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RESEARCH**

APPLICATION NUMBER:

202714Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: NDA 202714/Kyprolis (carfilzomib)

PMR 1 Description:

Conduct a randomized controlled trial per Protocol PX-171-009, as finalized, to compare carfilzomib-lenalidomide dexamethasone with lenalidomide dexamethasone in a population of patients with myeloma, whose disease has relapsed after previous response to at least one but not more than three prior therapies, to assess efficacy and safety. Patients' disease is required to show evidence of progression after prior therapy. The trial includes 792 patients. The randomization will balance known important prognostic factors. The goal of the trial is to evaluate the primary endpoint of progression-free survival (PFS) for the carfilzomib containing arm, as determined by an independent review committee blinded to the treatment given.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>01/2010</u>
	Study/Trial Completion:	<u>12/2013</u>
	Final Report Submission:	<u>06/2014</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Requirement under subpart H to verify clinical benefit

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

RCT in patients with myeloma, PFS endpoint, trial design to isolate the carfilzomib effect.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
RCT for efficacy (and safety)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____ RCK
(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: NDA 202714/ Kyprolis (carfilzomib)

PMR 2 Description:

Conduct a randomized clinical trial in patients receiving carfilzomib to identify and characterize the cardiac toxicities associated with carfilzomib. You have agreed to conduct this trial as a cardiac sub-trial within your ongoing Protocol 2011-003 (ENDEAVOR). 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.

The main trial protocol (2011-003) must require a baseline resting ECG and transthoracic ECHO to assess left ventricular (LV) function on all patients. If transthoracic ECHO is not available at some sites, MUGA will be acceptable for baseline screening LVEF evaluation. For the cardiac sub-trial, a subset of patients from the main trial will be assessed for LV and right ventricular (RV) function with transthoracic ECHO (or MUGA for those sites using MUGA at baseline) periodically throughout trial treatment and at the time of the End-of-Treatment visit, using similar test procedures and equipment to allow serial intra-patient comparisons. This cardiac sub-trial must include a minimum of 100 patients and a maximum of 300 patients total (50 to 150 patients per treatment arm). Specific details regarding the interpretation of LVEF changes must be pre-specified and outlined in the SAP for this cardiac toxicity trial. For the sub-trial, readers of the ECHOs/MUGAs must be blinded to the protocol treatment given.

In addition, any patient in the main trial who has a cardiac adverse event (AE) that is considered a clinically significant AE must have an ECHO performed to assess LV and RV function as part of the evaluation of that AE.

Submit a complete cardiac sub-trial protocol for review and concurrence before commencing the sub-trial.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>01/2013</u>
	Study/Trial Completion:	<u>11/2015</u>
	Final Report Submission:	<u>05/2016</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

Unmet need

- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Evaluate the cardiac safety of the drug in a controlled clinical trial in patients receiving carfilzomib to identify and characterize the cardiac toxicities associated with carfilzomib

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

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

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a prospective randomized controlled clinical trial in patients receiving carfilzomib to identify and characterize the cardiac toxicities associated with carfilzomib

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
RCT for efficacy (and safety)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
 - _____
Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____ RCK
(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: NDA 202714/Kyprolis (carfilzomib)

PMR 3 Description:

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. You have agreed to conduct this pulmonary sub-trial within your ongoing Protocol 2011-003. On all patients enrolled in the main trial, 2011-003, during screening, obtain a baseline transthoracic ECHO to estimate the pulmonary artery pressures and to assess right ventricular size, thickness, and function, and to serve as the baseline ECHO for later comparisons on all patients. In the pulmonary sub-trial, among a minimum of 100 patients and a maximum of 300 patients total (50 to 150 patients per treatment arm), assess this sub-group periodically for pulmonary artery pressures and right ventricular function with repeat transthoracic ECHO throughout trial 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 in the main trial also, to include at least the following: time course of onset and resolution, oximetry and/or blood gases, and consultation with a pulmonary specialist, when clinically appropriate, to provide further documentation of the nature of the emergent condition. Document the response to oxygen supplementation and other treatment measures. For the sub-trial, readers of the ECHOs/MUGAs must be blinded to the treatment given.

In the pulmonary sub-trial protocol, 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, for all patients enrolled in the main trial, any patient who has a cardiac or pulmonary AE that is considered a clinically significant AE must have a follow-up ECHO at the time of the event to assess LV, RV, and pulmonary artery function. Submit a complete pulmonary sub-trial protocol for review and concurrence before commencing the sub-trial.

PMR/PMC Schedule Milestones:

Final Protocol Submission:

01/2013

Study/Trial Completion:

11/2015

Final Report Submission:

05/2016

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Evaluate the pulmonary safety of the drug in a controlled clinical trial in patients receiving carfilzomib to identify and characterize the cardiac toxicities associated with carfilzomib

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

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

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a prospective randomized controlled clinical trial in patients receiving carfilzomib to identify and characterize the cardiac toxicities associated with carfilzomib

Required

Observational pharmacoepidemiologic study

Registry studies

Primary safety study or clinical trial

Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

Thorough Q-T clinical trial

Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

Pharmacokinetic studies or clinical trials

Drug interaction or bioavailability studies or clinical trials

Dosing trials

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

RCT for efficacy (and safety)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

RCK

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: NDA 202714/Kyprolis (carfilzomib)

PMR 4 Description: Conduct a clinical trial (2011-003 ENDEAVOR) to evaluate the safety of a 30-minute intravenous infusion of carfilzomib at the dose of 20/56 mg/m² in patients with multiple myeloma.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	03/2012
	Study/Trial Completion:	11/2015
	Final Report Submission:	05/2016

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Newer information suggests that carfilzomib may have improved safety and efficacy characteristics if infused over 30-minutes intravenously at the dose of 20/56 mg/m² in patients with multiple myeloma.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

We expect that the drug will be used in practice on a different schedule than the schedule tested for the approval trial. The safety of the newer schedule is not established.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

RCT or single-arm trial sufficient to characterize safety of the 30 minute schedule with the higher drug doses (20/56 mg/m ²) regimen.
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Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____ RCK
(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: NDA 202714/Kyprolis (carfilzomib)

PMR 5 Description: Conduct a clinical trial (PX-171-007) to evaluate the safety of a 30-minute intravenous infusion of carfilzomib at the dose of 20/56 mg/m² in patients with multiple myeloma.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>08/2007</u>
	Study/Trial Completion:	<u>06/2014</u>
	Final Report Submission:	<u>12/2014</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Newer information suggests that carfilzomib may have improved safety and efficacy characteristics if infused over 30-minutes intravenously at the dose of 20/56 mg/m² in patients with multiple myeloma.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

We expect that the drug will be used in practice on a different schedule than the schedule tested for the approval trial. The safety of the newer schedule is not established.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

RCT or single-arm trial sufficient to characterize safety of the 30 minute schedule with the higher drug doses (20/56 mg/m ²) regimen.
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Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____ RCK
(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: NDA 202714/Kyprolis (Carfilzomib)

PMR 6 Description:

Conduct a clinical trial in patients with hepatic impairment to assess safety and PK characteristics of carfilzomib administered as a 30 minute infusion. The number of patients enrolled in the trial should be sufficient to detect PK differences that would warrant dosage adjustment recommendations in the labeling. The duration of the trial should be sufficient (several cycles) to reasonably characterize potential safety issues. The PK sampling scheme should be optimized to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol. Submit your protocol for Agency review and concurrence prior to initiation.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>03/2013</u>
	Study/Trial Completion:	<u>12/2015</u>
	Final Report Submission:	<u>05/2016</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Assess safety in hepatic impairment pts

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Assess safety in hepatic impairment pts

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
RCT for efficacy (and safety)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____ RCK
(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: NDA 202714/Kyprolis (carfilzomib)

PMR 7 Description:

Conduct one or more clinical trials including Phase 3 Protocol 2011-003, supplemented as needed by an additional trial, to evaluate the PK, safety, and efficacy of carfilzomib in patients with varying degrees of renal impairment and those on chronic dialysis 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 who receive carfilzomib doses of 20/56 mg/m² using the 30 minute infusion as planned in your upcoming Phase 3 trial Protocol 2011-003. Collect PK samples following carfilzomib doses of 56 mg/m² or highest clinical dose in the protocol. Submit your protocol for Agency review and concurrence prior to initiation.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>03/2013</u>
	Study/Trial Completion:	<u>12/2015</u>
	Final Report Submission:	<u>05/2016</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____ RCK
(signature line for BLAs)

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/s/

KAREN E BENGTSON
07/19/2012

ROBERT C KANE
07/19/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Final Label and Labeling Review

Date: June 12, 2012

Reviewer: Kimberly DeFronzo, RPh, MS, MBA
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, Pharm.D., BCPS
Division of Medication Error Prevention and Analysis

Drug Name(s) and Strength(s): Kyprolis (Carfilzomib) for Injection
60 mg per vial

Application Type/Number: NDA 202714

Applicant/Sponsor: Onyx Pharmaceuticals, Inc.

OSE RCM #: 2011-3708

*** This document contains proprietary and confidential information that should not be released to the public.***

1. INTRODUCTION

This review evaluates the revised container label and carton labeling for Kyprolis (Carfilzomib) for Injection 60 mg per vial submitted in response to the Division of Medication Error Prevention and Analysis's (DMEPA's) previous comments to the Applicant in OSE review #2011-3708, dated February 3, 2012.

This review also evaluates the [REDACTED] (b)(4) that the Applicant proposes to be used on packaging of commercial products used for their Patient Assistance Program. This program is being made available for patients who are uninsured or have no insurance coverage for Carfilzomib for Injection and meet specific financial eligibility criteria.

2. METHODS AND MATERIALS

DMEPA reviewed the revised container label (submitted on May 22, 2012) and carton labeling (submitted May 15, 2012) and compared them against our recommendations made in OSE review #2011-3708 (see Appendix A for images of the revised container label and carton labeling).

Additionally, DMEPA reviewed the [REDACTED] (b)(4) submitted by the Applicant on May 22, 2012 (see Appendix B for image).

3. RESULTS

Review of the revised label and labeling determined that all previous recommendations were implemented by the Applicant.

[REDACTED] (b)(4)

4. CONCLUSIONS AND RECOMMENDATIONS

The revised container labels and carton labeling adequately addressed our concerns from a medication error perspective; thus, we do not have any further comments.

Additionally, we have not identified any safety concerns with the proposed [REDACTED] (b)(4)

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Sue Kang, at 301-796-4216.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KIMBERLY A DE FRONZO
06/12/2012

IRENE Z CHAN
06/12/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: May 25, 2012

To: Karen Bengtson, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Nisha Patel, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)

Subject: Comments on draft labeling (Package Insert) for Kyprolis™
(carfilzomib) for Injection
NDA 202714

In response to your consult dated November 14, 2011, we have reviewed the draft Package Insert (PI) for Kyprolis and offer the following comments. DPDP has made these comments using the version dated May 18, 2012. Please note that comments on the draft carton and container labels were provided on May 10, 2012.

Section	Statement from draft	Comment
Highlights, Dosage and Administration		Do premedication instructions with dexamethasone need to be included in this section or cross-referenced?
Highlights, Warnings and Precautions	(b) (4)	Please consider including the following additional risk information from Section 5.2 the full PI: “Death due to cardiac arrest has occurred within a day of KYPROLIS administration.”
Highlights, Warnings and Precautions	Tumor lysis syndrome: Monitor for and treat promptly. (5.3)	Please consider including the following additional risk information from Section 5.3 of the full PI to communicate how to prevent TLS: “Prior to receiving KYPROLIS, ensure that patients are well hydrated.”

Section	Statement from draft	Comment
Highlights, Warnings and Precautions	(b) (4)	(b) (4)
2.4 Dose Modifications Based on Toxicities 5 WARNINGS AND PRECAUTIONS		Please ensure that all relevant “Warnings and Precautions” from Section 5 that require dose modifications are listed in Table 2 (Section 2.4). Similarly, please ensure that the “Warnings and Precautions” in Section 5 are only cross-referenced to Section 2.4 if Table 2 describes that specific Warning or Precaution.
2.4 Dose Modifications Based on Toxicities		(b) (4)
2.4 Dose Modifications Based on Toxicities		Should the toxicity “Dyspnea” state (b) (4) to ensure consistency with the “Warnings and Precautions” section of the PI?
(b) (4)		
12.1 Mechanism of Action	(b) (4)	Is this statement supported by substantial evidence (emphasis added)? Since it refers to animal data and the terms (b) (4), (b) (4), and “delayed” are promotional in tone, the sponsor could use this statement to overstate the efficacy of the drug. Please consider deleting these terms and quantifying data if available.
12.3 Pharmacokinetics	Carfilzomib was rapidly and extensively metabolized. Following intravenous administration of doses $\geq 15 \text{ mg/m}^2$, carfilzomib was rapidly cleared from the systemic circulation with a half-life of ≤ 1 hour on Day 1 of Cycle 1.	Are these statements supported by substantial evidence (emphasis added)? The terms “rapidly”, “modest”, “minor”, and “marginal” are promotional in tone and could be used to overstate the efficacy of the drug. Please consider deleting these terms and quantifying data if available.

Section	Statement from draft	Comment
	<p>In an in vitro study using human liver microsomes, carfilzomib showed modest direct and time-dependent inhibitory effect on human cytochrome CYP3A4/5.</p> <p>Cytochrome P450-mediated mechanisms play a minor role in the overall metabolism of carfilzomib.</p> <p>P-gp: Carfilzomib is a P-gp substrate and showed marginal inhibitory effects on P-glycoproteins (P-gp) in a Caco-2 monolayer system.</p>	

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/s/

NISHA PATEL
05/25/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: May 10, 2012

To: Karen Bengtson, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Nisha Patel, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)

Subject: Comments on carton and container labels for Kyprolis™
(carfilzomib) for Injection
NDA 202714

In response to your labeling consult dated November 14, 2011, and follow-up e-mail dated May 9, 2012, we have reviewed the draft carton label and draft container label for Kyprolis™ (carfilzomib) for Injection. DPDP has made these comments using the carton and container labels submitted to DPDP on May 9, 2012. Please note that comments for the draft package insert will be provided at a later date when a substantially complete labeling is available.

DPDP does not have any comments on the draft carton and container labels at this time.

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/s/

NISHA PATEL
05/10/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

MEMORANDUM

Date: May 3, 2012

From: Elizabeth L. Durmowicz, MD, Medical Officer

Through: Hari Cheryl Sachs, MD, Team Leader
Lisa Mathis, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Thomas Herndon and Nicole Gormley, Clinical Reviewers
Al Deisseroth, MD, Clinical Team Leader
Division of Hematology Products (DHP)

Re: pediatric labeling

Sponsor: Onyx Pharmaceuticals, Inc.

Drug: carfilzomib

Route of Administration: intravenous

Indication (proposed): treatment of patients with relapsed and refractory multiple myeloma

Application: NDA 202714

Submission Dates: January 31, 2011 and September 26, 2011

Consult Question: DHP requests pediatric review of the proposed labeling for the package insert.

Materials Reviewed:

- Proposed labeling submitted with original NDA September 26, 2011 (EDR Location: [\\CDSESUB1\EVSPROD\NDA202714\0001](#))

Brief Background:

On September 26, 2011 the Sponsor submitted an original New Drug Application for carfilzomib, a proteasome inhibitor and new molecular entity, 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.

Carfilzomib was granted orphan designation for the indication of multiple myeloma on January 18, 2008.

Reviewer Comment:

In the January 31, 2011 submission, the Sponsor states their intent to request a waiver of pediatric studies under PREA; however, because carfilzomib has orphan status for multiple myeloma, PREA does not apply.

PROPOSED SPONSOR LABELING (Submitted September 26, 2011):

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of TRADENAME in pediatric patients have not been established.

(b) (4)

Reviewer Comment:

Because carfilzomib has not been studied and is not approved for use in the pediatric population, the proposed language for the Pediatric Use subsection, "The safety and effectiveness of TRADENAME in pediatric patients have not been established", is acceptable. Although review of the literature and clinical trials.gov did not identify any pediatric investigations with carfilzomib, if the Division identifies a unique risk in a particular pediatric population from clinical or nonclinical data, this risk should be described in the Pediatric Use section.

When a product is not approved in the pediatric population, all relevant pediatric information should be included only in the Pediatric Use subsection (8.4) to avoid an implied indication. However, if a pediatric safety risk is identified, this safety information must not only be described in 8.4, but also included in the CONTRAINDICATIONS section and/or the WARNINGS AND PRECAUTIONS section, as required by regulation (21 CFR 201.57(c)(9)(iv)(E)).

(b) (4)

Conclusions and Recommendations:

Assuming that no specific pediatric safety risk has been identified with carfilzomib, the proposed language for the Pediatric Use subsection is acceptable [REDACTED] (b) (4)

PMHS participated in the labeling meeting on May 3, 2012, and communicated the above recommendations.

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/s/

ELIZABETH L DURMOWICZ
05/03/2012

HARI C SACHS
05/08/2012

LISA L MATHIS
05/10/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: April 13, 2012

TO: Karen Bengtson, Regulatory Project Manager
Thomas Herndon, M.D., Medical Officer
Albert Deisseroth, M.D., Team Leader
Division of Hematology Products (DHP)

FROM: Anthony Orenca, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202714

APPLICANT: Onyx Pharmaceuticals, Inc.

DRUG: carfilzomib
NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Standard Review
INDICATION: Relapsed and refractory multiple myeloma

CONSULTATION REQUEST DATE: June 8, 2012
DIVISION ACTION GOAL DATE: July 27, 2012
PDUFA DATE: July 27, 2012

I. BACKGROUND:

Carfilzomib as a single agent has demonstrated clinical activity in relapsed and refractory multiple myeloma and non-Hodgkins lymphoma patients. The drug is a selective proteasome inhibitor that binds most specifically to the chymotrypsin-like protease.

A single adequate study was submitted in support of this NDA submission.

