Renal impairment (severe/moderate/mild/none)	0/21/34/41	0/5/15/20	7/8/12/8	0/4/11/22	0/3/8/17

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups?

Dosage regimen adjustments for carfilzomib are not recommended to any specific population.

2.3.2.1 Elderly

A population PK analysis included subjects with age ranging from 36 to 87 years old and showed that age does not influence the disposition of carfilzomib.

2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study?

The applicant has not conducted clinical studies with carfilzomib in pediatric patients and does not plan to conduct any pediatric trials. The sponsor intends to apply for a waiver of the requirement for pediatric assessment. Because carfilzomib was granted orphan designation on 1/08/2008 and orphan drugs are not required to comply with PREA requirements, the sponsor is likely to receive waiver.

2.3.2.3 Gender

Population PK analysis showed that gender has no influence on the PK of carfilzomib.

2.3.2.4 Race, in particular differences in exposure and/or response in Caucasians, African-Americans, and/or Asians

Population PK analysis showed that race has no influence on the PK of carfilzomib.

2.3.2.5 Renal impairment

A renal impairment study was conducted in patients with normal renal function and those with mild, moderate, and severe renal impairment and those on chronic dialysis. Patients received carfilzomib doses of 15 mg/m^2 for cycle 1, 20 mg/m^2 for cycle 2, and those who tolerate 20 mg/m^2 during cycle 2 received doses of 27 mg/m^2 for cycles 3 and beyond. Carfilzomib was administered as intravenous infusion over 2-10 minutes on days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle. The mean treatment duration was 5.5 cycles. The study enrolled a total of 50 patients and carfilzomib AUC and Cmax estimates were obtained from 43 patients (**Table 9**).

Table 9: Summary of renal impairment study characteristics

Renal Impairment Category	Estimated CrCL Range	Enrolled (N)	Last Cycle Started (mean (SD))	PK Samples (N)
Normal	>80 mL/min	12	5.9 (3.18)	8
Mild Impairment	50–80 mL/min	12	5.6 (3.40)	12
Moderate Impairment	30–49 mL/min	10	4.8 (4.57)	8
Severe Impairment	< 30 mL/min	8	7.4 (4.53)	7
On Chronic Dialysis	On Chronic Dialysis	8	3.6 (2.72)	8

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Pharmacokinetic results showed that the AUC and Cmax of carfilzomib are not influence by the presence of renal impairment. As shown in Error! Reference source not found., the Cmax and AUC of carfilzomib are overlapping in patients with normal renal function and patients with mild, moderate, severe renal impairment and those on chronic dialysis. Therefore, renal function does not influence the pharmacokinetics of carfilzomib. In addition, the safety profile of carfilzomib appears to be consistent across all renal categories (**Table 10**).

Figure 8. Individual and mean (red bar) AUC (A) and Cmax (B) vs. renal function category

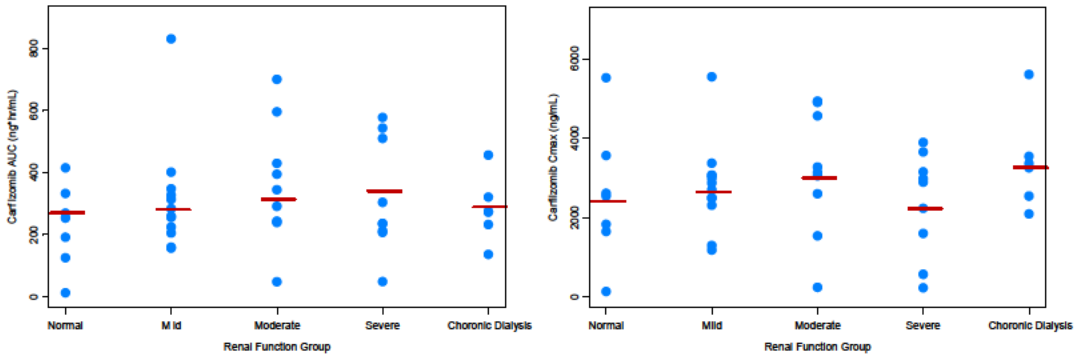

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Table 10: Summary of adverse events (AE) stratified by renal function category