Protocol PX-171-003

This Phase 2 study was conducted as a multicenter, open-label, single-arm trial in approximately 20 centers in North America. The primary objective was to evaluate the best Overall Response Rate (ORR), defined as stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) for two cycles of carfilzomib in subjects with multiple myeloma who previously received bortezomib and either thalidomide or lenalidomide, relapsed after two or more therapies, and were refractory to the most recently received therapy. A 25% or lesser response, progression during salvage therapy or within 60 days of completion of salvage therapy is characterized as refractory disease in multiple myeloma.

Carfilzomib was evaluated for its best overall response rate at the end of two cycles, assessed as stringent complete response, complete response, very good partial response, or partial response. Stringent complete response was defined as absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence and monoclonal free light chain ratio findings (Note: An abnormal ratio reflecting presence of an abnormal clone was κ/λ of $> 4:1$ or $< 1:2$). Complete response was defined as negative immunofixation on the serum and urine, disappearance of any soft tissue plasmacytomas, and $\leq 5\%$ plasma cells in bone marrow. Very good partial response was defined as serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein with urine M-protein level < 100 mg per 24 hours. Partial response was defined by a $\geq 50\%$ reduction of serum M-protein and reduction in 24 hour urinary M-protein by $\geq 90\%$ or to < 200 mg per 24 hours.

The primary analysis objective was to estimate the best overall response rate in evaluable subjects with disease measurable via protein electrophoresis at the end of two cycles of treatment. Evaluable subjects with insufficient data for an assessment of efficacy were counted as non-responders in the primary efficacy analysis.

II. RESULTS:

Name of CI City, State	Protocol/Study Site	Insp. Date	Final Classification*
Sagar Lonial, M.D. Atlanta, GA	Protocol PX171-003 Site #11	January 4-23, 2012	VAI
David Siegel, M.D. Hackensack, NJ	Protocol PX171-003 Site #15	January 10 to 27, 2012	VAI
Ravi Vij, M.D. St. Louis, MO	Protocol PX171-003 Site #18	December 12-19, 2011	VAI
Onyx Pharmaceuticals Inc. Houston, TX	Sponsor	January 6 to 20, 2012	VAI

*Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations from regulations. Data unreliable/Critical findings may affect data integrity.
Preliminary= The Establishment Inspection Report (EIR) has not been received and findings are based on preliminary communication with the field.

CLINICAL STUDY SITE INVESTIGATOR

1. Sagar Lonial, M.D., Ph.D. /Site #11

Atlanta, GA

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from January 4-23, 2012. A total of 18 subjects were screened, 15 subjects were enrolled and 3 subjects completed the study. There were 6 documented deaths among the 15 subjects enrolled during the study. A 100% verification of the informed consent forms was done. An audit of 7 subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents, for randomized subjects whose records were audited, were verified against the case report forms and NDA subject line listings and no discrepancies were noted. There was no under-reporting of serious adverse events.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection. Minor regulatory observations of relevance included the following:

- (a) For Subject 3-11-266, the latest informed consent version approved by the IRB on 3/17/2009 was not used; instead the informed consent form dated 10/22/2008 was used.
- (b) For Subject 3-11-258's Cycle #1 Day #3 and Day #10 of treatment, the clinical site sent serum chemistry tests to laboratories not listed on the Form FDA 1572.

On March 20, 2012 DHP's medical team explained to OSI that these findings were considered minor.

d. Data acceptability/reliability for consideration in the NDA review decision.

The regulatory deficiencies noted above, related to lack of adherence to the study protocol were considered minor or sporadic in nature, and do not significantly impact overall study data reliability. Data submitted by this clinical site appear acceptable for this specific indication.

2. David Siegel, M.D./Site #15

Hackensack, NJ

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from January 10 to 27, 2012. A total of 43 subjects were screened, 39 subjects were enrolled, and 8 subjects completed the study. [Note: 23 patients had disease progression and did not complete the study, 3 withdrew informed consent, and 5 subjects experienced adverse events and withdrew from the study.] A 100% review of screened subjects' informed consent forms was performed. An audit of 24 of 43 screened subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and NDA subject line listings. In general, this clinical site appeared to be in compliance with Good Clinical Practices.

A Form FDA 483 was issued at the end of the inspection. Essentially, these observations were related to inaccurate or incomplete reporting processes and deficiencies in not conducting an investigation according to the research plan. Selected minor regulatory observations of clinical relevance included the following examples:

(a) Two serious adverse events, for Subjects 3-15-460 and 3-15-464, were not reported within 24 hours of knowledge, but 48 hours to 1 week later, respectively.

(b) Plasmacytoma screening was reported as “not done” on their Case Report Forms for Subjects 3-15-428, -433, -438, -440, -442, -443, -444, -462, -468, -471 and -472.

However, these observations were contained in the principal investigator’s completed dictation notes.

(c) For Subject 3-15-436, the Extent of Disease Measurement CRF reported an SPEP M-spike value of 1.37 g/dL, but Quest laboratories reported a value of 1.27 g/dL, for the specimen collected on July 7, 2009.

The List of Inspectional Observations was discussed at length with DHP’s medical team on March 20 and 21, 2012. Although these observations appeared to be regulatory deficiencies, these findings were considered not critical or clinically significant by OSI or DHP.

d. Data acceptability/reliability for consideration in the NDA review decision.

The regulatory deficiencies noted above, related to lack of adherence to the study protocol are considered sporadic or minor in nature and do not significantly impact overall study data reliability. Data submitted by this clinical site appear acceptable for this specific indication.

3. Ravi Vij, M.D. /Site #18

St. Louis, MO

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from December 14 to 19, 2011. A total of 27 subjects were screened, 22 subjects were enrolled, and 21 subjects completed the study. There was no under-reporting of serious adverse events to the Sponsor. A 100% review of screened subjects’ informed consent forms was performed. An audit of subjects’ records was conducted in 100% of records for inclusion and exclusion criteria, and 75% of records for the primary efficacy endpoint. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents, for randomized subjects whose records were audited, were verified against the case report forms and NDA subject line listings and no discrepancies were found.

At the end of the inspection, a Form FDA 483 was issued. Although reported to Sponsor, the clinical site failed to report five serious adverse events (SAEs) within 7 calendar days to the IRB, as per IRB requirements. These minor regulatory observations of relevance were all related to the site's internal mechanism of reporting SAEs to the IRB, and included the following:

- (a) Subject 3-18-637's SAE report form was completed on September 22, 2008, but not reported to the IRB until October 6, 2008;
- (b) Subject 3-18-645's SAE report form was completed on (i) April 16, 2009, but not reported to the IRB until May 1, 2009; (ii) April 22, 2009, but not reported to the IRB until May 4, 2009 and (iii) October 20, 2009 but not reported to the IRB until November 3, 2009 for these multiple hospitalizations, and
- (c) Subject 3-18-644's SAE report form was completed on March 25, 2009, but not reported to the IRB until April 13, 2009.

The List of Inspectional Observations was discussed with DHP's medical team on March 20, 2012. Although these observations appeared to be regulatory deficiencies, these findings were considered not critically significant by OSI or DHP.

d. Data acceptability/reliability for consideration in the NDA review decision.

The minor regulatory deficiencies noted above, related to lack of adherence to the study protocol are considered sporadic in nature and do not impact significantly the overall study data reliability. Data submitted by this clinical site appear acceptable for this specific indication.

SPONSOR

4. Onyx Pharmaceuticals, Inc.

San Francisco, CA

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.810, from January 6 to 20, 2011.

Documents related to Site #11, Site #15 and Site #46, respectively were reviewed. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed FDA form 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

b. Limitations of inspection

None.

c. General observations/commentary

A Form FDA 483, Inspectional Observations, was issued at the end of inspection. The ORA field staff found the following relevant items:

(a) Deficiencies in Sponsor conducting an investigation in accordance with the general investigational plan and protocols as specified in the IND. Specifically, there were inadequate Sponsor procedures in place to review protocol deviations identified by the CRO.

Medical Officer's comments: The Sponsor did not have adequate mechanisms or a plan to address repeated protocol deviations reported by the clinical monitors, but responded that they have implemented an updated corrective or preventive action plan to address these sporadic and non-critical findings. This plan includes a clear documentation and escalation process for monitors who encounter protocol deviations at the site level and will also ensure adequate and ongoing review of deviations and oversight of the deviation escalation plan by Onyx study team leads.

(b) Sponsor did not provide clinical investigators with information needed to conduct the study properly. Specifically, protocol or good clinical practices training records for numerous sub-investigators at clinical Sites #11, #15, and #18 were not documented adequately.

Medical Officer's comments: Although there appears to be lack of training of sub-investigators, the Sponsor is taking remediation steps to prevent its recurrence. Further, given that the efficacy endpoints were objectively quantified as serum and urine laboratory or bone marrow measurement, with no critical evidence of under-reporting of serious adverse events by Sponsor in their oversight, there appeared to be no significant impact on data reliability.

Onyx (Sponsor) responded to the Form FDA 483, List of Inspectional Observations, in their February 2, 2012 letter. In summary, the Sponsor agreed to revise its standard operating procedures dealing with protocol deviations, violations and waivers. As part of their corrective action plan, Onyx is in the process of implementing ongoing review and oversight of the protocol deviations. Onyx plans to review whether clinical sites are in compliance with the investigational research plan and include periodic checks of clinical site deviations to ensure site compliance with updated processes. Further, the firm will document training of all pertinent staff such as clinical sub-investigators, update clinical trial procedures, and assess current clinical trial monitoring plans.

d. Data acceptability/reliability for consideration in the NDA review decision.

The study appears to have been conducted adequately despite the minor or sporadic regulatory deficiencies observed. Data submitted by this sponsor appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For this Phase 2 open-label, single-arm study, three domestic clinical investigator sites and the application Sponsor were inspected in support of this application for Study Protocol PX-171-003. The regulatory deficiencies observed for Sagar Lonial, M.D. (Site #11), David Siegel, M.D. (Site #15) and Ravi Vij, M.D. (Site #18) appeared to be isolated, sporadic, minor or not critical in nature. Sponsor regulatory deficiencies were also considered minor and the Sponsor is in the process of implementing their corrective action plans. Based on review of inspectional findings for these clinical investigators, the study data collected appear generally reliable in support of the requested indication.

{See appended electronic signature page}

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/s/

ANTHONY J ORENCIA
04/13/2012

JANICE K POHLMAN
04/13/2012

TEJASHRI S PUROHIT-SHETH
04/13/2012

**Interdisciplinary Review Team for QT Studies Consultation:
QT Study Review**

IND or NDA	NDA 202714
Generic Name	Carfilzomib
Sponsor	Onyx Pharmaceuticals, Inc.
Indication	Relapsed and Refractory Multiple Myeloma
Dosage Form	Solution for i.v. Injection
Drug Class	Proteasome inhibitor
Therapeutic Dosing Regimen	Intravenous infusion administered over 2 to 10 min on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. Cycle 1: 20 mg/m ² Cycle 2 and beyond: 27 mg/m ²
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not Determined (36 mg/m ² was highest studied dose)
Submission Number and Date	SDN 002, 09/27/2011
Review Division	DHP

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No large change in QTc (i.e., >20 ms) was detected in this trial following administration of carfilzomib (15 mg/m², 20 mg/m² and 36 mg/m²). The largest upper bound of the 2-sided 90% confidence interval (CI) for the mean change from baseline was 35.3 ms, observed at 20 min post-dose on day 15 of cycle 1 for the dose of 36 mg/m². Because of the lack of demonstrated assay sensitivity, the results should be interpreted as having ruled out a mean effect of about 20 ms.

In the phase 2, open-label, single-arm study (PX-171-005), 50 patients with multiple myeloma and different levels of renal function received carfilzomib 15 mg/m². In another phase 1b/2, open-label, single-arm study (PX-171-007), 64 patients with solid tumors, multiple myeloma, or lymphoma received a dose of 20 mg/m² and 36 mg/m². Overall summary of findings are presented in Table 1 and Table 2.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Carfilzomib (15 mg/m², 20 mg/m²) in Study PX-171-005 (FDA Analysis)

Treatment	Cycle	Day	Time Post Dose (h)	ΔQTcF (ms)	90% CI (ms)
Carfilzomib 15 mg/m ²	1	1	24	3.96	(-2.7, 11)
Carfilzomib 15 mg/m ²	1	15	0.33	8.00	(-0.092, 16)
Carfilzomib 20 mg/m ²	2	15	0.33	9.44	(1.5, 17)

Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Carfilzomib (20 mg/m², 36 mg/m²) in Study PX-171-007 (FDA Analysis)

Treatment	Cycle	Day	Time Post Dose (h)	ΔQTcF (ms)	90% CI (ms)
Carfilzomib 20 mg/m ²	1	1	0.033	3.42	(0.6, 6.3)
Carfilzomib 36 mg/m ²	1	1	1.0	8.28	(2.6, 13.9)
Carfilzomib 36 mg/m ²	1	15	0.33	18.12	(0.9, 35.3)

The suprathreshold dose (36 mg/m²) produces mean C_{max} and AUC values of 1.4- and 1.6-fold the mean C_{max} and AUC for the therapeutic dose (27 mg/m²). The studied carfilzomib exposures appear to be greater than those for the predicted worst case scenario (severe renal impairment at the 27 mg/m² dose). At these concentrations there are no detectable prolongations of the QT-interval. It is expected from a phase 2 renal impairment study that the patients with severe renal dysfunction exhibit only 20% lower clearance. This is supported by PK data from patients with severe renal impairment at 15 mg/m² dose level, collected in this QT study. There is no accumulation because of short half-life of carfilzomib.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS TO THE REVIEW DIVISION

Sponsor did not submit ECGs related to the QT studies PX-171-005 and PX-171-007. We strongly recommend sponsor to submit the ECGs to the warehouse.

2 PROPOSED LABEL

2.1 SPONSOR PROPOSED LABEL

The sponsor did not propose any labeling statements pertaining to effect of carfilzomib on QT interval.

2.2 QT-IRT RECOMMENDED LABEL

We have the following label recommendations which are suggestions only. We defer the final labeling decisions to the review division.

The effect of single and multiple doses of carfilzomib 15, 20 and 36 mg/m² on QTc interval was evaluated in a single-arm, open-label study in 114 patients with relapsed solid tumors, multiple myeloma, or lymphoma. No large changes in mean QTc interval (i.e., >20 ms) from baseline based on Fridericia correction method were detected in this study. Because of lack of positive control in the study, small increase in mean QTc interval (i.e., <10 ms) cannot be ruled out. The dose of 36 mg/m² is adequate to represent the high exposure clinical scenario.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Carfilzomib (formerly PR-171) is a tetrapeptide epoxyketone-based irreversible inhibitor of the chymotrypsin-like (CT-L) activity of the 20S proteasome. Proteasome inhibition leads to the accumulation of polyubiquitinated protein substrates within cells and to the selective induction of apoptosis in malignant cells while sparing non-malignant cells. Carfilzomib is currently being developed for treatment of hematologic malignancies and solid tumor malignancies.

3.2 MARKET APPROVAL STATUS

Carfilzomib is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

From IB (August 2011)

“The effects of carfilzomib on the human ether-à-go-go-related gene (hERG), an in vitro surrogate for the delayed rectifier current (IKr) in human ventricles, were also studied. An IC₅₀ for the inhibitory effect of carfilzomib on hERG potassium current was established at 2.1 μM.”

Reviewer’s Comments: Carfilzomib inhibits hERG current, the IC₅₀ is within the range of the human C_{max} exposure achieved with a supratherapeutic dose.

3.4 PREVIOUS CLINICAL EXPERIENCE

From IB (August 2011)

-Safety in Phase 1 studies.

“Study PX-171-001. A total of 29 patients (10 MM, 1 WM, 15 NHL, and 3 Hodgkin disease) at 3 clinical centers were enrolled between September 2005 and April 2007 and were treated at carfilzomib doses ranging from 1.2 to 20 mg/m². No DLTs were observed in the initial 7 cohorts at doses ranging from 1.2 to 15 mg/m². At the 20 mg/m² dose level, 2 of 5 patients experienced DLTs of febrile neutropenia and chills (1 patient) and

thrombocytopenia (1 patient) during Cycle 1. Three additional patients were enrolled and the MTD was established at 15 mg/m².

Table 3: Study PX-171-001: Incidence of Grade 3 or 4 Treatment Emergent Adverse Events

Preferred Term ^{a,b}	Total Patients All Grades	Worst Severity of Grade 3	Worst Severity of Grade 4
Patients w/ at least 1 AE ^c	29 (100%)	11 (37.9%)	3 (10.3%)
Fatigue	14 (48.3%)	1 (3.4%)	0
Dyspnea	8 (27.6%)	1 (3.4%)	1 (3.4%)
Hemoglobin decreased	4 (13.8%)	1 (3.4%)	0
Chills	4 (13.8%)	1 (3.4%)	0
Abdominal pain	4 (13.8%)	1 (3.4%)	0
AST increased	3 (10.3%)	1 (3.4%)	0
Thrombocytopenia	2 (6.9%)	0	2 (6.9%)
Pain	2 (6.9%)	1 (3.4%)	0
Alkaline phosphatase increased	2 (6.9%)	1 (3.4%)	0
Syncope	1 (3.4%)	1 (3.4%)	0
Skin infection	1 (3.4%)	1 (3.4%)	0
Neutropenia	1 (3.4%)	1 (3.4%)	0
Hyperglycemia	1 (3.4%)	1 (3.4%)	0
Gastrointestinal hemorrhage	1 (3.4%)	1 (3.4%)	0
Febrile neutropenia	1 (3.4%)	1 (3.4%)	0
Disease progression	1 (3.4%)	1 (3.4%)	0
Anemia	1 (3.4%)	1 (3.4%)	0
ALT increased	1 (3.4%)	1 (3.4%)	0
Acute bronchitis	1 (3.4%)	1 (3.4%)	0

Source: PX-171-001 post-text Tables 14.3.1.2.1 and 14.3.1.5.

^a Investigator reported AE terms were coded using MedDRA (version 8.1).

^b Patients were counted only once for each preferred term.

^c Patients may be counted in more than 1 row.

Source: IB, Table 3.

“Study PX-171-002 (Dose Escalation, Part 1): A total of 37 patients (21 MM, 15 NHL, and 1 Hodgkin disease) at 3 clinical centers were enrolled and treated at doses ranging from 1.2 to 27 mg/m².

“At the 1.2 mg/m² dose level, 1 of 3 patients experienced DLTs of Grade 3 fatigue and Grade 3 AST in Cycle 1. This had not been reported to the Sponsor in a timely manner and dose escalation had proceeded to 2.4 mg/m² without additional patients being enrolled at the 1.2 mg/m² dose level. The eighth patient to receive 20 mg/m² experienced a DLT of Grade 3 renal failure on Day 4 of Cycle 1, and the sixth patient to receive 27 mg/m² experienced a DLT of Grade 3 hypoxia on Day 3 of Cycle 1.

“Across the dose cohorts, all 37 patients (100%) experienced at least 1 treatment-emergent adverse event (TEAE). These events were generally Grades 1 or 2 in severity. Table 5 displays AEs that occurred in greater than 15% of patients in the study. The most frequently reported AEs (irrespective of attribution) were nausea (59.5% of patients),

fatigue (51.4%), anemia (45.9%), constipation (43.2%), pyrexia (40.5%), cough (37.8%), and vomiting (35.1%).

“Treatment-emergent thrombocytopenia was seen in 4 patients with a Grade 4 severity. Although the severity of platelet decreases appeared dose-related, the majority of cases of Grade 3 and higher thrombocytopenia occurred in patients with MM and were complicated by disease progression. No adverse trends in heart function (as assessed by electrocardiogram [ECG], echocardiogram, and serum troponin levels) were seen.

-Safety: phase 1b and phase 2 studies

“PX-171-003 – Part 1 (A0): This was an open-label, single-arm, multicenter, Phase 2 investigation of a single dose level of carfilzomib given as monotherapy for patients with relapsed and refractory MM. Patients received carfilzomib 20 mg/m² administered IV on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle.

“Other than treatment-related fatigue (experienced by 54.3% of patients) and nausea (26.1%), the most frequently reported AEs that were considered by the Investigator to be possibly or probably related to carfilzomib were laboratory in nature: anemia (45.7%), thrombocytopenia (41.3%), blood creatinine increased (28.3%), and lymphopenia (26.1%). These findings are consistent with the findings from the Phase 1 studies of carfilzomib (Studies PX-171-001 and PX-171-002).

“Study PX-171-003 – Part 2 (A1). Most patients (86.8%) experienced at least one Grade 3 or higher AE, and all of the most frequently reported Grade 3 or higher AEs (regardless of attribution) were hematological, as follows: thrombocytopenia (28.9%), anemia (23.7%), lymphopenia (19.5%), and neutropenia (10.9%). Apart from disease progression, frequently reported ($\geq 5\%$) nonhematological Grade 3 or higher AEs include pneumonia (9.4%), fatigue (7.5%), and various dys-electrolytemias including hyponatremia (8.3%), hypophosphatemia (6.0%), and hypercalcemia (5.3%).

“Cardiac Disorders: Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular function have been reported, including reports in patients with no risk factors for decreased left ventricular ejection fraction. Serious cardiac reactions and even death have occurred following the administration of carfilzomib.”

Reviewer’s Comments: No clinically relevant ECG changes were reported.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of carfilzomib’s clinical pharmacology.

4 SPONSOR’S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol for study PX-171-005 prior to conducting this study under IND 71057. The QT-IRT did not review the protocol for study PX-171-007 prior to conducting this study. The sponsor submitted the study reports PX-171-005 and PX-171-007 for carfilzomib, including electronic datasets. Sponsor did not submit the ECGs to the warehouse.

The sponsor submitted data from a phase 2 study (PX-171-005) in patients with renal impairment and phase 1b/2 (PX-171-007) study.

4.2 QT STUDY

4.2.1 Title

Study PX-171-005

Phase 2 Study of the Safety and Pharmacokinetics of Carfilzomib in Subjects with Relapsed and Refractory Multiple Myeloma and Varying Degrees of Renal Function.

Study PX-171-007

Phase 1b/2, Multicenter Open-label Study of the Safety and Activity of Carfilzomib in Subjects with Relapsed Solid Tumors, Multiple Myeloma or Lymphoma.

4.2.2 Protocol Number

PX-171-005 and PX-171-007

4.2.3 Study Dates

Study PX-171-005: November 2008 – March 2010

Study PX-171-007: September 2007 – July 2010

4.2.4 Objectives

Study PX-171-005:

- Primary Objective: To assess the influence of renal impairment on the PK of carfilzomib in subjects with multiple myeloma
- Secondary Objectives: Evaluation of the QT/QTc interval prolongation in all subjects receiving carfilzomib by intensive 12-lead electrocardiogram (ECG) monitoring.

Study PX-171-007

- Primary Objectives: To evaluate the safety and tolerability of carfilzomib and to estimate the overall response rate (ORR) after 4 cycles of carfilzomib in subjects with relapsed solid tumors
- Secondary Objectives:
 - To evaluate the ORR throughout the study period
 - To evaluate the durability of responses
 - To evaluate progression-free survival and time to progression
 - To define PK and PD parameters of carfilzomib in solid tumor and myeloma patients
 - To evaluate the potential for QT/QTc interval prolongation in solid tumor and myeloma patients at select sites by intensive 12-lead ECG monitoring.

4.2.5 Study Description

4.2.5.1 Design

Study PX-171-005

This was a Phase 2, open-label, single-arm, multicenter study in patients with multiple myeloma who had relapsed or progressive disease after at least 1 or 2 prior therapeutic treatments or regimens. Five groups of multiple myeloma patients, representing different levels of renal function, were evaluated.

Study PX-171-007

This was an open-label, multicenter, Phase 1b/2 study was conducted to evaluate the safety and efficacy of single-agent carfilzomib in adults with solid tumors, multiple myeloma, or lymphoma who had relapsed disease following conventional therapy. Carfilzomib was assessed as a 2- to 10-min i.v. injection or as a 30-min i.v. infusion. The Phase 1b portions were designed to determine the maximum tolerated dose (MTD) of carfilzomib, in sequential cohorts using a modified 3 + 3 dose escalation scheme. The MTD established in the Phase 1b portion of the study was administered to solid tumor patients participating in the Phase 2 portion of the study.

4.2.5.2 Controls

The sponsor used neither placebo nor positive (moxifloxacin) controls for either study.

4.2.5.3 Blinding

The studies were not blinded as neither placebo nor active controls were studied.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Study PX-171-005

Patients received 15 mg/m² on days 1, 2, 8, 9, 15, and 16 of the first 28-day cycle. If no grade 3-4 adverse events were experienced the patient could then titrate their dose to 20 mg/m² for the second cycle of treatment. If 20 mg/m² was tolerated, an additional dose escalation to 27 mg/m² was permitted at Cycle 3 or at subsequent cycles. No additional dose escalation of carfilzomib above 27 mg/m² was permitted.

Study PX-171-007

Three dose levels were planned, as follows:

- 20 mg/m² (all doses): Patients received 20 mg/m² on each dosing (day 1, 2, 8, 9, 15, 16) day of each 28-day cycle.
- 20/27 mg/m² (20 mg/m² on Day 1 and Day 2 to establish initial tolerability, then 27 mg/m² for the remainder of treatment)
- 20/36 mg/m² (20 mg/m² on Day 1 and Day 2 to establish initial tolerability, then 36 mg/m² for the remainder of treatment)

4.2.6.2 Sponsor's Justification for Doses

Study PX-171-005

“Preliminary data suggest that carfilzomib as a single agent can produce substantial response rates in myeloma subjects across a variety of dosing cohorts. Responses were seen over a wide therapeutic window, from 15 to 27 mg/m². Greater than 70% proteasome inhibition was seen at 11 mg/m² doses and higher in whole blood samples taken 1 hour after the first dose. The final analysis of the human PK data is ongoing but appears to be rapid and similar to the results from the animal studies. Carfilzomib is rapidly cleared from plasma with an elimination half life of < 60 minutes at the 15 mg/m² dose. In the Phase 2 multiple myeloma single-agent trials (PX-171-003 and PX-171-004), 20 mg/m² has been the standard dose. While the 27 mg/m² dose may be superior to 20 mg/m², this dose needs further investigation to determine if the first-dose side effects can be effectively managed. The effect of varying degrees of renal impairment on safety, PK, and PDn has not been studied extensively. Therefore, as a conservative measure, the initial dose for this protocol is 15 mg/m². Subjects will be allowed to escalate the dose to 20 mg/m² starting in Cycle 2 if 15 mg/m² is well tolerated in Cycle 1, defined as absence of any treatment-related adverse event requiring dose reduction, delay or the dose to be held in Cycle 1.

“After review of the first 21 subjects enrolled in this study, no new safety issues have been observed. In addition, there are no reports of acute renal failure or significant changes in creatinine clearance in the subjects treated. Based on this information and the safety evaluation of the PX-171-003 that has a very similar treatment population, the protocol is being amended (Amendment 1) to allow escalation of the carfilzomib dose to 27 mg/m² at Cycle 3 and subsequent cycles for subjects who tolerate the 20 mg/m² dose. The Cycle 1 and 2 dose will remain the same to maintain the consistency of the analysis of the primary objective.”

(Source: Sponsor’s Protocol for Study PK-171-005)

Study PX-171-007

“Preliminary data suggest that carfilzomib as a single agent can produce substantial response rates in myeloma subjects across a variety of dosing cohorts. Responses were seen over a wide therapeutic window, from 15 to 27 mg/m². Maximum proteasome inhibition was seen at doses 15 mg/m² and higher in whole blood samples taken 1 hour after the first dose. The final analysis of the human pharmacokinetics data is ongoing but appears to be rapid and similar to the results from the animal studies. Carfilzomib is rapidly cleared from plasma with a terminal half-life of 12–24 minutes at the 20 mg/m² dose. While the 27 mg/m² dose may be superior to 20 mg/m², this dose needs further investigation to determine if the first dose side effects can be effectively managed. Thus, the starting dose for this protocol is 20 mg/m². Dose escalation may proceed to a maximum of 36 mg/m².”

(Source: Sponsor’s Protocol for Study PK-171-007)

Reviewer’s Comments: The selected doses appear reasonable to cover the clinical high exposure scenario: 27-mg/m² dose in patients with severe renal impairment. The supratherapeutic dose (36 mg/m²) produces mean C_{max} and AUC values of 1.4- and 1.6-fold the mean C_{max} and AUC for the therapeutic dose (27 mg/m²). However, there was

high variability in C_{max} since the PK samples were collected at the end of the i.v. infusion and the infusion times for subjects ranged from 2 min to 10 min. Patients with severe renal impairment did not show increased C_{max} . However, they are expected to exhibit ~20% increase in AUC compared to patients with normal renal function. The maximum studied dose (36 mg/m^2) produced C_{max} and AUC values that were 35% and 60% greater than the 27-mg/m^2 dose values. Thus, the observed exposures in this QT study are expected to cover the clinical high exposure scenario.

4.2.6.3 Instructions with Regard to Meals

No dosing instructions were made with regards to meals. Patients were required to be well hydrated prior to dosing.

Reviewer's Comments: Carfilzomib is a product for i.v. administration. Therefore effect of food on carfilzomib exposure is not expected.

4.2.6.4 ECG and PK Assessments

Study PX-171-005

PK plasma samples to measure carfilzomib and metabolites were collected on day 1 and day 15 before dosing, at the end of the injection, 5, 15, 30, and 60 min, and 1.5, 2, 4, 6 and 24 h post-dose.

ECGs were performed for Cycle 1 on days 1 and 15 and for Cycle 2 on Day 15. The schedule of triplicate ECG measurements on each collection day included pre-dose, 5 minutes and 15 min, and 1, 2, 4, and 24 h post-dose.

Study PX-171-007

PK plasma samples to measure carfilzomib and metabolites were collected on Cycle 1 Day 1 and Cycle 2 on Day 16 at pre-dose, 5 min post start of infusion, 15 min post start of infusion, at end of infusion and at 5, 15, and 30 min, and 1, 2, and 4 h after the end of the infusion.

ECGs were performed for Cycle 1 on days 1 and 15, in triplicate. Measurements were collected prior to dosing, and 5 min, 20 min, 1, 2, 4, and 24 h post-dose.

Reviewer's Comments: The timing of PK samples and ECGs appears acceptable. The QT effect was evaluated over a 24-h period after both single dose and steady-state dose administration.

4.2.6.5 Baseline

A within day pre-dose baseline measurement was used for both studies.

4.2.7 ECG Collection

ECGs were recorded at the site for each trial patient and sent to a central laboratory, (b) (4) for a treatment-blinded high-resolution measurement of the cardiac intervals and morphological assessment by a central cardiologist blinded to the study identifiers.

Digital ECGs were created by the central ECG laboratory and processed via its validated data management system, EXPERT. Interval duration measurements were collected using computer assisted caliper placements on three consecutive beats. Trained analysts

reviewed all ECGs for correct lead and beat placement and adjudicated the pre-placed algorithm calipers as necessary using the proprietary validated electronic caliper system applied on a computer screen (manual adjudication methodology). A cardiologist then verified the interval durations and performed the morphology analysis, noting any T-U wave complex that suggested an abnormal form compatible with an effect on cardiac repolarization.

The ECG analysis was performed on all enrolled patients with at least one available baseline and one on-treatment ECG. The ECG analysis was conducted in triplicate ECG obtained from Lead II and when Lead II was not analyzable, then Lead V5, followed by the most appropriate lead. ECG readers were blinded to patient identifiers, treatment and visit.

Screening and end-of-trial ECGs were obtained and analyzed at the sites and not subjected to central ECG laboratory evaluations.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

-Study PX-171-005

Fifty Multiple Myeloma (MM) patients were enrolled, demographic characteristic are summarized in Table 4.

Table 4: Patient Demographics and Baseline Characteristics (All Enrolled Patients)

Variable	Statistic or Category	Group 1 (N=12)	Group 2 (N=12)	Group 3 (N=10)	Group 4 (N=8)	Group 5 (N=8)	Total (N=50)
Age (years)							
	N	12	12	10	8	8	50
	Mean (StD)	64.5 (5.70)	63.5 (7.85)	66.2 (9.65)	73.0 (8.23)	56.0 (7.91)	64.6 (9.01)
	Median	64.5	61.0	68.0	75.0	56.5	64.0
	Min, Max	55, 72	55, 79	46, 79	57, 85	45, 67	45, 85
Age group [n (%)]							
	< 65 years	6 (50.0)	8 (66.7)	4 (40.0)	1 (12.5)	7 (87.5)	26 (52.0)
	≥ 65 years	6 (50.0)	4 (33.3)	6 (60.0)	7 (87.5)	1 (12.5)	24 (48.0)
Gender [n (%)]							
	Female	4 (33.3)	8 (66.7)	3 (30.0)	3 (37.5)	4 (50.0)	22 (44.0)
	Male	8 (66.7)	4 (33.3)	7 (70.0)	5 (62.5)	4 (50.0)	28 (56.0)
Ethnicity [n (%)]							
	African American	2 (16.7)	2 (16.7)	4 (40.0)	1 (12.5)	2 (25.0)	11 (22.0)
	Asian/Pacific Islander	0 (0.0)	2 (16.7)	0 (0.0)	0 (0.0)	1 (12.5)	3 (6.0)
	Caucasian	10 (83.3)	8 (66.7)	6 (60.0)	7 (87.5)	5 (62.5)	36 (72.0)
ECOG performance status [n (%)]							
	0	4 (33.3)	2 (16.7)	0 (0.0)	2 (25.0)	0 (0.0)	8 (16.0)
	1	8 (66.7)	9 (75.0)	9 (90.0)	1 (12.5)	5 (62.5)	32 (64.0)
	2	0 (0.0)	1 (8.3)	1 (10.0)	5 (62.5)	3 (37.5)	10 (20.0)
Serum Creatinine (μmol/L)							
	N	11	12	10	8	ND	ND
	Mean (StD)	79.08 (15.071)	94.58 (26.094)	180.95 (54.373)	262.23 (108.307)		
	Median	81.30	92.35	192.25	241.80		
	Min, Max	55.7, 102.5	53.9, 141.4	81.3, 247.5	150.3, 424.3		
Neuropathy grade [n (%)]							
	0	0 (0.0)	2 (16.7)	1 (10.0)	1 (12.5)	0 (0.0)	4 (8.0)
	1	10 (83.3)	7 (58.3)	7 (70.0)	4 (50.0)	5 (62.5)	33 (66.0)
	2	2 (16.7)	3 (25.0)	2 (20.0)	3 (37.5)	3 (37.5)	13 (26.0)

Source: [Table 14.1.4](#) and [Table 14.3.5.2.11](#)

Group 1, CrCL > 80 mL/minute (normal); Group 2, CrCL 50-80 mL/minute (mild impairment);

Group 3: CrCL 30-49 mL/minute (moderate impairment), Group 4: CrCL < 30 mL/minute (severe impairment);

Group 5 chronic hemodialysis.

StD = standard deviation, min = minimum, max = maximum. ND = not done. Screening creatinine summaries are not presented for Group 5, and total summaries are not presented for creatinine and neuropathy.

Source: CSR, Table 12

-Study PX-171-007

For this report, only the results for patients (solid tumors, MM, lymphoma) who received a bolus dose of treatment have been analyzed. Patients who received carfilzomib by infusion will be analyzed in a subsequent analysis. Fourteen (14) patients were enrolled in Phase 1b Bolus cohorts to determine the MTD of a bolus administration given over 10 minutes. Sixty-five (65) patients were enrolled in Phase 2 bolus cohorts. Patients had to be > 18 years with the only cardiac exclusion being:

- Congestive heart failure (New York Heart Association class III to IV), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, or myocardial infarction within 6 months prior to first dose.