Variable [a]	Normal (N=12)	Mild (N=12)	Moderate (N=10)	Severe (N=8)	Dialysis (N=8)	Total (N=50)
With at least 1 AE [n (%)]	11 (91.7)	12 (100.0)	10 (100.0)	8 (100.0)	6 (75.0)	47 (94.0)
AE [n (%)] With at least 1 treatment-related	10 (83.3)	12 (100.0)	10 (100.0)	8 (100.0)	5 (62.5)	45 (90.0)
Grade 3 or higher AE [n (%)]	7 (58.3)	7 (58.3)	7 (70.0)	5 (62.5)	4 (50.0)	30 (60.0)
With AE leading to discontinuation of study drug [n (%)]	3 (25.0)	5 (41.7)	6 (60.0)	1 (12.5)	1 (12.5)	16 (32.0)
Who died within 30 days of last dose of study drug [n (%)]	0 (0.0)	1 (8.3)	0 (0.0)	1 (12.5)	3 (37.5)	5 (10.0)

2.3.2.6 Hepatic impairment

The sponsor did not conduct a study in subjects with impaired hepatic function. The sponsor also did not conduct a human ADME study. The sponsor stated during a Clinical Pharmacology End-of-Phase 2 meeting that was held on 4/30/2008 that they were planning to do human excretion studies but none were submitted with the NDA.

A pharmacokinetic and excretion study in rats showed approximately 30.5% of the metabolic products of carfilzomib undergo biliary elimination. However, since these metabolites are inactive, it is not clear whether hepatic impairment would influence the safety or efficacy of carfilzomib. However, since carfilzomib caused grade 3/4 liver enzyme elevation in a relatively high number of patients (6.4%), the evaluation of the PK and safety of carfilzomib in patients with varying degrees of hepatic impairment maybe important. Therefore, the reviewer proposes the sponsor conduct a dedicated hepatic impairment study under a PMR.

2.3.2.7 What pharmacogenetics information is there in the application and is it important or not?

None.

2.3.2.8 What pregnancy and lactation use information is there in the application?

The proposed carfilzomib label states that carfilzomib can cause fetal harm when administered to a pregnant woman and women should avoid pregnancy while taking carfilzomib. No further pregnancy and lactation information is provided in the proposed label. Pharmacology and toxicology reviewers will address pregnancy and lactation related issues in greater depth.

2.3.2.9 Other human factors that are important to understanding the drug's efficacy and safety?

There are no other known important human factors to the understanding of carfilzomib safety and efficacy.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

There were no specific studies or analyses designed to evaluate the effects of extrinsic factors such as herbal products, diet, smoking or alcohol use on the PK of carfilzomib.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes. In *in vitro* drug-drug interaction studies, carfilzomib was determined to be a moderate inhibitor of CYP3A4.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Carfilzomib is metabolized via protein peptidase and epoxide hydrolysis. In addition, the sponsor showed that the presence of various CYP enzyme inhibitors did not influence the in vitro metabolism rate of carfilzomib (**Table 11**).

Table 11: Effect of cytochrome P450 inhibitors on the in vitro rate of carfilzomib metabolism

Inhibitor	Inhibition on metabolism of probe substrate			Carfilzomib metabolism rate constant k (mean ± SD, min^{-1})	
	P450 isozyme	Metabolism of probe substrate	Inhibition (%)	Without inhibitor	With inhibitor
Fyrafilline (30 µM)	CYP1A2	phenacetin-O-deethylation	79	0.015 ±0.0003	0.016 ±0.002
Montelukast (30 µM)	CYP2C8	Amodiaquine N-deethylation	83	0.018 ±0.001	0.014 ±0.001
Sulfaphenazole (10 µM)	CYP2C9	4'-hydroxy-diclofenac	75	0.0097 ± 0.0015	0.0073 ± 0.0012
(+)-N-3-benzylnirvanol (10 µM)	CYP2C19	S-mephenytoin-4'-hydroxylation	78	0.013 ±0.0004	0.016 ±0.002
Qunidine (10 µM)	CYP2D6	Dextromethorphan *O*-demethylation	97	0.0093 ± 0.0001	0.013 ± 0.001
Ketoconazole (10 µM)	CYP3A	Midazolam 1'-hydroxylation	91	0.010 ± 0.002	0.012 ± 0.002

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2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

CYP Enzyme Inhibition

In an *in vitro* study, carfilzomib was shown to caused direct inhibition of human CYP3A4/5 (as measured by midazolam 1'-hydroxylation) with an IC_{50} value 1.6 µM in human liver microsomes. Carfilzomib also appeared to be a competitive inhibitor of human CYP3A4/5 (as measured by midazolam 1'-hydroxylation) with a K_i value of 1.7 µM (**Table 12**). Carfilzomib caused time-dependent inhibition of human CYP3A4/5 (as measured by testosterone 6 -hydroxylation and midazolam 1'-hydroxylation), as an increase in inhibition was observed after carfilzomib was pre-incubated with human liver microsomes in the presence of NADPH for 30 minutes (**Table 12**). Carfilzomib showed no or minimal direct or time dependent inhibition of CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 with IC50 values of > 10 µM and undetermined Ki values by study design (**Table 12**).