Five centers were used to recruit 79 patients with solid tumors, MM or lymphoma. Of the 14 patients enrolled in the Phase 1b portion of the study, 6 (42.9%) were female. Ten patients (71.4%) were white; 4 patients (28.6%) were Hispanic. The median age was 59.5 years (range: 36 to 75 years), and 4 patients (28.6%) were ≥ 65 years old at study entry. Of the 65 patients enrolled in the Phase 2 portion of the study, 38 (58.5%) were female. Fifty-seven patients (87.7%) were white; other racial and ethnic groups were African American (4 patients, 6.2%), Hispanic (3 patients, 4.6%), and Asian/Pacific Islander (1 patient, 1.5%). The median age was 62 years (range: 41 to 87 years), and 26 patients (40.0%) were ≥ 65 years old at study entry.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The timecourse of mean change from baseline and QTcF upper confidence limits for various time points are shown in Figure 1, Figure 2, Table 5 and Table 6. The x-axis for these plots depict the categorical sequence of measurements rather than real-time. This permits a visual comparison of the QTcF change from baseline within day and between cycles.

Table 5: ECG Central Tendency Confidence Limits (Study PX-171-005) at 15/20 mg/m². C1 refers to Cycle 1 and D1 Refers to Day 1

Time	Non-Hemodialysis				Chronic Hemodialysis			
	N	Estimate	Lower CI [1]	Upper CI [1]	N	Estimate	Lower CI [1]	Upper CI [1]
C1D1: 2/5 Min	41	4.4	0.8	8.0	7	0.9	-2.9	4.7
C1D1: 20 Min	12	5.7	1.2	10.1	7	3.0	-3.1	9.0
C1D1: 1 Hr	39	6.0	2.4	9.7	8	2.6	-3.6	8.8
C1D1: 2 Hr	11	6.8	-2.8	16.4	8	-1.0	-7.0	5.0
C1D1: 4 Hr	12	14.0	6.7	21.2	8	1.1	-8.0	10.3
C1D1: 24 Hr	12	1.2	-6.2	8.6	7	7.7	-13.3	28.7
C1D15: Pre-Dose	37	0.4	-5.2	5.9	6	0.9	-16.6	18.4
C1D15: 2/5 Min	37	4.0	-1.4	9.4	6	-0.6	-19.1	17.9
C1D15: 20 Min	14	12.6	5.1	20.1	7	-3.7	-22.6	15.2
C1D15: 1 Hr	34	4.0	-2.1	10.2	7	1.9	-14.7	18.4

[1] Lower/Upper Bounds= lower/upper two-sided 90% (equal to one-sided 95%) data-based confidence limit.

(Source: Sponsor's Table 14.2.3-20, Study Report TR-480-171)

Table 6: ECG Central Tendency Confidence Limits (Study PX-171-007) at 20/36 mg/m². C1 Refers to Cycle 1 and D1 Refers to Day 1

Time	ECG Central Tendency Confidence Limits[1] QTc Fridericia (ms)			
	N	Estimate	Lower CI [1]	Upper CI [1]
C1D1 - 2/5 Min	36	3.3	0.4	6.3
C1D1 - 1 Hr	34	0.9	-1.9	3.6
C1D15 - Pre-Dose	31	-4.6	-8.3	-1.0
C1D15 - 2/5 Min	28	0.8	-3.0	4.6
C1D15 - 1 Hr	28	0.2	-3.6	4.0

[1] Lower/Upper Bounds= lower/upper two-sided 90% (equal to one-sided 95%) data-based confidence limit.

(Source: Sponsor's Table 14.2.3-18, Study Report TR-0481-171)

4.2.8.2.2 Assay Sensitivity

Reviewer's Comments: Assay sensitivity cannot be evaluated as neither placebo nor active control were studied for effects on the QT interval.

4.2.8.2.3 Categorical Analysis

Table 7 and Table 8 detail the results of studies PX-171-005 and PX-171-007 as change from baseline and new outliers from baseline for cycle 1, day 1 and cycle 1, day 15 combined.

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Table 7: Time-Averaged Mean Change from Baseline and New Outliers at Pose-Baseline Time Points for ECGs by Group (Study PX-171-005)

	Treatment Group: Renal Status									
	Group 1 Normal		Group 2 Mildly Impaired		Group 3 Moderate Impaired		Group 4 Severely Impaired		Group 5 Chronic Hemodialysis	
	Cycle 1	Cycle 2	Cycle 1	Cycle 2	Cycle 1	Cycle 2	Cycle 1	Cycle 2	Cycle 1	Cycle 2
Total N	12	9	12	9	10	6	7	4	8	4
Heart Rate in bpm (mean change from baseline)	-1.6	-1.8	+1.5	+0.5	-1.2	-1.1	+0.8	+6.9	-0.3	-2.7
Heart Rate tachycardic outliers N (%)	0	0	0	0	0	0	0	0	0	0
Heart Rate bradycardic outliers N (%)	0	0	0	0	0	0	0	0	0	0
PR in ms (mean change from baseline)	+1.7	+5.6	+0.5	+7.7	+6.4	+1.2	+4.2	-4.7	+4.3	+1.9
PR outliers N (%)	0	0	0	0	1 (10%)	0	0	0	0	0
QRS in ms (mean change from baseline)	+1.7	+5.1	-2.2	-1.6	-4.3	-12.0	-1.5	-4.5	-0.8	+1.2
QRS outliers N (%)	0	0	0	0	0	0	0	0	0	0
QT in ms (mean change from baseline)	+11.5	+14.3	-2.6	+1.9	+4.9	+8.0	+4.7	-10.1	+2.1	+12.4
QT new >500 ms N (%)	0	0	0	0	0	0	1 (14%)	0	0	0
QTcF in ms (mean change from baseline) **	+9.6	+11.9	-0.2	+1.9	+2.6	+4.8	+7.2	+4.9	+1.3	+6.8
QTcF new >500 ms N (%)	0	0	1 (8%)	0	0	0	1 (14%)	0	0	0
QTcF new >480 ms N (%)	0	1 (11%)	1 (8%)	0	0	0	2 (29%)	0	1 (13%)	0
QTcF 30-60 ms inc N (%)	3 (25%)	3 (33%)	2 (17%)	0	2 (20%)	1 (17%)	1 (14%)	0	0	1 (25%)
QTcF >60 ms inc N (%)	0	0	0	0	0	0	0	0	1 (13%)	0
QTcB in ms (mean change from baseline)	+8.6	+10.7	+1.1	+1.8	+1.4	+3.0	+8.4	+12.6	+1.0	+3.7
QTcB new >500 ms N (%)	0	1 (11%)	1 (8%)	0	1 (10%)	0	0	0	1 (13%)	0
QTcB new >480 ms N (%)	2 (17%)	2 (22%)	0	0	0	1 (17%)	2 (29%)	0	4 (50%)	0
QTcB 30-60 ms inc N (%)	4 (33%)	2 (22%)	2 (17%)	0	2 (20%)	2 (33%)	3 (43%)	1 (25%)	1 (13%)	1 (25%)
QTcB >60 ms inc N (%)	0	1 (11%)	0	0	0	0	0	0	1 (13%)	0
New abnormal U waves N (%)	0	0	0	0	0	0	0	0	0	0
New ST segment depression changes N (%)	0	0	0	0	0	0	0	0	0	0
New ST segment elevation	0	0	0	0	0	0	0	0	0	0

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changes N (%)										
New T wave inverted N (%)	0	0	0	0	0	0	0	0	0	0
New AF N (%)	0	0	0	0	0	0	0	0	0	0
New 2 nd Degree Heart Block N (%)	0	0	0	0	0	0	0	0	0	0
New 3 rd Degree Heart Block N (%)	0	0	0	0	0	0	0	0	0	0
New Complete RBBB N (%)	0	0	0	0	0	0	0	0	0	0
New Complete LBBB N (%)	0	0	0	0	0	0	0	0	0	0
New MIN (%)	0	0	0	0	0	0	0	0	0	0

bpm = beats per minute; ms=milliseconds; QTcB: Bazett correction; AF=atrial fibrillation QTcF= Fridericia correction; RBBB=right bundle branch block; LBBB= left bundle branch block, MI= myocardial infarction; "new" means not present at baseline and only seen after baseline.

(Source: Table 3-1, Sponsor's Study Report TR-0480-171)

Table 8: Time-Averaged Mean Change from Baseline and New Outliers at Post-Baseline Time Points for ECGs by Group for All Patients (Study PX-171-007)

	Treatment Group
	MTD =Phase II
Carfilzomib dose in mg/m² received:	20/36 mg/m²
Total N *	37
Heart Rate in bpm (mean change from baseline)	0.2
Heart Rate tachycardic outliers N (%)	0 (0%)
Heart Rate bradycardic outliers N (%)	1 (3%)
PR in ms (mean change from baseline)	-0.4
PR outliers N (%)	0 (0%)
QRS in ms (mean change from baseline)	-0.9
QRS outliers N (%)	0 (0%)
QT in ms (mean change from baseline)	0.9
QT new >500 ms N (%)	0 (0%)
QTcF in ms (mean change from baseline) **	1.0
QTcF new >500 ms N(%)	0 (0%)
QTcF new >480 ms N (%)	1 (3%)
QTcF 30-60 ms inc N (%)	0 (0%)
QTcF >60 ms inc N (%)	0 (0%)
QTcB in ms (mean change from baseline)	1.2
QTcB new >500 ms N(%)	1 (3%)
QTcB new >480 ms N (%)	1 (3%)
QTcB 30-60 ms inc N (%)	1 (3%)
QTcB >60 ms inc N (%)	0 (0%)
New abnormal U waves N (%)	0
New Complete RBBB changes N (%)	1 (3%)
New Complete LBBB changes N (%)	0 (0%)
New T wave inverted N (%)	0
New AF, 2nd and 3 rd Degree Heart Block, ST segment depression, MI N (%)	0

bpm = beats per minute; ms=milliseconds; QTcB: Bazett correction; AF=atrial fibrillation; QTcF= Fridericia correction; RBBB=right bundle branch block; LBBB= left bundle branch block, MI= myocardial infarction; "new" means not present at baseline and only seen after baseline.

*6 patients who were dosed on Cycle 1 Day 1 did not escalate to 36 mg/m², however, have been included in the intent to treat group as part of the time-averaged analysis

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(Source: Table 3-1, Sponsor's Report TR-0481-171)

4.2.8.3 Safety Analysis

-Study PX-171-005: A total of 37 patients (74.0%) have discontinued from the study, 21 (42.0%) had a final visit and 16 (32.0%) did not have a final visit. Reasons for not having a final visit were as follows: non-fatal progressive disease in 6, fatal progressive disease in 4, non-fatal AE in 3, withdrawal of consent in 3, and other reason in 1 (patients could have more than 1 reason). The most common non-hematologic AEs were fatigue (56.0%), nausea and diarrhea (each 36.0%), hypokalemia (32.0%), constipation and hypomagnesemia (each 30.0%), dyspnea (28.0%), peripheral edema(26.0%), pyrexia and back pain (each 22.0%), and disease progression and pneumonia (each 20.0%).

Five patients died on study (ie, within 30 days of discontinuing study treatment). The primary cause of death was disease progression for all 5 patients. Four additional patients died during follow-up: 2 of disease progression, 1 due to end-stage renal disease, and 1 due to sepsis, the latter of which started within a few days of the last dose of study drug.

-Study PX-171-007: Most patients receiving carfilzomib as a 2- to 10-minute IV injection discontinued before completing the maximum allowed 12 cycles of treatment (92.9% in Phase 1b, 96.9% in Phase 2). Reasons for discontinuation were PD (64.3% vs 64.6% in Phase 1b vs Phase 2, respectively), AEs (14.3% vs 10.8%), withdrew consent (7.1% vs 6.2%), and other (7.1% vs 15.4%). Other reasons for discontinuation were clinical progression (5 patients), physician discretion (4 patients) or lack of clinical benefit (2 patients).

Table 9: Disposition of Patients: Phase 2, 2- to 10-Minute IV Injection

Characteristic	Tumor Type					Total (N=65)
	NSCLC (N=15)	SCLC (N=9)	Ovarian (N=15)	Renal (N=10)	Other (N=16)	
Adverse Events Resulting in Study Drug Discontinuation^a						
Cardiac failure congestive	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Hyponatraemia	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Infusion related reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.5)
Malignant pleural effusion	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Neuritis	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	1 (1.5)
Pneumonia	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Septic shock	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Spinal cord compression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.5)

Source: Table 14.1.1.2.2

^a Patients may be counted in more than 1 row.

Source: CSR, Table 10

No Phase 1b patient receiving carfilzomib as a 2- to 10-minute IV injection died within 30 days of the last dose of carfilzomib. In Phase 2, 5 patients died within 30 days of treatment and none of the deaths were attributed by the investigator to study drug. Four

were attributed to progressive disease and 1 was attributed to hepatorenal syndrome unrelated to study drug.

All SAEs among patients enrolled in the Phase 1b portion receiving carfilzomib as a 2- to 10-minute IV injection are summarized in Table 32. SAEs were experienced by 1 patient (33.3%) at the 20 mg/m² dose level, 1 patient (25.0%) at the 20/27 mg/m² dose level, and 4 patients (57.1%) at the 20/36 mg/m² dose level. No single SAE was experienced by more than 1 patient in Phase 1b.

Two SAEs were considered treatment-related, and both were experienced by patients at the 20/36 mg/m² dose level.

Reviewer's comments: In study PX-171- 005 five patients died; in all cases, the main cause of death was disease progression. In study PX-171-007 phase 1, one subject at the 20/36 mg/m² dose level, experienced Grade 1 increased blood pressure, beginning on Study Day 8, and Grade 1 increased heart rate, beginning on Study Day 36. The events were both considered possibly related to carfilzomib and resolved within 1 day. For patients who received carfilzomib as a 2- to 10-min i.v. injection in Phase 2, there was one Grade 3 congestive heart failure event beginning on day 2, patient had a history of hypertension and atrial fibrillation.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The carfilzomib PK results are presented in Table 10. Following administration of 36-mg/m² C_{max} and AUC values in the QT study were 1.4- and 1.6-fold, respectively values with 27-mg/m² carfilzomib, the intended maximum clinical dose. There is no accumulation because of short half-life of carfilzomib.

Table 10: Summary of Carfilzomib PK Parameters in Cycle 1 (Study PX-171-007)

PK Parameters	Dose Level 20 mg/m ² Day 1 Pooled Data ^a (n = 30)	Dose Level		
		20/20 mg/m ²	20/27 mg/m ²	20/36 mg/m ²
		20 mg/m ² Day 16 (n = 3)	27 mg/m ² Day 16 (n = 5)	36 mg/m ² Day 16 (n = 13)
AUC _{last} (hr·ng/mL)	251 (92.0)	269 (61.7)	379 (24.8)	594 (52.5)
AUC _{inf} (hr·ng/mL) ^b	223 (104)	269 (61.7)	349 (18.2)	663 (51.4)
AUC _{ext} (%) ^b	0.153 ± 0.245	0.0715 ± 0.0290	0.111 ± 0.107	0.151 ± 0.194
C _{max} (ng/mL)	2390 (104)	3410 (51.5)	4232 (48.8)	5718 (46.5)
t _{max} (hr)	0.0500 (0, 0.167)	0.0333 (0.0333, 0.0500)	0.0500 (0.0333, 0.133)	0.0500 (0.0333, 0.117)
t _{1/2} (hr) ^b	0.444 (0.152, 2.20)	1.10 (0.998, 1.13)	0.351 (0.261, 0.917)	0.869 (0.382, 1.81)
CL (L/hr) ^b	263 ± 398	136 ± 52.8	150 ± 30.9	116 ± 48.6
V _{ss} (L) ^b	223 ± 328	215 ± 92.5	101 ± 63.7	158 ± 94.1
V _{ss} (L) ^b	27.7 ± 48.6	7.75 ± 3.77	11.1 ± 4.45	9.33 ± 4.80
λ _z (1/hr) ^b	1.46 ± 0.929	0.645 ± 0.0431	1.89 ± 0.883	0.837 ± 0.373
MRT _{inf} (hr) ^b	0.0902 ± 0.0319	0.0562 ± 0.0113	0.0814 ± 0.0481	0.0805 ± 0.0218

AUC_{last}, AUC_{inf} and C_{max}: geometric mean (geometric CV%) presented; t_{max} and t_{1/2} median (minimum, maximum) presented; arithmetic mean ± SD presented for all parameters unless otherwise stated.

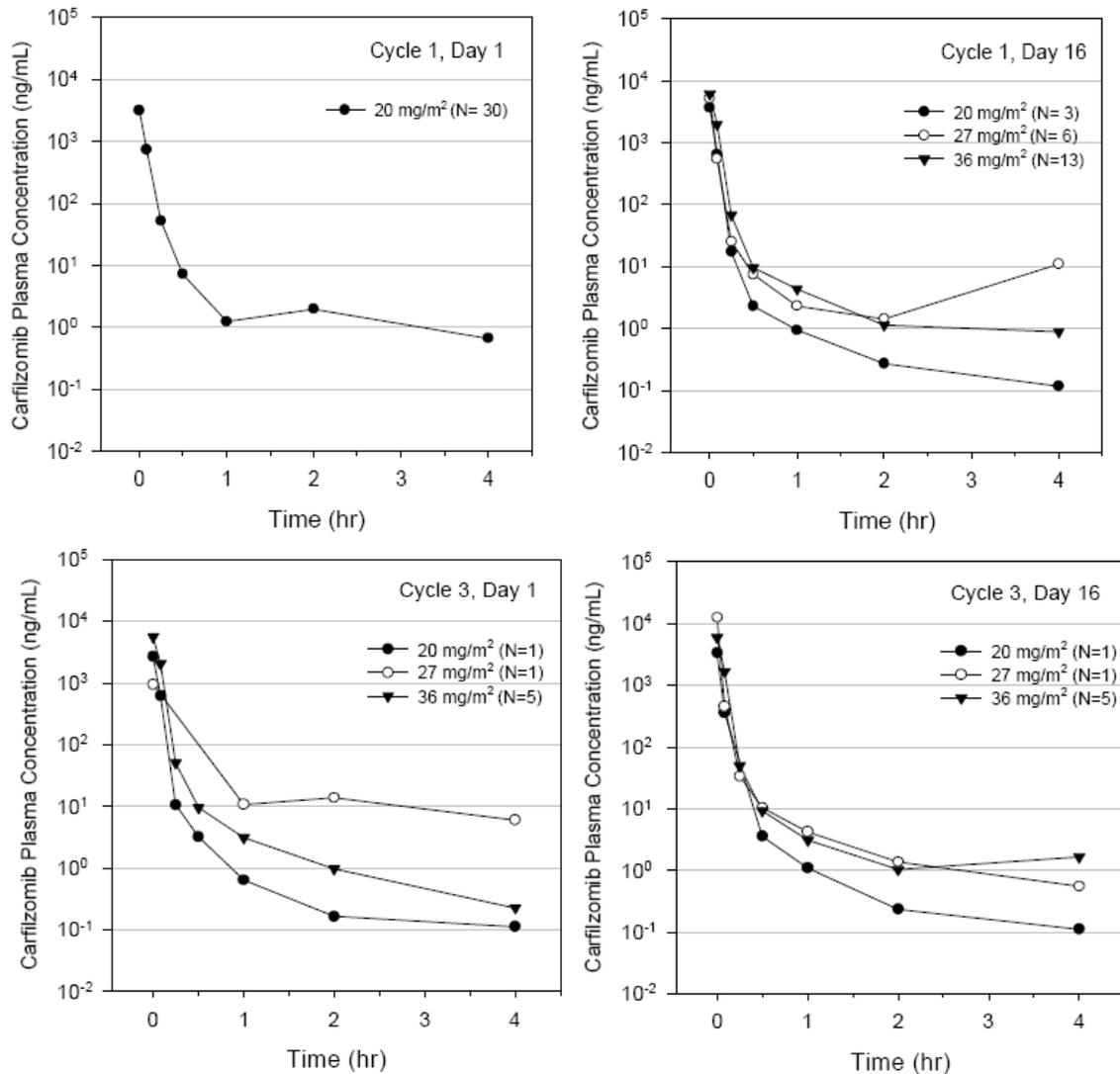
^a For Cycle 1 only, Day 1 data was pooled across dose levels since all patients received the same dose of 20 mg/m² on Day 1.

^b n=23 (Day1), n=4 (Day 16, 27 mg/m²), n=10 (Day 16, 36 mg/m²).

(Source: Table 4, Plasma Pharmacokinetic Report for Study PX-171-007)

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Figure 3: Mean Carfilzomib Concentrations vs. Nominal Sampling Time by Study Cycle and Day (Study PX-171-007)



(Source: Figure 1, Plasma Pharmacokinetic Report for Study PX-171-007)

4.2.8.4.2 Exposure-Response Analysis

Table 11 details the PK/PD model results showing that the slopes of the relationships for plasma concentration of carfilzomib and the predicted QTc change at C_{max} . It should be noted that due to insufficient sample size, narrow range of concentrations and matches of PK samples, ECGs only at 2/5 minutes and 1 h and only on cycle 1 day 1, conclusions made from these data are only preliminary.

Table 11: Change from Baseline vs. Carfilzomib Plasma Concentration – Estimates for the Linear Mixed Model (Study PX-171-007)

QTc Fridericia and QTc Bazett (msec) Electrocardiographic Population						
QT Parameter				Carfilzomib		
	Slope of Plasma Conc. Effect on Δ QTc	Standard Error of Slope of Plasma Conc. Effect on Δ QTc	p-value	Overall Model Fit	Predicted QTc at Average Cmax 1500 ng/mL	One-sided Upper 95% Confidence Bound of Predicted QTc [2]
QTcF	-0.0012	0.0039	0.7653	0.1148	-1.2486	8.4826
QTcB	-0.0020	0.0046	0.6768	0.0708	-1.7475	9.7672

[1] Linear Mixed Model is fit for change from baseline versus the plasma concentration as a fixed effect with subject included in the model as a random effect

[2] Lower/Upper Bound = lower/upper one-sided 95% linear mixed model based confidence limit.

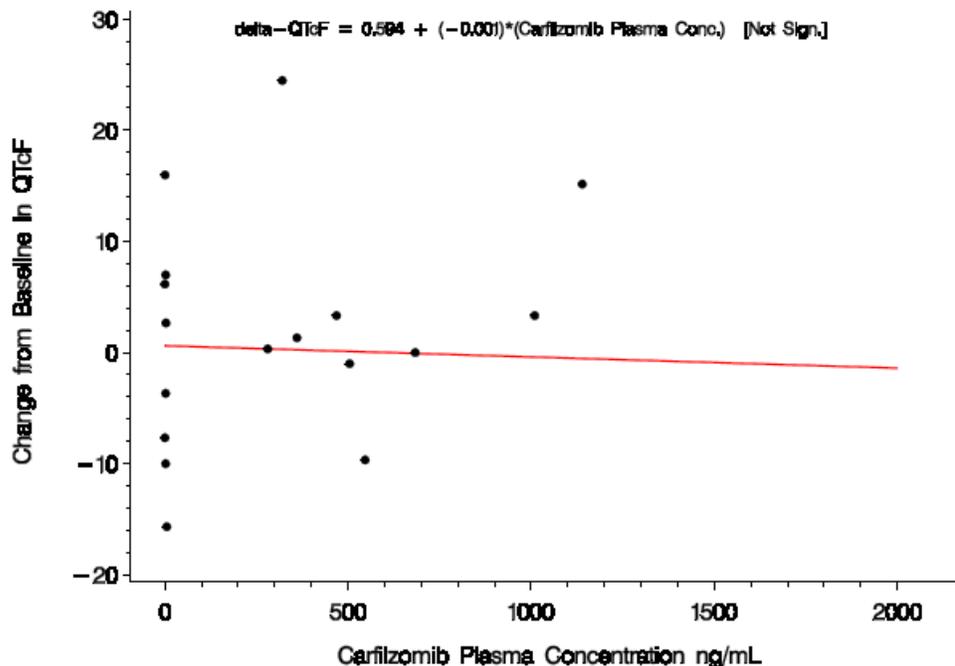
Concentration for prediction of QTc effect was chosen near upper value observed

PKPD model has insufficient range, sample times, and sample size for valid conclusions. PKPD models do not fit

(Source: Sponsor's Table 14.2.3-20 from Study Report TR-0481-171)

Figure 4 shows the relationship between QTcF duration and plasma concentration from paired samples taken in all patients at any time point:

Figure 4: Change from Baseline vs. Carfilzomib Plasma Concentrations (Study PX-171-007)



(Source: Sponsor's Figure 14.5.2.1 from Study Report TR-0481-171)

Reviewer's Comments: The sponsor's analysis appears acceptable. However, the sample size is sufficiently small that no conclusions can be drawn as to whether a significant exposure-response relationship for QTcF exists. The sponsor's exposure-response

analysis appears to include only data from study PX-171-007. The reviewer's analysis pools these data with the QTcF data from study PX-171-005 as well as additional data from study PX-171-007 submitted to the agency on 1/27/2012.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The relationship between different correction methods and RR are presented in Figure 5 and Figure 6 for study PX-171-005, day 15 of Cycle 1. The QTcF correction method appeared reasonable.

Figure 5: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line) (Study PX-171-005)

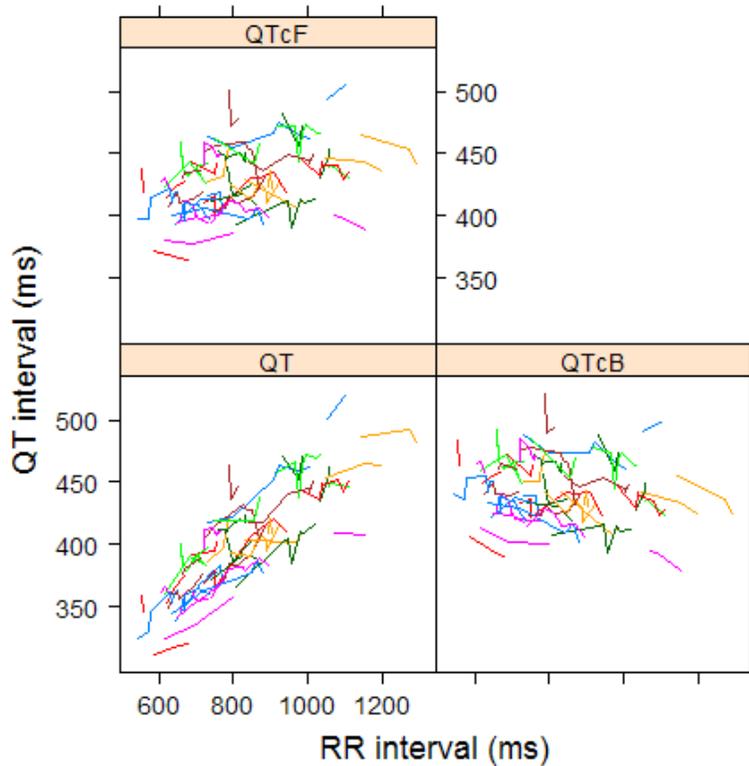
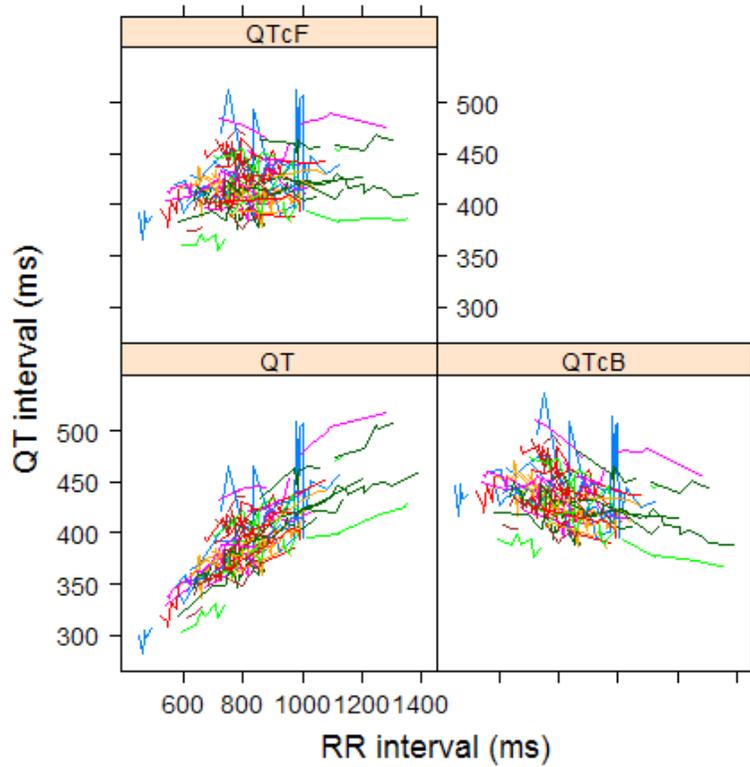


Figure 6: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line) (Study PX-171-007)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Carfilzomib

The mean, 90% CI and standard error are shown for each time point of QTcF evaluation in Table 12 for study PX-171-005 and in Table 13 for study PX-171-007.

Table 12: Analysis Results of Δ QTcF for Carfilzomib 15 mg/m² (Cycle 1) and 20 mg/m² (Cycle 2) (Study PX-171-005)

Cycle	Day	Time (h)	Δ QTcF: Carfilzomib		
			N	Mean (90%CI)	SE
1	1	0.033	48	5.35 (2.3, 8.4)	1.8
1	1	0.33	19	7.07 (4.1, 10)	1.7
1	1	1	47	6.10 (3.3, 8.9)	1.7
1	1	2	19	2.39 (-3.1, 7.9)	3.2
1	1	4	20	1.18 (-3.7, 6.1)	2.8
1	1	24	19	3.96 (-2.7, 11)	3.9
1	15	0.033	43	5.59 (0.33, 11)	3.1
1	15	0.33	21	8.00 (-0.092, 16)	4.7
1	15	1	41	4.15 (-1.4, 9.7)	3.3
1	15	2	18	3.46 (-3.7, 11)	4.1
1	15	4	19	5.42 (-4.1, 15)	5.5
1	15	24	17	1.35 (-7.9, 11)	5.3
2	15	0.033	31	9.41 (3.4, 15)	3.5
2	15	0.33	16	9.44 (1.5, 17)	4.6
2	15	1	31	6.83 (1.1, 13)	3.4
2	15	2	16	8.56 (-0.13, 17)	5.0
2	15	4	15	7.10 (-0.0043, 14)	4.0
2	15	24	11	4.24 (-5.0, 13)	5.1

Table 13: Analysis Results of Δ QTcF for Carfilzomib 20 mg/m² and 36 mg/m², Cycle 1 (Study PX-171-007)

Dose	Day	Time (h)	Δ QTcF Carfilzomib		
			N	Mean (90% CI)	S.E.
20 mg/m ²	1	0.033	38	3.42 (0.6,6.3)	1.70
	1	0.083	29	0.95 (-1.6,3.5)	1.51
	1	0.333	29	0.50 (-2.6,3.6)	1.80
	1	1	62	2.38 (0.5,4.3)	1.16
	1	2	27	2.42 (-1.0,5.8)	1.99
	1	4	29	0.69 (-2.9,4.3)	2.12
	1	24	23	-4.98 (-8.7,-1.3)	2.14
36 mg/m ²	1	0.083	5	-0.20 (-9.0,8.6)	4.11
	1	0.333	6	5.61 (-0.3,11.6)	2.95
	1	1	6	8.28 (2.6,13.9)	2.79
	1	2	6	3.78 (-4.3,11.8)	4.00
	1	4	6	1.56 (-4.8,7.9)	3.16
	1	24	5	1.73 (-6.8,10.3)	4.00
	15	-1	42	-0.59 (-6.3,5.1)	3.37
	15	0.033	28	0.80 (-3.0,4.6)	2.23
	15	0.083	11	16.88 (0.2,33.5)	9.19
	15	0.333	11	18.12 (0.9,35.3)	9.50

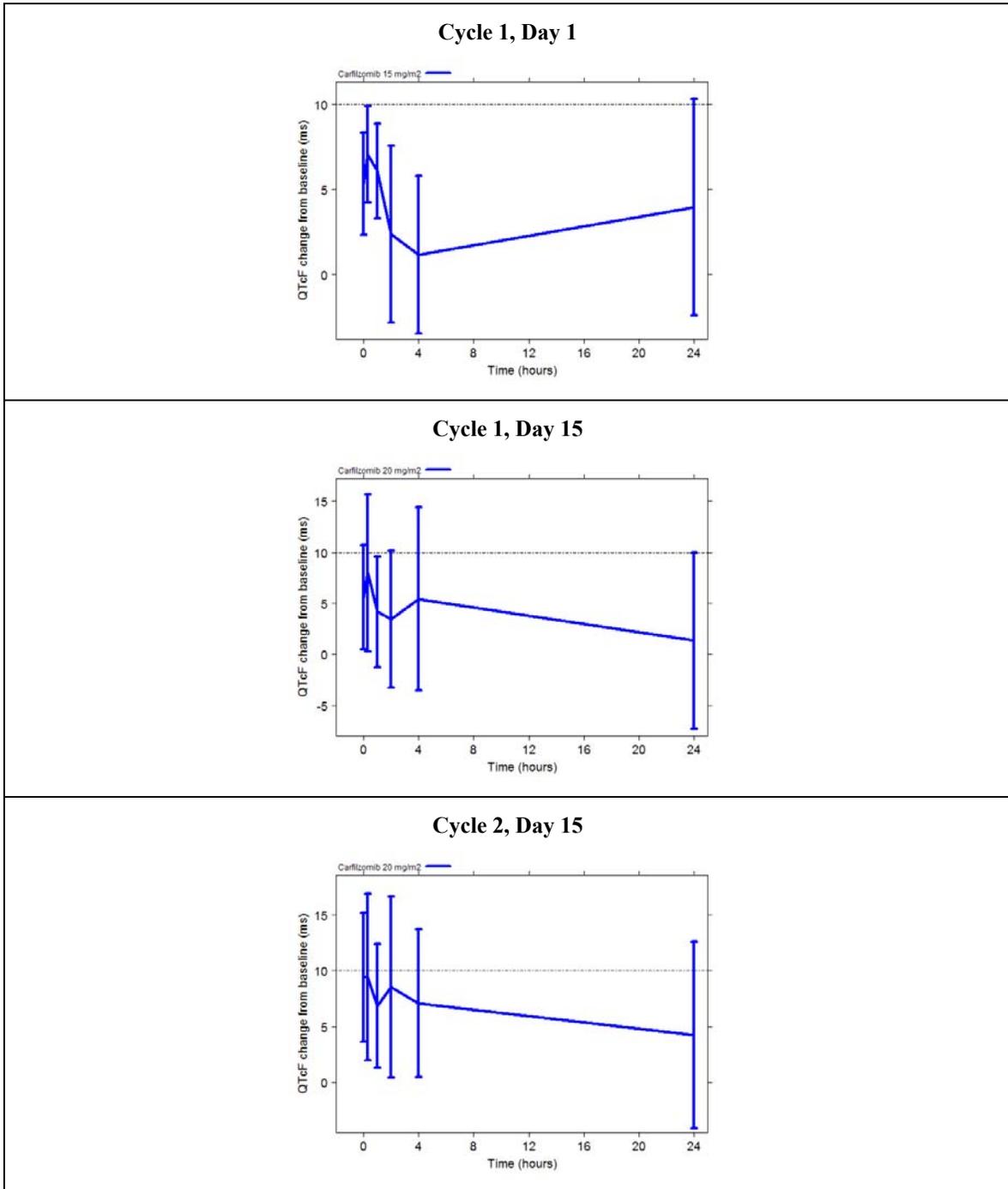
15	1	39	5.29 (-0.4,11.0)	3.39
15	2	11	11.27 (-4.9,27.4)	8.92
15	4	11	6.67 (-6.6,19.9)	7.32
15	24	11	8.12 (-6.3,22.6)	7.98

The largest upper bounds of the 2-sided 90% CI for the mean change from baseline for carfilzomib 15 mg/m², 20 mg/m² and 36 mg/m² were 17, 6.3 and 35.3 ms, respectively.