Table 12: *In vitro* evaluation of Carfilzomib as an inhibitor of human CYP enzymes

		Direct inhibition			Time-dependent inhibition		
		Zero-minute preincubation			30-minute preincubation		
Enzyme	CYP Reaction	IC_{50} (µM)	Inhibition at 10 µM (%) [a]	K_i (µM)	IC_{50} (µM)	Inhibition at 10 µM (%) [a]	Potential for time-dependent inhibition [b]
CYP1A2	Phenacetin *O*-deethylation	>10	12	ND	>10	NA	little or no
CYP2C8	Amodiaquine *N*-dealkylation	>10	0.74	ND	>10	NA	little or no
CYP2C9	Diclofenac 4′-hydroxylation	>10	16	ND	>10	10	little or no
CYP2C19	*S*-Mephenytoin 4′-hydroxylation	>10	26	ND	>10	16	little or no
CYP2D6	Dextromethorphan *O*-demethylation	>10	21	ND	>10	3.2	little or no
CYP3A4/5	Testosterone 6β-hydroxylation	>10	32	ND	0.97	81	yes [d]
CYP3A4/5	Midazolam 1′-hydroxylation	1.6	80	1.7 [c]	0.49	90	yes [e]

Not determined by study design

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CYP Enzyme Induction

The objective of this study was to determine the induction potential of cytochrome P450 (CYP) isoforms by carfilzomib in fresh cultured human hepatocytes. Carfilzomib was incubated with hepatocytes at concentrations of 0, 0.1, 0.5, 2.5 uM for testing CYP1A2, and CYP3A4 induction. Each enzyme was tested with 3 donor livers. Hepatocytes were also incubated with appropriate controls, including prototypical

inducing agents (3-naphthoflavone for CYP1A2, rifampicin for 3A4). After 3 days of exposure, enzyme induction was determined in situ with probe substrates selective for CYP1A2 and CYP3A4 isoforms. The induction potential of carfilzomib for CYP3A4 was also determined by measuring mRNA expression.

At the concentrations tested, carfilzomib was not an inducer of CYP1A2 and CYP3A4. Instead, carfilzomib caused a reduction in both CYP1A2 and CYP3A4 catalytic activity. Concentration-dependent decrease in CYP3A4 mRNA expression was also observed when the hepatocytes were treated with carfilzomib, suggesting that the reduction of CYP3A4 activity may be partially attributable to CYP3A4 mRNA down-regulation.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

The extent to which carfilzomib acts as an inhibitor or a substrate of P-glycoprotein (P-gp) has been assessed in a Caco-2 monolayer system by bi-directional permeability determination.

The efflux ratio of carfilzomib ranged from 6.3 to 14.5 at carfilzomib concentrations of 0.1, 1, and 3 µM (**Table 13**). Digoxin was used as the positive control in parallel to demonstrate the validity of the experiments. The efflux ratio of carfilzomib was reduced to 1.4 and 3.8 in the presence of 10 µM cyclosporine A and ketoconazole, respectively. From these results, carfilzomib appears to be a P-gp substrate.

Table 13: Permeability and recovery of carfilzomib and digoxin in Caco-2 cells

Treatment	Parameter	A-B Direction				B-A Direction				Efflux Ratio
		R 1	R2	R3	Average ± SD	R1	R2	R3	Average ± SD	
Carfilzomib (0.1 µM)	P_{app} ($\times 10^{-6}$cm/s)	10.6	7.5	3.0	7.0 ± 3.8	67.1	36.0*	58.5	62.8 ± 6.0	9.0
	% Recovery	43.3	51.8	46.7	47.3 ± 4.3	87.2	101*	91.1	89.2 ± 2.8	
Carfilzomib (1 µM)	P_{app} ($\times 10^{-6}$cm/s)	4.2	3.0	3.5	3.6 ± 0.6	44.5	56.9	53.9	51.8 ± 6.5	14.5
	% Recovery	26.6	43.1	41.0	36.9 ± 9.0	49.0	72.7	68.9	63.5 ± 12.7	
Carfilzomib (3 µM)	P_{app} ($\times 10^{-6}$cm/s)	4.2	4.2	4.9	4.4 ± 0.4	24.6	31.2	28.5	28.1 ± 3.4	6.3
	% Recovery	35.6	36.0	28.6	33.4 ± 4.2	41.5	47.6	46.6	45.3 ± 3.3	
Digoxin (10 µM)	P_{app} ($\times 10^{-6}$cm/s)	0.7	0.8	0.8	0.7 ± 0.1	11.3	11.3	15.4	12.7 ± 2.4	17.0
	% Recovery	81.1	81.5	89.2	83.9 ± 4.6	86.1	87.6	93.7	89.1 ± 4.0	

*Failed post-experimental LY; excluded from calculations

Carfilzomib at 3 µM, the highest soluble concentration, inhibited the efflux transport of digoxin by 25% in the Caco-2 system while the known P-gp inhibitors, cyclosporine A and ketoconazole at 10 µM each, eliminated the efflux transport of digoxin completely (**Table 14**). These results show carfilzomib is a weak inhibitor of P-gp.

Table 14: P-gp inhibition: Permeability and recovery of digoxin in Caco-2 cells

Treatment	Parameter	A-B Direction				B-A Direction				Efflux Ratio
		R 1	R2	R3	Average ± SD	R1	R2	R3	Average ± SD	
Digoxin	P_{app} ($\times 10^{-6}$cm/s)	0.7	0.8	0.8	0.7 ± 0.1	11.3	11.3	15.4	12.7 ± 2.4	17.0
	% Recovery	81.1	81.5	89.2	83.9 ± 4.6	86.1	87.6	93.7	89.1 ± 4.0	
Digoxin + Carfilzomib	P_{app} ($\times 10^{-6}$cm/s)	0.9	0.7	0.9	0.8 ± 0.1	8.2	12.5	10.9	10.5 ± 2.1	13.1
	% Recovery	81.5	86.2	91.6	86.4 ± 5.1	91.3	100	102	98.0 ± 5.9	
Digoxin + CsA	P_{app} ($\times 10^{-6}$cm/s)	2.9	2.9	3.8	3.2 ± 0.5	3.6	3.6	3.5	3.6 ± 0.0	1.1
	% Recovery	83.2	88.1	94.9	88.8 ± 5.9	99.0	107	105	104 ± 4.2	
Digoxin + Ketoconazole	P_{app} ($\times 10^{-6}$cm/s)	3.6	2.6	3.1	3.1 ± 0.5	3.0	2.6	3.1	2.9 ± 0.2	0.9
	% Recovery	83.0	84.4	92.7	86.7 ± 5.2	93.5	94.5	98.8	95.6 ± 2.8	

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

No experiments were conducted in other metabolic or transporter systems. However, since the drug has a peptide backbone and has a very short half-life, other metabolic and transporter systems are unlikely to be very important in the disposition of carfilzomib.

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Yes, the label states that patients should be pre-medicated with 4 mg of dexamethasone during the first two cycles (2 months) of treatment. Therefore, dexamethasone will be co-administered with carfilzomib for the first 12 doses of carfilzomib. The pharmacokinetic interaction potential of dexamethasone and carfilzomib has not been evaluated. However, the proposed combination was evaluated for safety and efficacy during the pivotal phase 2 study, therefore any future combination dosing will replicate the combination dose that was tested in the pivotal phase 2 study. Furthermore, based on available information, the two drugs are unlikely to have any meaningful interaction. Because carfilzomib is not metabolized by P450 enzymes, the only scenario would be for carfilzomib to increase exposure to the CYP3A4 metabolized dexamethasone. Such a scenario is unlikely because in an in vivo study, carfilzomib did not increase exposure to the known CYP3A4 substrate midazolam (**Figure 9**).