5.2.1.2 Graph of Δ QTcF Over Time

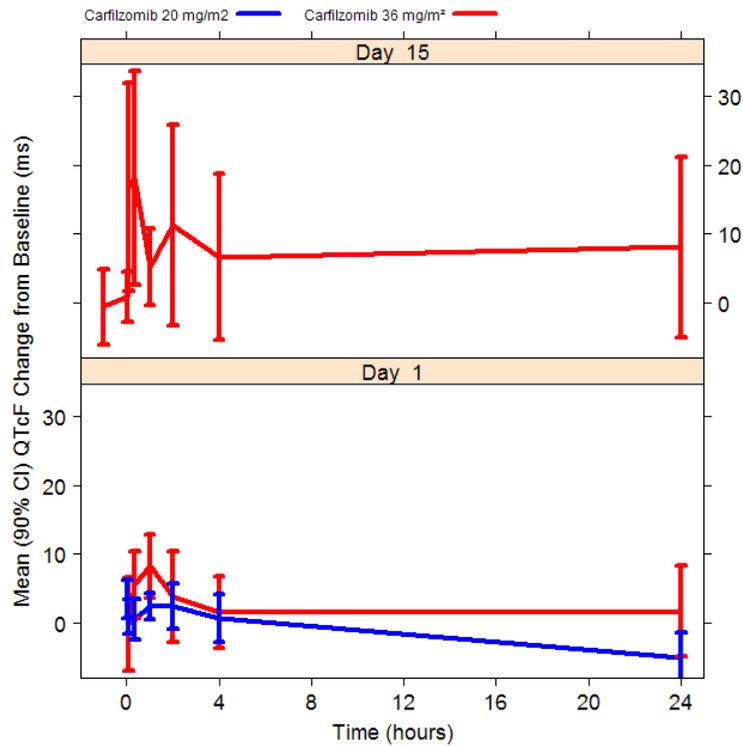
The following figure displays the time profile of Δ QTcF for different treatment groups.

Figure 7: Mean and 90% CI Δ QTcF Timecourses for Day 1, Cycle 1 (Top Panel), Day 15, Cycle 1 (Middle Panel), and Day 15, Cycle 2 (Bottom Panel) (Study PX-171-005)



Best Available Copy

Figure 8: Mean and 90% CI ΔQTcF Timecourse (Study PX-171-007)



5.2.1.3 Categorical Analysis

Table 14 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms and > 480 ms.

Table 14: Categorical Analysis for QTcF

Treatment Group	Total N		Value ≤ 450 ms		480 ms < Value	
	# Subj.	# Obs.	# Subj. (%)	# Obs. (%)	# Subj. (%)	# Obs. (%)
Carfilzomib 15/20 mg/m ²	49	575	28 (57.1%)	462 (80.3%)	5 (10.2%)	11 (1.9%)
Carfilzomib 20 mg/m ²	69	306	58 (84.1%)	270 (88.2%)	2 (2.9%)	5 (1.6%)
Carfilzomib 36 mg/m ²	43	218	37 (86%)	194 (89%)	2 (4.7%)	7 (3.2%)

Table 15 lists the categorical analysis results for Δ QTcF.

Table 15: Categorical Analysis of Δ QTcF

Treatment Group	Total N		Value \leq 30 ms		60 ms < Value	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Carfilzomib 15/20 mg/m ²	49	526	37 (75.5%)	11 (22.4%)	1 (2%)	1 (0.2%)
Carfilzomib 20 mg/m ²	68	237	68 (100%)	237 (100%)	0 (0%)	0 (0%)
Carfilzomib 36 mg/m ²	42	198	41 (97.6%)	191 (96.5%)	1 (2.4%)	7 (3.5%)

5.2.2 HR Analysis

The same analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 16 and Table 17. The largest upper limits of 90% CI for the HR mean change from baseline are 13, 7.5, and 21.3 bpm for carfilzomib 15 mg/m², 20 mg/m², and 36 mg/m².

Table 16: Analysis Results of Δ HR for Carfilzomib 15 mg (Cycle 1) and 20 mg/m² (Cycle 2) (Study PX-171-005)

Cycle	Day	Time (h)	Δ HR: Carfilzomib		
			N	Mean (90%CI)	SE
1	1	0.033	48	-1.8 (-3.1, -0.62)	0.73
1	1	0.33	19	-2.75 (-5.2, -0.35)	1.4
1	1	1	47	-1.03 (-2.5, 0.45)	0.88
1	1	2	19	1.11 (-1.9, 4.1)	1.7
1	1	4	20	7.9 (3.5, 12)	2.6
1	1	24	19	-1.16 (-4.1, 1.8)	1.7
1	15	0.033	43	-2.05 (-4.2, 0.11)	1.3
1	15	0.33	21	-1.34 (-4.1, 1.4)	1.6
1	15	1	41	-0.699 (-3.0, 1.6)	1.4
1	15	2	18	3.01 (-0.33, 6.3)	1.9
1	15	4	19	5.94 (2.4, 9.4)	2.0
1	15	24	17	-1.76 (-6.1, 2.6)	2.5
2	15	0.033	43	-1.34 (-3.9, 1.2)	1.5
2	15	0.33	21	0.479 (-4.1, 5.1)	2.6
2	15	1	41	-1.14 (-3.8, 1.6)	1.6
2	15	2	18	3.90 (-1.0, 8.8)	2.8
2	15	4	19	7.84 (2.6, 13)	3.0
2	15	24	17	2.36 (-3.2, 7.9)	3.0

Table 17: Analysis Results of Δ HR for Carfilzomib 20 mg/m² and 36 mg/m², Cycle 1 (Study PX-171-007)

Dose	Day	Time (h)	N	Δ HR Carfilzomib	
				Mean (90%CI)	S.E.
20 mg/m ²	1	0.033	38	-1.15 (-2.4,0.1)	0.76
	1	0.083	29	-2.15 (-4.4,0.1)	1.32
	1	0.333	29	-1.09 (-3.2,1.0)	1.26
	1	1	62	0.55 (-1.0,2.1)	0.94
	1	2	27	2.03 (-0.8,4.8)	1.64
	1	4	29	4.98 (2.4,7.5)	1.49
	1	24	23	-0.88 (-3.6,1.8)	1.56
36 mg/m ²	1	0.083	5	-1.47 (-5.9,2.9)	2.06
	1	0.333	6	0.94 (-4.0,5.9)	2.45
	1	1	6	2.39 (-0.2,4.9)	1.26
	1	2	6	5.83 (3.2,8.5)	1.31
	1	4	6	15.28 (9.3,21.3)	2.99
	1	24	5	2.33 (-0.9,5.5)	1.50
	15	-1	42	1.08 (-1.1,3.2)	1.27
	15	0.033	28	-0.77 (-3.3,1.8)	1.49
	15	0.083	11	2.15 (-2.0,6.3)	2.31
	15	0.333	11	3.09 (-0.8,7.0)	2.13
	15	1	39	1.86 (0.0,3.8)	1.12
	15	2	11	6.92 (2.9,11.0)	2.23
	15	4	11	12.21 (7.8,16.6)	2.41
15	24	11	4.67 (0.8,8.5)	2.12	

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval.

The outlier analysis results for PR are presented in Table 18.

Table 18: Categorical Analysis for PR

Treatment Group	Total N		PR \geq 200 ms	
	# Subj.	# Obs.	# Subj. (%)	# Obs. (%)
Carfilzomib 15/20 mg/m ²	48	565	14 (29.2%)	90 (15.9%)
Carfilzomib 20 mg/m ²	68	300	8 (11.8%)	26 (8.7%)
Carfilzomib 36 mg/m ²	43	218	3 (7%)	14 (6.4%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. There are 6 (12%), 4 (11%), and 4 (11%) subjects who experienced QRS interval greater than 110 ms following carfilzomib 15 mg/m², 20 mg/m², and 36 mg/m², respectively.

The outlier analysis results for QRS are presented in Table 19.

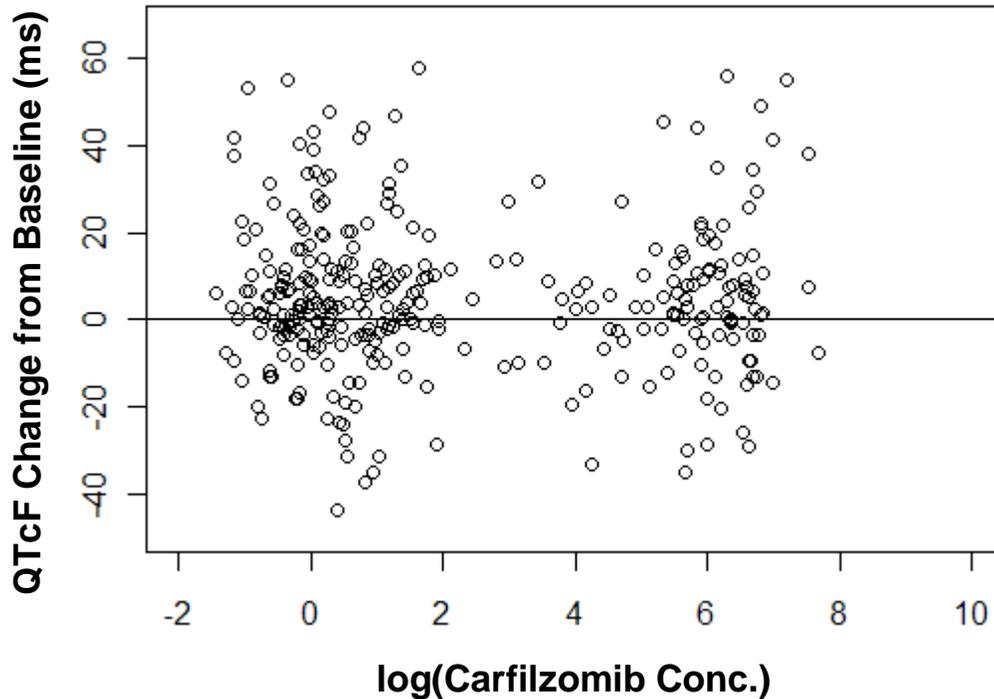
Table 19: Categorical Analysis for QRS

Treatment Group	Total N		QRS \geq 110 ms	
	# Subj.	# Obs.	# Subj. (%)	# Obs. (%)
Carfilzomib 15/20 mg/m ²	49	575	6 (12.2%)	44 (7.7%)
Carfilzomib 20 mg/m ²	69	306	5 (7.2%)	13 (4.2%)
Carfilzomib 36 mg/m ²	43	218	4 (9.3%)	8 (3.7%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between Δ QTcF and carfilzomib concentrations for combined data from study PX-171-005 and study PX-171-007 is visualized in Figure 9 with no evident exposure-response relationship.

Figure 9: Δ QTcF vs. Carfilzomib Concentration. Points Represent Data for Both Study PX-171-005 and PX-171-007 for All Cycles and Days Where Corresponding Concentration and QTcF data Were Available.



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

No significant ventricular arrhythmias or sudden cardiac death occurred in these studies.

5.4.2 ECG assessments

-Study PX-171-005: Sponsor did not submit ECGs

-Study PX-171-007: Sponsor did not submit ECGs

5.4.3 PR and QRS Interval

Twenty five subjects had postbaseline PR > 200 ms. From those subjects, 19 subjects had baseline PR >200 ms. Only one subject had a 25% increase over baseline and was clinically meaningful (293 ms; period 1 day 15).

Fifteen subjects had baseline QRS > 110 ms without post baseline increases.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic Dose ^a	Intravenous infusion administration over 2 to 10 minutes on Days 1, 2, 8, 9, 15, and 16 of a 28-day Cycle Cycle 1: 20 mg/m ² Cycle 2 and beyond: 27 mg/m ²	
Maximum Tolerated Dose	Not determined for the schedule and rate of administration proposed for marketing	
Principal Adverse Events	<p>The most common AEs, defined as any AE occurring in at least 25% of all patients, were: fatigue (55.5%), anemia (46.8%), nausea (44.9%), thrombocytopenia (36.3%), dyspnea (34.6%), diarrhea (32.7%), pyrexia (30.4%), upper respiratory tract infection (28.3%), headache (27.6%), and cough (26.0%).^b Carfilzomib dosing should be withheld and/or modified in patients in whom the creatinine level increases 2-fold or higher from baseline, active or suspected infection, Grade 3 or 4 neutropenia, Grade 4 thrombocytopenia, congestive heart failure (CHF) or other serious cardiac events, serious dyspnea or other pulmonary events, and other Grade \geq 3 non hematological events.^c</p> <p>The rates of discontinuation of carfilzomib for individual AEs other than progressive disease were less than 2%. The most frequent events included pneumonia (1.9%), congestive cardiac failure (1.7%), dyspnea (1.7%), hypercalcemia (1.7%), acute renal failure (1.7%), and increased blood creatinine level (1.3%). Hypercalcemia and acute renal failure and increased blood creatinine level are also signs of progressive disease.^d</p>	
Maximum Dose Tested	Single Dose	No single dose studies were performed
	Multiple Dose	36 mg/m ² : In trial PX-171-007, solid tumor patients were dose escalated on Day 8 of Cycle 1 from 20 mg/m ² to 36 mg/m ²
Exposures Achieved at Maximum Tested Dose	Single Dose	N/A
	Multiple Dose ^e	36 mg/m ² (N = 13) C _{max} : 5718 ng/mL (46.5%) AUC _{last} : 594 hr·ng/mL (52.5%) AUC _{inf} : 663 hr·ng/mL (51.4%)
Range of Linear PK ^f	15–36 mg/m ² using dosing regimen described above	
Accumulation at Steady State	Carfilzomib is rapidly cleared systematically after IV administration. The elimination of carfilzomib was well characterized up to 4 hours post-dose, considering that the mean AUC _{extrapolated} required in the calculation of AUC _{inf} was < 1% across dose levels. Exposure on Day 1 was similar to Day 16, demonstrating no accumulation between doses.	
Metabolites	<p>3 Primary Metabolites:</p> <ul style="list-style-type: none"> • M14 (morpholino-homophenylalanine) derived from peptide hydrolysis. Lacks activity as a proteasome inhibitor • M15 (morpholino-homophenylalanine-leucine) derived from peptide hydrolysis. Lacks activity as a proteasome inhibitor • M16 (diol of carfilzomib) derived from epoxide hydrolysis. Lacks activity as a proteasome inhibitor 	

Absorption	Absolute/Relative Bioavailability	N/A Carfilzomib is an intravenously administered drug
	T _{max} (hours) ^g Median (range)	Carfilzomib: 0.0417 (0.0333, 0.117) M14: 0.542 (0.283, 1.17) M15: 0.308 (0.283, 0.583) M16: 0.117 (0.0833, 0.150)
Distribution	Vd/F or Vd Mean ± SD (CV%)	MM ^g - V _{area} : 104 ± 82 L (78%) ST ⁱ - V _{area} : 223 ± 328 L (147%)
	% Bound ^k	97.8 ± 0.6
Elimination	Route ^g	Renal Excretion: Carfilzomib: < 1% of dose M14: Approximately 30% of dose M15: < 2% of dose M16: A minor metabolite in urine, not quantified. Other routes: To be determined
	Terminal t _{1/2} (hours) Mean (range) ^g	Carfilzomib: 0.398 (0.375, 0.626) M14: 1.53 (1.2, 3.5) M15: 1.47 (1.13, 1.78) M16: 0.64 (0.425, 1.03)
	CL Mean ± SD (CV%)	MM ^g - 15 mg/m ² : 151 ± 79.3 L/hr (52.5%) MM ^h - 20 mg/m ² : 123 ± 28.4 L/hr (23%) ST ⁱ - 20 mg/m ² : 263 ± 398 L/hr (152%)
Intrinsic Factors	Age	No significant effect in population PK analysis ^j
	Sex	No significant effect in population PK analysis ^j
	Race	Unable to determine due to small non-Caucasian population ^j
	Hepatic and Renal Impairment	From a population PK analysis: In patients with severe renal impairment (CrCl < 30 mL/min), CL was reduced by 20% from the typical value for patients with normal renal function. ^k Hepatic Impairment Trial was not conducted.
Extrinsic Factors	Drug Interactions	DDI study with midazolam as CYP3A substrate: No effect of single and repeat dosing of carfilzomib at 27 mg/m ² on the PK of midazolam ^l . No other DDI human studies were conducted based on the results of preclinical inhibition, induction and transporter studies
	Food Effects	N/A Carfilzomib is administered intravenously.