2.4.2.7 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

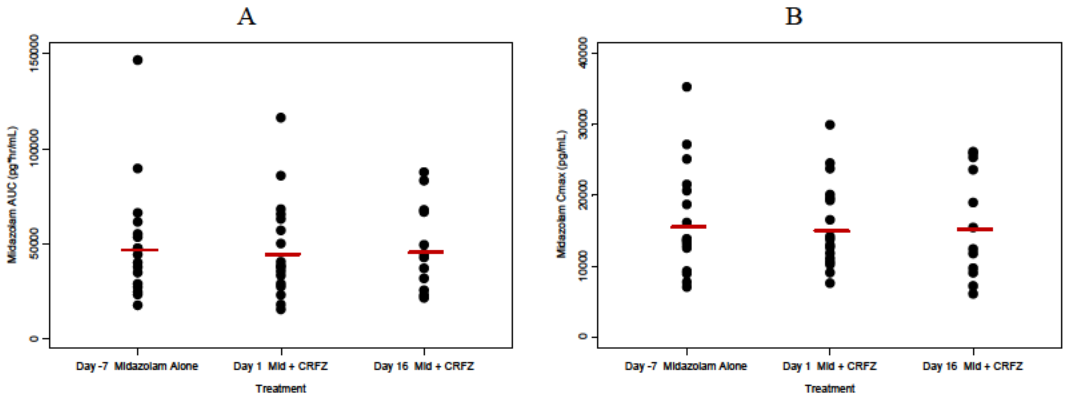
Since *in vitro* drug-drug interaction (DDI) studies indicated carfilzomib is a moderate inhibitor of CYP3A4, the sponsor conducted an *in vivo* DDI study in patients by administrating the known CYP3A4 substrate midazolam in the absence and presence of carfilzomib as outlined below. Since carfilzomib was also determined to be a time dependent inhibitor of CYP3A4, the clinical DDI study was also designed to assess if the time dependent CYP3A4 inhibition is present in patients. The study design of the DDI study was as follows:

- **Period 1**: Day –7 (+ up to 3 days) prior to cycle 1, patients received a single oral dose of midazolam at 2 mg. The washout for midazolam was to last for up to 7 days. PK blood samples were collected on day –7

- **Period 2:** The same patients were treated with at carfilzomib 27 mg/m^2 intravenously on days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle. Midazolam at 2 mg was co-administered orally immediately on days 1 and 16. PK samples were collected on days 1 and 16.

The plasma concentrations data for midazolam were collected on days -7, 1, and 16 to determine whether the PK of midazolam can be influenced by carfilzomib. The AUC and Cmax of midazolam were not influenced when coadministered with carfilzomib on days 1 and 16 as depicted in **Figure 9,** which indicates that chronic carfilzomib dosing is unlikely to inhibit the *in vivo* metabolism of CYP3A4 substrates.

Figure 9. Individual and mean (red bar) AUC (A) and Cmax (B) of midazolam in the absence and presence of carfilzomib.



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2.4.2.8 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Since no pharmacodynamic (PD) markers were identified and measured during carfilzomib development, the potentials for PD drug-drug interactions are unknown.

2.4.2.9 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

No.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

No.

2.5 General Biopharmaceutics

Carfilzomib is formulated for intravenous administration. As such, solubility, permeability and dissolution issues will not influence the exposure to carfilzomib.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

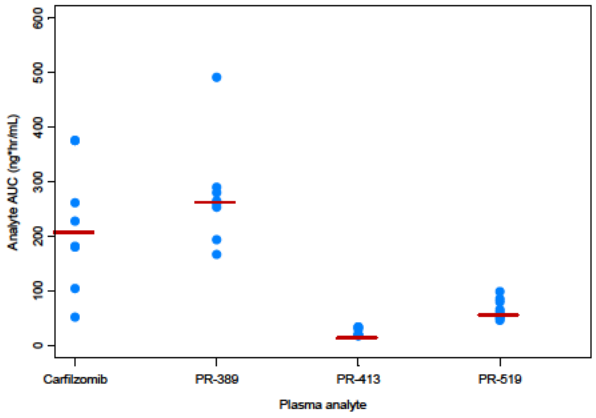
Following administration of carfilzomib, the active pharmacological moiety remains to be carfilzomib; none of the carfilzomib metabolites have shown any biological activity. The plasma concentrations were measured and analyzed using validated methods, as described below.

2.6.2 Which metabolites have been selected for analysis?

PK analysis was performed for metabolites, PR-389, PR-413, and PR-519 in study PX-171-005 (the renal impairment study). In this study, the plasma and urine concentrations of carfilzomib and each of the three metabolites were analyzed. Compared to carfilzomib, metabolites PR-389, PR-413, and PR-519 have relative mean plasma AUC of 100%, 11%, and 30% in patients with normal renal function (Error! Reference source not found.). APPEARS THIS WAY ON ORIG NAL

Plasma concentration of metabolite PR-519 in MM patients with renal impairment was similar to the one observed in patients with normal renal function. For the metabolites PR-389(M14) and PR-413 (M15), AUC increased relative to the degree of renal impairment suggesting that renal excretion is an important route of elimination for these metabolites. These metabolites lack the active functional group of the parent drug, and thus lack activity as proteasome inhibitors. Further, the sponsor states that these metabolites have no known biologic activity.

Figure 10. Individual and mean (red bar) AUC (A) and Cmax (B) carfilzomib and its metabolites.



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In the urine, the mean total amount of PR-389 excreted (TAe) was approximately 2-fold greater for patients with normal renal function compared to those with severe renal impairment, while the TAe of PR-413 was minimal, with amounts less than 2% of the administered dose. The concentrations of PR-519 in urine were not determined in this trial.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total carfilzomib plasma concentrations were measured in clinical studies.

2.6.4 What bioanalytical methods are used to assess concentrations?

A bioanalytical method was developed and validated for the determination of carfilzomib, PR-389, PR-413, and PR-519 in human plasma (sodium heparin) by liquid chromatography atmospheric pressure ionization tandem mass spectrometry (LC-API/MS/MS) detection. PR-103, PR-371, PR-412, and PR-369, deuterated analogs of the corresponding analytes, were used as the internal standards. The lower limit of quantitation (LLOQ) for carfilzomib was 0.300 ng/mL and for PR-389, PR-413, and PR-519 was 0.500 ng/mL. The calibration curves were acceptable over a range of 0.300-300 ng/mL for carfilzomib and 0.500-500 ng/mL for PR-389, PR-413, and PR-519.

Quality control (QC) samples (three concentrations) prepared in control human plasma (sodium heparin) were analyzed to determine intra- and inter-assay accuracy and precision of the assay and were also used to assess analyte stability. Intra- and inter- assay accuracy values were within ±15% deviation from nominal concentration for all analytes. Intra- and inter-assay precision values were ≤15% for all analytes.

2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

The range of the standard curve for total carfilzomib concentrations is 0.3-300 ng/mL. It appears the upper limit of the standard curve is much smaller than then clinical the observed maximum concentrations of up to 2000 ng/mL.

2.6.6 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

See section 2.6.5 above.

2.6.7 What are the accuracy, precision, and selectivity at these limits?

The intra- and inter-assay accuracy values were within ±15% deviation from nominal concentration for all analytes. The intra- and inter-assay precision values were ≤15% for all analytes.

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/s/

BAHRU A HABTEMARIAM
06/06/2012

CHRISTINE E GARNETT
06/06/2012

JULIE M BULLOCK
06/06/2012

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 202-714 (0001)	**Reviewer:** Houda Mahayni, Ph.D.	
Submission Date:	September 26, 2011		
Division:	DHP	**Biopharmaceutics Team Leader:** Angelica Dorantes, Ph.D.	
Applicant:	ONYX Pharmaceuticals, Inc.		
Trade Name:	------	**Date Assigned:**	October 5, 2011
Generic Name:	Carfilzomib for Injection	**Date of Review:**	May 23, 2012
Indication:	Multiple Myeloma	**Type of Submission:** Original NDA	
Formulation/strengths	Injection/(60 mg/vial)		
Route of Administration	Intravenous		

SUBMISSION:

The Applicant submitted a 505 (b) (1) NDA for carfilzomib, a proteasome inhibitor, for the treatment of multiple myeloma. Carfilzomib is administered intravenously (IV) slowly over 2 to 10 minutes, twice weekly on consecutive days for 3 weeks, followed by a 12-day rest period.

Over the course of clinical development, the Applicant developed 2 injectable dosage forms, Carfilzomib Injection (frozen solution drug product), and Carfilzomib for Injection (lyophilized drug product). The Carfilzomib Injection dosage form is a sterile frozen solution in a single-use vial that contains 2 mg/mL carfilzomib, (b) (4) sulfobutylether beta-cyclodextrin (SBECD, Captisol®), and (b) (4) citrate (b) (4) The Carfilzomib for Injection dosage form is also a sterile single-use vial with lyophilized powder, which upon reconstitution with Water for Injection (WFI) also contains 2 mg/mL carfilzomib, (b) (4) SBECD, and (b) (4) citrate (b) (4). Therefore, upon reconstitution, the concentration of carfilzomib and excipients in the reconstituted solution from Carfilzomib for Injection is the same as Carfilzomib Injection.