Expected High Clinical Exposure Scenario	No cases of overdosage with carfilzomib were reported during clinical trials in which doses of up to 36 mg/m ² , administered over 2 to 10 minutes, were repeatedly delivered. Carfilzomib is an irreversible inhibitor of the proteasome; there are no known specific antidotes. However, carfilzomib is rapidly cleared and proteasome activity is regenerated in most tissues within 72 hours, likely due to new proteasome transcription and translation. In the event of an overdosage, patient's vital signs should be monitored and appropriate supportive care given. ^m
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^a ISE Section 2.4 Proposed Indication and Dosing/Administration

^b ISS Section 7.2.2.1 Phase 2 Multiple Myeloma Studies: Common Adverse Events

^c ISS Section 2.4.2.3 Dosage Modifications

^d ISS Section 7.3.5.1 Phase 2 Multiple Myeloma Studies: Discontinuations due to Adverse Events

^e Trial PX-171-007 (TR-0475-171): Solid Tumor patients. Samples taken Cycle 1 Day 16. C_{max} and AUC_{last}: Geometric mean (geometric CV%) (TR-0475-171)

^f Determined across trials PX-171-005 (TR-0479-171) (Multiple Myeloma, 15 mg/m² on Cycle 1) and PX-171-007 (TR-0475-171) (Solid Tumor)

^g PX-171-005 (TR-0479-171) (Multiple Myeloma): Cycle 1 Day 1 (Carfilzomib Dose: 15 mg/m²), normal renal function cohort; N = 8

^h PX-171-005 (TR-0479-171) (Multiple Myeloma): Cycle 2 Day 15 (Carfilzomib Dose: 20 mg/m²), normal renal function cohort; N = 8

ⁱ PX-171-007 (TR-0475-171) (Solid Tumor): Cycle 1 Day 1. Carfilzomib Dose: 20 mg/m². N = 30

^j TR-0482-171 Population Pharmacokinetic-Pharmacodynamic Analysis of Carfilzomib Efficacy and Tolerability Endpoints in Multiple Myeloma and Solid Tumor Malignancies Addendum

^k PX-171-005 (TR-0452-171) (Multiple Myeloma): Normal renal function cohort. Carfilzomib Dose: 15 and 20 mg/m². Carfilzomib plasma levels: 64.7–4712 ng/mL.

^l PX-171-008 (TR-0453-171) Phase Ib Open-Label, Non-Randomized Study on the Effects of Carfilzomib on Pharmacokinetics of Midazolam in Subjects with Solid Tumors

^m ISS Section 10.7 Overdose

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

/s/

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03/07/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: February 3, 2012
Application Type/Number: NDA 202714
To: Ann Farrell, MD, Director
Division of Hematology Products
Through: Todd Bridges, RPh, Team Leader
Kellie Taylor, PharmD, MPH, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis
From: Kimberly DeFronzo, RPh, MS, MBA, Safety Evaluator
Division of Medication Error Prevention and Analysis
Subject: Label and Labeling Review
Drug Name and Strengths: Kyprolis (Carfilzomib) for Injection
60 mg per vial
Applicant/sponsor: Onyx Pharmaceuticals, Inc.
OSE RCM #: 2011-3708

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis' (DMEPA's) evaluation of the proposed container label, carton and package insert labeling for Kyprolis (Carfilzomib) for Injection 60 mg per vial, a 505(b)(1) application under NDA 202714, submitted on September 27, 2011, to identify vulnerability that could lead to medication errors.

1.1 PRODUCT INFORMATION

Kyprolis (Carfilzomib) for Injection 60 mg per vial is 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 inhibitor and an immunomodulatory agent. The recommended dose of Kyprolis is 20 mg/m² in Cycle 1, escalating to 27 mg/m² in Cycle 2, to be administered intravenously over 2 to 10 minutes, twice weekly on consecutive days for 3 weeks (Days 1, 2, 8, 9, 15, 16), followed by a 12-day rest period (Days 17 to 28). Dose adjustment may be used to manage adverse events that occur during treatment. No dosing adjustment is necessary for patients with pre-existing renal insufficiency and no pharmacokinetic studies were conducted in patients with hepatic impairment.

Prior to administration, each vial of Kyprolis needs to be reconstituted with 29 mL of Sterile Water for Injection, USP (not provided) for a final concentration of 2 mg/mL of carfilzomib. The final volume after reconstitution with 29 mL sterile water for injection is 30.9 mL which ensures a 30 mL deliverable volume containing 60 mg carfilzomib in accordance with USP <1151>. The overfill in each vial is (b)(4) of carfilzomib.

Kyprolis is packaged in a single-use, (b)(4) vial (b)(4). It is supplied as individually cartoned single-use vial containing a deliverable dose of 60 mg of Carfilzomib as a white to off-white lyophilized cake or powder (NDC 76075-101-01). It should be stored refrigerated at 2°C to 8°C (36°F to 46°F) in the original package.

2 METHODS AND MATERIALS

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following to identify vulnerabilities that may lead to medication errors:

- Container Labels submitted September 27, 2011 - see Appendix A for image
- Carton Labeling submitted September 27, 2011 - see Appendix B for image
- Insert Labeling submitted September 27, 2011 (no image)

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling are unacceptable and introduce vulnerability that can lead to medication errors. We provide recommendations to the Division in Section 3.1 and to the Applicant in Section 3.2. We recommend these revisions be made to the label and labeling prior to approval of the product.

If you have further questions or need clarifications, please contact Sue Kang, OSE Project Manager, at 301-796-4216.

3.1 COMMENTS TO THE DIVISION

A. *Insert Labeling*

1. The Dosage and Administration Section in the Highlights of the Prescribing Information describes the recommended dose as “20/27 mg/m²” which may lead to misinterpretations of the intended dose due to the ambiguity caused by the use of the slash. Therefore, this information should be revised to clearly state the actual recommended dose.
2. The Dosage and Administration Section in the Full Prescribing Information discussion should avoid the use of abbreviations (e.g., IV) and ensure that all numbers cited in tables (e.g., Table 1) and texts (e.g., 250 *mL* to 500 mL) are accompanied by the appropriate unit of measure to avoid confusion and/or misinterpretation.
3. The following comments pertain to the “Reconstitution and Preparation for Intravenous Administration” section 2.6 under the Dosage and Administration Section in the Full Prescribing Information:
 - a. Add the statement [REDACTED] (b) (4) following the “single use” statement on line 3 under section 2.6.
 - b. Remove [REDACTED] (b) (4) it is sufficient to only state the recommended diluent of Sterile Water for Injection, USP.
 - c. Express stability timeframe in *hours* to avoid possible confusion with *days* in Table 3. For example: Clearly state “24 hours” and [REDACTED] (b) (4) since the table heading of “in Hours” can easily be overlooked by a busy healthcare professional.
4. The “How Supplied/Storage and Handling” Section in the Full Prescribing Information should clearly state “60 mg Carfilzomib per vial” instead of [REDACTED] (b) (4) following the NDC number.

3.2 COMMENTS TO THE APPLICANT

A. *Container Label*

1. Ensure the prominence of the established name (including the dosage form “for Injection”) is at least ½ the size of the proprietary name taking into account typography, layout, contrast, and other printing features to ensure

it has prominence commensurate with the proprietary name as per 21 CFR 201.10(g)(2).

2. Revise the presentation of the strength statement to read “60 mg per vial” or “60 mg/vial”.
3. Replace the hyphen within the temperature designations with the word “to” for improved clarity and to be consistent with USP standards. We recommend not using the hyphen between the numbers since a hyphen can be misinterpreted as a minus sign when discussing temperatures. Therefore, revise the statement to read “Store refrigerated at 2°C to 8°C (36°F to 46°F)”.
4. Add the statement “Once reconstituted with 29 mL of Sterile Water for Injection, the resultant concentration is 2 mg/mL” above the statement that reads “The reconstituted lyophilized product...”
5. Remove the words (b) (4) following the strength designation as it is redundant and crowds the label.
6. Remove the word (b) (4) as it is unnecessary information and crowds the label.
8. Revise the statement (b) (4) to read “Single-use vial. Discard unused portion.” (b) (4)

The statement “Discard unused portion.” further serves as an important reminder that unused portion should be discarded.
9. Relocate the statement “For Intravenous Administration Only.” from the side panel to the front panel and ensure equal prominence to the statement “Single-use vial. Discard unused portion.” However, the use of adequate white space separating these statements is necessary since close proximity of these statements may lead healthcare professionals to misinterpret the meaning as giving the entire vial via intravenous route of administration.
10. Reduce the font size, unbold, and relocate the statement “Rx only” to the bottom of the label to reduce crowding near the strength and other important information.
11. Reduce the prominence of the manufacturer’s information to avoid competing with other important information.

B. Carton Labeling

1. Revise the carton labeling as per comments A1 through A9 above.
2. Add the strength designation “60 mg per vial” to the top flap of the carton labeling under the established name.
2. Reduce the prominence of the company name “Onyx” and the red circular graphic on the side panel. As currently presented, the company name may be misinterpreted as a product name.

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

KIMBERLY A DE FRONZO
02/03/2012

TODD D BRIDGES
02/03/2012

CAROL A HOLQUIST
02/03/2012



Center for Drug Evaluation and Research

Division of Cardiovascular and Renal Products

Consultation and Medical Review, NDA 202714

DATE: Consult requested: 27 September 2011
Date Reassigned: 21 November 2011
Desired Completion date: 16 December 2011

FROM: Preston M. Dunmon, M.D., Medical Officer
Division of Cardiovascular and Renal Products, HFD-110

THROUGH: Norman Stockbridge, M.D., Ph.D., Division Director
Division of Cardiovascular and Renal Products, HFD-110

TO: Karen Bengtson, RPM / Nicole Gormley, MO
Division of Hematology Products

SPONSOR: Onyx Pharmaceuticals
DRUG CLASS: Antineoplastic
TRADE NAME: Carfilzomib
FORMULATION: IV

APPLICATION No: NDA 202714
RELATED APP No: IND 71,057

PROPOSED INDICATION: for the treatment of patients with relapsed and refractory multiple myeloma (MM) who have received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent.

CONSULT QUESTION: Please provide insight into what other information we should request of the sponsor that would help characterize the cardiovascular safety profile of this product. After receipt of additional information, we would appreciate your assistance evaluating the significance of the cardiac arrests, heart failure, and pulmonary hypertension cases noted in the safety database.

DOCUMENTS AVAILABLE FOR REVIEW:

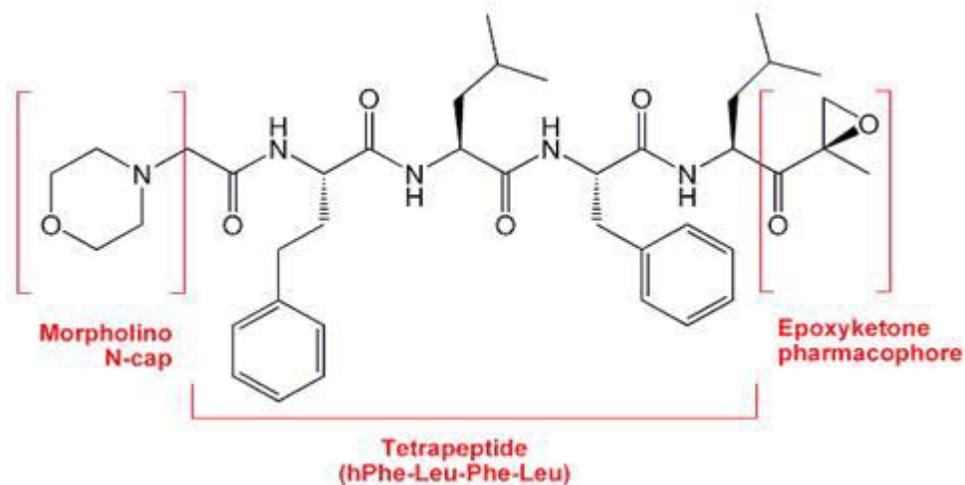
NDA 202,714 consult for DCRP
NDA 202,714 and supporting submissions
IND 71,057 and supporting submissions
Bortezomib (Velcade) label, revised/approved November 2011

Introduction

Carfilzomib is an irreversible, rapidly acting synthetic small molecule proteasome inhibitor being submitted under subpart H for accelerated approval based on available safety and efficacy data from prior phase I and phase II trials. Two confirmatory phase III trials are in progress. The proposed indication for carfilzomib is for the treatment of patients with relapsed and refractory multiple myeloma (MM) who have received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent.

The chemical name of the compound is (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide. The molecular formula is C₄₀H₅₇N₅O₇ and the molecular weight is 719.91. The chemical structure of carfilzomib is shown in [Figure 1](#).

Figure 1. Chemical Structure of Carfilzomib



The pivotal study submitted by the sponsor is PX-171-003-Part 2. This is a phase II, single arm trial. The integrated summary of safety is comprised of a safety data base of 768 patients. Five hundred twenty six patients were enrolled on phase II trials conducted by Onyx. Of this subset of patients, 118 (22.4%) patients had a cardiac adverse event. In study PX-171-003, there was a 7% incidence of adverse events for the grouped cardiac failure term, which included events of congestive heart failure, pulmonary edema, ejection fraction decreased, and acute pulmonary edema. Additionally, the ISS states that there were 9 (1.7%) cases of pulmonary hypertension. However, a search of the provided narratives using the term “pulmonary hypertension” resulted in 9 additional cases. In these cases, pulmonary hypertension was reported as occurring in the narrative, but was not listed as an AE. This suggests that there may be significant underreporting of cardiac events and pulmonary hypertension in particular. Lastly, there were seven cardiac events with death reported as the outcome. The cardiotoxic effects of carfilzomib were demonstrated in preclinical studies as well. It is hypothesized that the highly reactivity of the epoxyketone moiety in this compound may be contributing to some of its toxicity.

DCRP is consulted to identify what other information the review division should request of the sponsor that would help characterize the cardiovascular safety profile of this product, and then, after receiving additional data from the sponsor, to assist in evaluating the significance of the cardiac arrests, heart failure, and pulmonary hypertension cases noted in the safety database.

Regulatory and Scientific Background – Bortezomib (Velcade)

Cardiotoxicity is a known complication of other agents with this mechanism of action. Specifically, the one FDA-approved inhibitor of the chymotrypsin-like (CT-L) activity of the 20S proteasome, bortezomib (velcade), is labeled as follows (November, 2011):

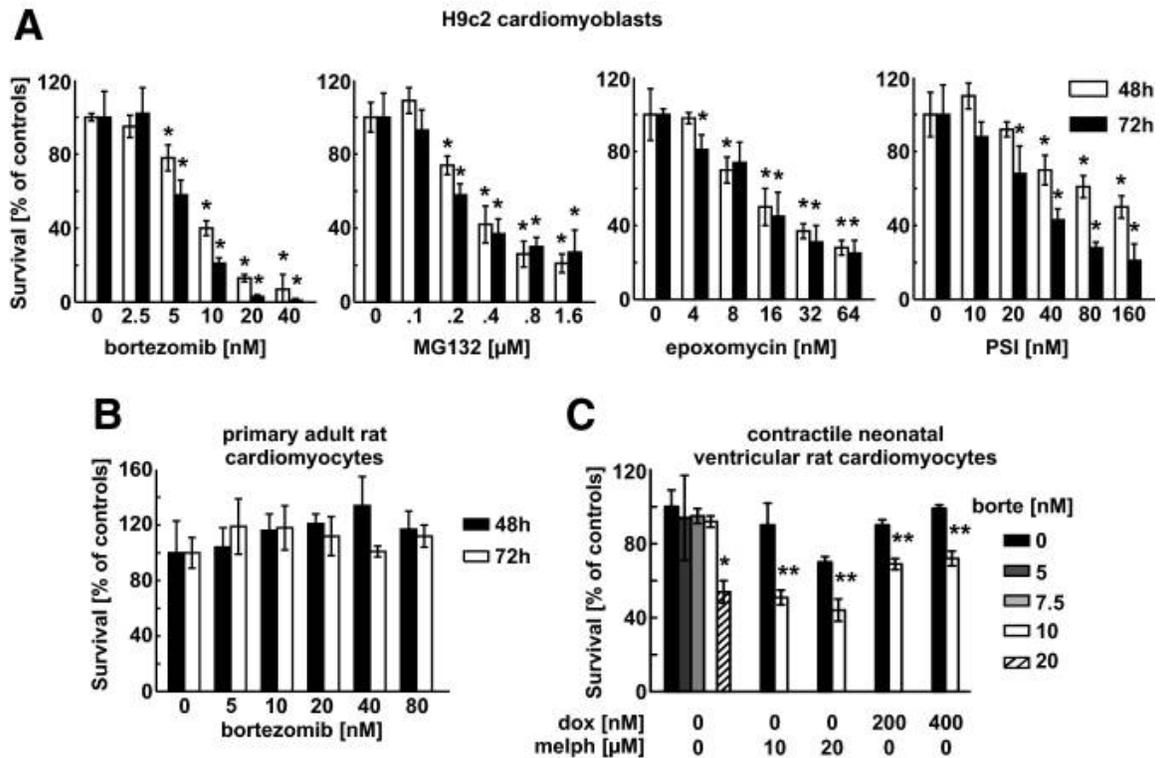
- Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins.... Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types *in vitro*. Bortezomib causes a delay in tumor growth *in vivo* in nonclinical tumor models, including multiple myeloma.
- Cardiovascular Toxicity: Studies in monkeys showed that administration of dosages approximately twice the recommended clinical dose resulted in heart rate elevations, followed by profound progressive hypotension, bradycardia, and death 12 to 14 hours post dose. Doses $\geq 1.2 \text{ mg/m}^2$ induced dose-proportional changes in cardiac parameters. Bortezomib has been shown to distribute to most tissues in the body, including the myocardium. In a repeated dosing toxicity study in the monkey, myocardial hemorrhage, inflammation, and necrosis were also observed.
- Chronic Administration: In animal studies at a dose and schedule similar to that recommended for patients (twice weekly dosing for 2 weeks followed by 1-week rest), toxicities observed included severe anemia and thrombocytopenia, and gastrointestinal, neurological and lymphoid system toxicities. Neurotoxic effects of bortezomib in animal studies included axonal swelling and degeneration in peripheral nerves, dorsal spinal roots, and tracts of the spinal cord. Additionally, multifocal hemorrhage and necrosis in the brain, eye, and heart were observed.
- From clinical trials, the incidence of hypotension (postural hypotension, orthostatic hypotension and hypotension NOS) was 13% in patients treated with velcade. Hypotension was Grade 1 or 2 in the majority of patients and Grade 3 in 3% and \geq Grade 4 in < 1%. Three percent (3%) of patients had hypotension reported as an SAE, and 1% discontinued due to hypotension.... In addition, 2% of patients experienced hypotension and had a syncopal event. Doses of antihypertensive medications may need to be adjusted in patients receiving velcade.