Carfilzomib Injection was used in the early Phase 1 studies. However, Carfilzomib for Injection was used in late Phase 2 and Phase 3 studies and is the intended commercial presentation.

Carfilzomib for Injection drug product lots used in the pivotal clinical study (PX-171-003A1) were manufactured a (b) (4) and the primary stability lots were manufactured at (b) (4) (b) (4)), the proposed commercial manufacturing site.

The Biopharmaceutics review will focus on evaluating the manufacturing site change.

BIOPHARMACEUTIC INFORMATION:

Carfilzomib for Injection is a sterile injection, powder, lyophilized, for solution. It is provided in a single-use vial (60 mg/vial). Prior to use, each vial is reconstituted with 29 mL of sterile Water for Injection to provide up to 60 mg deliverable dose as 2 mg/mL carfilzomib solution for intravenous administration.

The quantitative composition of Carfilzomib for Injection is summarized in Table 1.

Table 1: Composition of Carfilzomib for Injection

Ingredients	Function	Amount/Vial (Percent)	Amount/Vial (mg)
Carfilzomib	Active pharmaceutical ingredient	(b) (4)	
Sulfobutylether Beta-cyclodextrin	(b) (4)		
Anhydrous Citric Acid, USP, Ph. Eur.			
Sodium Hydroxide, NF	pH adjustment		
(b) (4)	(b) (4)		

Abbreviations: NF = National Formulary; Ph. Eur. = European Pharmacopoeia; USP = United States Pharmacopeia; — (b) (4)

(b) (4)

To assess the manufacturing site change, the Applicant compared lots manufactured at both sites (b) (4) Table 2 lists the lots compared and includes the drug substance (DS) lot used, target drug product (DP) scale, DP manufacturing site, DP date of manufacture, and the pivotal clinical study number or primary stability study used of these lots.

Table 2: Lots Manufactured at (b) (4) Used for Comparison

DP Lot	DS Lot	Target DP Scale (L)	DP Manufacturing Site	DP Manufacture Date	Pivotal Clinical Study No. or Primary Stability Use
(b) (4) 1459457	(b) (4) PR171FB0703, -PR171FB704	65	(b) (4)	February 2008	PX-171-003A1
1484728	PR171FB0703, -PR171FB705	65		July 2008	PX-171-003A1
1615085	(b) (4) 263/08-PX3	65		August 2008	PX-171-003A1
1625483		130		December 2008	PX-171-003A1
A60011		90		February 2010	Primary Stability
A60571	529/08-PX3	90		May 2010	Primary Stability
A61343		90		June 2010	Primary Stability

The Applicant compared lots manufactured at both (b) (4) to ensure that the investigational product and future commercial product are comparable. The Applicant evaluated several attributes including product formulation and manufacturing equipment and facility. The Applicant evaluated the acceptance criteria for the comparability assessment and the results are listed in Table 3 below.

Table 3: Comparability Assessment- Summary of Evaluated Biopharmaceutics Attributes with Acceptance Criteria

Category	Attribute	Acceptance Criteria	Results	Assessment
	DP Formulation	No change in composition of DP formulation and no change to ratios of excipients to DS and DP	The DP formulation in the (b) (4) lots contains (b) (4) carfilzomib, (b) (4) (b) (4) SBECD, and (b) (4) citric acid on a per vial basis. Ratios of excipients to DS are the same in bulk solution and result in the same DP formulation after lyophilization.	Comparable
	Compounding, Filing, and Lyophilization equipments	Compounding, filing, and lyophilization equipments are of similar design and operating principles	The compounding, filing, and lyophilization equipments are comparable. Change to fill weight did not impact product formulation or carfilzomib content per vial. Change in cycle parameter have no impact on lyophilized cake characteristics.	Comparable

The Applicant performed statistical analysis on lot release results obtained from comparing the (b) (4) sites to determine if there was evidence of differences in product quality between the two sites. The Applicant used non-parametric test (Wilcoxon Test) using SAS Version No. 9.1.3. The P values and assessment of the results are provided in Table 4. For P-values > 0.05, there is no evidence of any difference between the (b) (4) results. Therefore, the results are considered comparable between the manufacturing sites. P-values ≤ 0.05 are statistically significant, and if a test result was found significant, further assessment was performed.

Table 4: Comparison and Assessment of Lot Release Results

Test	Acceptance Criteria[a]	Site	Minimum	Average	Maximum	p-Value[b]	Assessment
pH	(b) (4)					Not performed	Comparable
Reconstitution Time (min)						Not performed	Comparable
Assay (% LC)						0.2286	Comparable
Uniformity of Dosage Units, Weight Variation						Not performed	Comparable
Water Content						0.0571	Comparable
Particulate Matter (b) (4)						Not performed	Comparable
Particulate Matter (b) (4)						Not performed	Comparable

[a] Proposed commercial acceptance criteria

[b] For p-values > 0.05, there is no evidence of any difference between the (b) (4) results; the results appear to be comparable between the companies.

LC: Label claim

All lot release results for DP manufactured at (b) (4) met the specification acceptance criteria at release.

RECOMMENDATION:

The drug product lots manufactured at both sites are comparable. The acceptance criteria were met.

From the Biopharmaceutics viewpoint, NDA 202-714 for Carfilzomib for Injection is recommended for APPROVAL.

Signature
Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Signature
Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: *NDA 202-714 DARRTS*

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/s/

HOUDA MAHAYNI
05/24/2012

ANGELICA DORANTES
05/24/2012

BIOPHARMACEUTICS FILING REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 202-714 (0001)	**Reviewer:** Houda Mahayni, Ph.D.	
Division:	DHP		
Applicant:	ONYX Pharmaceuticals, Inc.	**Biopharmaceutics Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	----		
Generic Name:	Carfilzomib for Injection	**Date Assigned:**	October 5, 2011
Indication:	Multiple Myeloma	**Date of Review:**	November 7, 2011
Formulation	Injection		
Route of Administration	Intravenous		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp Date**	**Date of informal/Formal Consult**	**PDUFA DATE**
September 26, 2011	September 27, 2011	October 5, 2011	March 27, 2012
Type of Submission:	Original NDA		
Type of Consult:	Manufacturing Site Change---**FILING REVIEW**		

REVIEW SUMMARY:

The Applicant submitted a 505 (b) (1) NDA for carfilzomib, a proteasome inhibitor, for the treatment of multiple myeloma. Carfilzomib is administered intravenously (IV) slowly over 2 to 10 minutes, twice weekly on consecutive days for 3 weeks, followed by a 12-day rest period. The Applicant stated that this NDA was granted a rolling review as part of the Fast Track Designation.

Over the course of clinical development, the Applicant developed 2 injectable dosage forms, Carfilzomib Injection (frozen solution drug product), and Carfilzomib for Injection (lyophilized drug product). The Carfilzomib Injection dosage form is a sterile frozen solution in a single-use vial that contains 2 mg/mL carfilzomib, (b) (4) sulfobutylether beta-cyclodextrin (SBECD, Captisol®), and (b) (4) citrate (b) (4). The Carfilzomib for Injection dosage form is also a sterile single-use vial with lyophilized powder, which upon reconstitution with Water for Injection (WFI) also contains 2 mg/mL carfilzomib, (b) (4) SBECD, and (b) (4) citrate (b) (4). Therefore, upon reconstitution, the concentration of carfilzomib and excipients in the reconstituted solution from Carfilzomib for Injection is the same as Carfilzomib Injection.

Carfilzomib Injection was used in the early Phase 1 studies. However, Carfilzomib for Injection was used in late Phase 2 and Phase 3 studies and is the intended commercial presentation.

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Anhydrous Citric Acid, USP, Ph. Eur.			
Sodium Hydroxide, NF	pH adjustment		
(b) (4)	(b) (4)		

Abbreviations: NF = National Formulary; Ph. Eur. = European Pharmacopoeia; USP = United States Pharmacopeia; —(b) (4)

(b) (4)

Carfilzomib for Injection drug product lots used in the pivotal clinical study (PX-171-003A1) were manufactured at (b) (4) and the primary stability lots were manufactured a (b) (4) the proposed commercial manufacturing site. The applicant compared lots manufactured at both (b) (4) to ensure that the investigational product and future commercial product are comparable.

The biopharmaceutics review will focus on the manufacturing site change.

RECOMMENDATION:

The ONDQA/biopharmaceutics team has reviewed NDA 202-714(0001) for filing purposes. We found this NDA filable from Biopharmaceutics perspective.

Houda Mahayni, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: NDA 202-714, DMesmer, SPope Miksinski, KBengtson, JBrown, JJee, MAdams

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HOUDA MAHAYNI
11/09/2011

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