- Other cardiac SAEs from clinical trials: angina pectoris, atrial fibrillation aggravated, atrial flutter, bradycardia, sinus arrest, cardiac amyloidosis, complete atrioventricular block, myocardial ischemia, myocardial infarction, pericarditis, pericardial effusion, *Torsades de pointes*, ventricular tachycardia.
- 2% of the patients died and the cause of death was considered by the investigator to be possibly related to study drug: including reports of cardiac arrest, congestive heart failure, respiratory failure, renal failure, pneumonia and sepsis.
- Postmarketing cardiac and pulmonary ADR experience: atrioventricular block complete, cardiac tamponade, acute diffuse infiltrative pulmonary disease.
- Warnings and precautions:
 - **Cardiac Disorders** - Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have been reported, including reports in patients with no risk factors for decreased left ventricular ejection fraction. Patients with risk factors for, or existing heart disease should be closely monitored. In the relapsed multiple myeloma study, the incidence of any treatment-emergent cardiac disorder was 15% and 13% in the velcade and dexamethasone groups, respectively. The incidence of heart failure events (acute pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock, pulmonary edema) was similar in the velcade and dexamethasone groups, 5% and 4%, respectively. There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established.
 - **Pulmonary Disorders** – there have been reports of acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration and Acute Respiratory Distress Syndrome (ARDS) in patients receiving velcade. Some of these events have been fatal. In a clinical trial, the first two patients given high-dose cytarabine (2g/m² per day) by continuous infusion with daunorubicin and velcade for relapsed acute myelogenous leukemia died of ARDS early in the course of therapy. There have been reports of pulmonary hypertension associated with velcade administration in the absence of left heart failure or significant pulmonary disease.

In the years following its approval in 2003, multiple reports of bortezomib-associated cardiotoxicities in patients have appeared in the literature, including congestive heart failure, complete heart block, cardiac arrhythmias, and cardiac arrest (Dasanu 2010, Hampton 2011, Honton 2010, Jerkins 2010, Yeh 2009). To further investigate the mechanisms of cardiotoxicity of bortezomib and other proteasome inhibitors, the effects of these agents were assessed in living rats, as well as in tissue cultures of rat cardiomyoblasts (Nowis, 2010). In these studies, bortezomib and three other proteasome

inhibitors (MG132, PSI, and epoxomycin) reduced survival of H9c2 rat myoblasts in a time and dose dependent manner, in the range of concentrations that induced cytostatic/cytotoxic effects in human tumor cells, as shown in **Figure 2** below:

Figure 2. Proteasome Inhibition in Rat Myoblasts

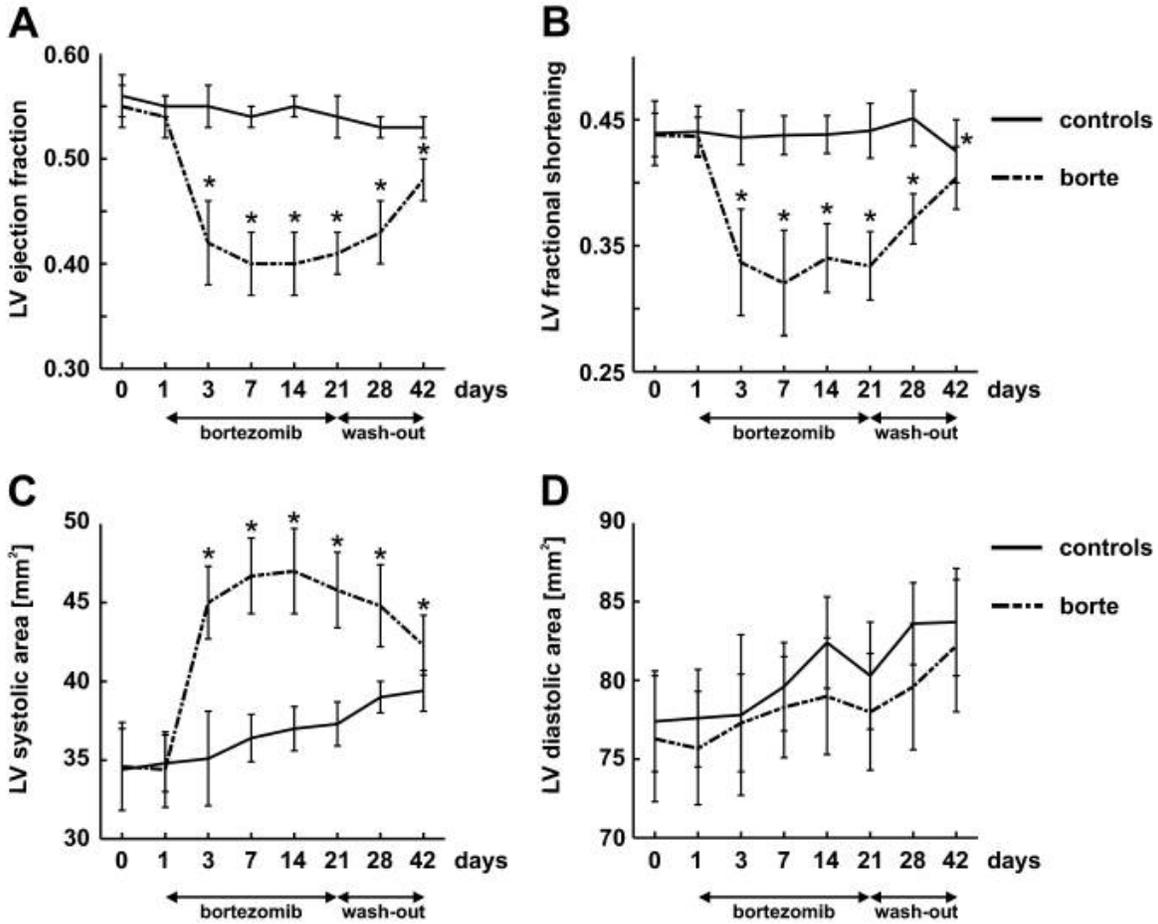


*Proteasome inhibitors induce cytostatic/cytotoxic effects in H9c2 rat cardiac myoblast cells. A: H9c2 cells were incubated for 48 or 72 hours with indicated concentrations of selected proteasome inhibitors: bortezomib, MG132, epoxomycin, and carbobenzoxy-l-Ile-Glu-(O-t-butyl)-Ala-Leucinal (PSI). The cytostatic/cytotoxic effects were measured with crystal violet staining. B: Primary ventricular cardiomyocytes isolated from adult rats were incubated with bortezomib. The cytostatic/cytotoxic effects were measured with crystal violet staining. C: Contractile neonatal ventricular rat cardiomyocytes were incubated with bortezomib. The cytostatic/cytotoxic effects were measured with XTT assay. Bars represent percent survival versus untreated controls. Data are mean ± SD *P < 0.05 versus controls (two-tailed Student's t-test). **P < 0.05 versus chemotherapy alone (two-tailed Student's t-test).*

As a consequence of proteasome inhibition, ultrastructural changes in these H9c2 myoblasts included the marked accumulation of polyubiquitinated proteins (indirect immunofluorescence) and the induction of ER stress as indicated by the induction of binding protein (BiP) expression (Western blot), as well as pronounced widening of ER lumen (TEM). Bortezomib treatment of these myoblasts also led to the formation of multilamellar and lysosomal/autophagosomal structures (TEM). In vivo treatment of Wistar rats with bortezomib at a dose that produced blood concentrations comparable

with those seen in humans produced a time-dependent and significant drop in left ventricular ejection fraction by echocardiography, as shown in **Figure 3** below:

Figure 3. Bortezomib Impairs LV Function



*Bortezomib reversibly impairs systolic, but not diastolic, heart muscle function in rats. Wistar rats were treated for 3 weeks with 0.2 mg/kg i.p. bortezomib (thrice weekly) followed by 3-week wash-out. Control animals received diluent. At indicated time points, echocardiographic examination was performed. Graphs present selected echocardiographic parameters in bortezomib-treated rats (scattered line) and control animals (solid line). Data are mean \pm SD. * $P < 0.001$ vs controls (two-tailed Student's t -test). **A:** LV ejection fraction. **B:** LV fractional shortening. **C:** LV systolic area. **D:** LV diastolic area.*

Bortezomib is administered as an intravenous (IV) bolus on Days 1, 4, 8, and 11 of a 21-day cycle at a dose of 1.3 mg/m^2 . At the 1.3 mg/m^2 dose, the mean maximum plasma concentration is in the range of 89 to 120 ng/mL with mean elimination half life ($t_{1/2}$)

ranging from 76 to 108 hours, [REDACTED]

(b) (4)

Carfilzomib

Carfilzomib is an irreversible inhibitor of the chymotrypsin-like (CT-L) activity of the 20S proteasome that has been submitted to FDA for approval (NDA 202714) 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 (i.e., patients who have failed bortezomib along with either thalidomide or lenalidomide).

According to the sponsor, carfilzomib is a potent, highly selective, irreversible inhibitor of the proteasome with a distinct pharmacology and safety profile relative to bortezomib:

- Carfilzomib is a tetrapeptide epoxyketone that selectively and potently inhibits the CT-L activity of the proteasome. Mechanistically, carfilzomib forms an irreversible, covalent adduct with the N-terminal threonine residue of the CT-L active sites of the constitutive proteasome (Beta5 subunit) and immunoproteasome (LMP7 subunit). In contrast, the dipeptide boronate bortezomib forms a reversible hemiacetyl adduct with the side chain hydroxyl of the N-terminal threonine in the same active sites. Proteasome inhibition by carfilzomib is prolonged relative to bortezomib in vitro and in animal models ([Demo et al. 2007](#)). Although carfilzomib has a pharmacokinetic (PK) $t_{1/2}$ of less than 1 hour, it is an irreversible inhibitor. Proteasome activity recovers with a $t_{1/2}$ of approximately 24 hours in human tumor cell lines in vitro and rodent tissues in vivo, most likely due to induction of new proteasome synthesis.
- Nonclinical studies support that carfilzomib, relative to bortezomib, results in a longer period of proteasome inhibition in vitro and in vivo and can be safely administered to animals at doses that result in more potent inhibition in blood and tissues than can be safely achieved with bortezomib.
- Carfilzomib inhibited proliferation and induced apoptosis in bortezomib-resistant multiple myeloma cell lines and samples from patients with clinical bortezomib resistance.
- Carfilzomib is highly selective for the proteasome relative to other protease classes and does not induce neurodegeneration in a model in which bortezomib was neurotoxic and inhibited a protease involved in neuronal cell survival. Preclinical studies have shown that bortezomib inhibits off target serine proteases such as HtrA2/Omi (known to be involved in neuronal survival) and induces neurite degeneration in vitro and this inhibition may contribute to the clinical toxicity.

- In rats and monkeys, carfilzomib can be administered safely at doses that result in near complete inhibition of the proteasome in blood on dose intensive schedule (e.g., weekly administration of daily dosing for 2 days [QD × 2]) that are not feasible with bortezomib.

The proposed to-be-marketed dose and schedule of administration is carfilzomib 20/27 mg/m² administered intravenously over 2–10 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 17–28). The 28-day period is considered a treatment cycle. In Cycle 1, carfilzomib is administered at a dose of 20 mg/m². If carfilzomib is well tolerated in Cycle 1, the dose should be escalated to 27 mg/m², beginning in Cycle 2 and continuing in subsequent cycles until disease progression or unacceptable toxicity occur.

Carfilzomib induces proteasome CT-L inhibition and, in vitro, it is cytotoxic to tumor cells [50% inhibitory concentration (IC₅₀) < 100 nM], including cells made resistant to bortezomib. When administered to animals at its MTD, carfilzomib induces greater levels of proteasome inhibition (≥ 80%) than have been reported for bortezomib.

IV carfilzomib administration resulted in suppression of proteasome CT-L activity when measured in blood 1 hour after the first dose. Inhibition of proteasome CT-L activity was comparable in whole blood and PBMCs. Proteasome inhibition was maintained for ≥ 48 hours following the first dose of carfilzomib for each week of dosing. Near-complete recovery of proteasome activity was observed in PBMCs between cycles.

On Day 1 of Cycle 1, average maximum concentration (C_{max}) values were 2,546 ng/mL and 3,060 ng/mL following administration of 15 and 20 mg/m², respectively. On Day 16 of Cycle 1, average C_{max} was 4564 ng/mL following administration of 27 mg/m², indicating a dose proportional increase in C_{max} across the dose range of 15 to 27 mg/m². In addition, a dose dependent increase in AUC was seen between 20 and 36 mg/m². Following repeated doses of carfilzomib at 15 and 20 mg/m², AUC and t_{1/2} were similar on Days 1 and 15 or 16 of Cycle 1, suggesting no systemic accumulation of carfilzomib.

IV administration of doses of 15 mg/m² or higher, carfilzomib is rapidly cleared from the systemic circulation of humans with a t_{1/2} of less than 1 hour. The systemic clearance, which ranged from 2.7 to 30 L/min, exceeds liver blood flow, suggesting that carfilzomib is largely cleared non-hepatically. Because carfilzomib is largely cleared through extrahepatic mechanisms, no study was conducted to compare the PK of carfilzomib in patients with hepatic impairment. Carfilzomib is eliminated primarily in the form of inactive peptide fragments with less than 1% excreted as parent drug. The volume of distribution at steady state (V_{ss}) ranged from 10 to 228 L, suggesting a wide tissue distribution of carfilzomib.

The metabolites do not have significant activity as 20S proteasome inhibitors. Cytochrome P450-mediated mechanisms play a minor role in the overall metabolism of carfilzomib. Pathways of carfilzomib elimination have not been characterized in humans.

Extensive analysis in renally impaired patients has indicated that dose adjustment of carfilzomib for baseline renal insufficiency is not required:

- The level of renal impairment did not have an apparent effect on C_{max} or AUC or on clearance of carfilzomib following single- or repeat-dose administration.
- Exposure levels of the metabolite M16 in patients with multiple myeloma and renal impairment were similar to those observed in patients with normal renal function. For the metabolites M14 and M15, exposure increased relative to the level of renal impairment.
- The level of renal impairment had no apparent effect on the PDn of carfilzomib.

Pop PK analysis suggests that the only significant covariate according to the sponsor was a reduction of carfilzomib plasma clearance by 20% in patients with severe renal impairment ($CrCl < 30$ mL/min). The covariates of patient sex, age, and race had no detectable influence on exposure.

In repeat-dose toxicity studies, carfilzomib was administered to rats and monkeys as an IV bolus dose daily for 5 days (QDx5) with nine days rest for two 14-day cycles (28 days total duration). Dose-limiting toxicities (DLTs) included toxicity to the gastrointestinal tract, bone marrow, pulmonary, and cardiovascular systems. At the maximum tolerated dose (MTD), a transient change in platelets without a reduction in the number of megakaryocytes may suggest that, as with bortezomib, inhibition of proteasome activity results in blockade of platelet budding from megakaryocytes.

In a cardiovascular safety study in monkeys, a single dose administration of carfilzomib at either 12 mg/m² (1 mg/kg) or 24 mg/m² (2 mg/kg) resulted in no observations of toxicity and no cardiovascular, pulmonary, or neurobehavioral signs or symptoms. Males that received 36 mg/m² showed evidence of premature ventricular complexes, decreased blood pressure, alterations in the electrocardiogram, and an increase in serum troponin-T concentration, but there was no prolongation of the QT interval. No formal ICH S7B trials have been conducted.

Pre-Clinical Safety

Animal data demonstrates the cardiotoxic potential of carfilzomib.

Specifically, the study in cynomolgus monkeys dosed at 36 mg/m² (less than two fold above the highest proposed to-be-marketed dose of 27 mg/m²) resulted in one animal experiencing PVCs, and a second demonstrating ischemic ECG changes, hypotension, tachycardia, elevated serum troponin, and clinical pallor. At necropsy, this animal demonstrated peribronchial edema, hydrothorax/hydropericardium, myocardial and epicardial tissue abnormalities, and a gelatinous mass adhering to the endocardium. In another study in monkeys, animals receiving 24 mg/m² on 2 consecutive days resulted in myocardial necrosis, azotemia, and elevated Troponin I.

In rats, a single-dose IV bolus of 48 mg/m² over 20 seconds resulted in death, while this same dose given over 30 minutes did not, in spite of the latter's near complete inhibition of proteasome activity in the heart.

In repeated-dose studies in rats and monkeys, DLTs for animals that lead to early deaths or sacrifices were related to cardiovascular abnormalities. Findings included fluid accumulation in the thoracic, pleural, or pericardial cavities; cardiac failure/necrosis; GI hemorrhage/necrosis; and renal tubular necrosis. In animals reaching scheduled sacrifice, myocardial hypertrophy, degeneration, necrosis, inflammation, and fibrosis were noted and resolved during non-dosing periods of 2 to 8 weeks.

Of note, similar findings as described above were observed in a safety pharmacology study conducted with bortezomib, so these types of pre-clinical findings may well represent a class effect. The sponsor notes that “these nonclinical findings suggest that proteasome inhibition in animals is associated with cardiotoxicity and that the dose of either carfilzomib or bortezomib capable of inducing these changes is lower than the human equivalent dose.”

Carfilzomib inhibited hERG in vitro with an IC₅₀ of 2.1 mcM; however, no QTc prolongation was detected in monkeys treated for 9 months at dosage levels up to 2 mg/kg (24 mg/m²) on the same cyclical dose schedule utilized in Phase 2 clinical studies.

With respect to non-clinical pulmonary toxicity, the sponsor states the following in the ISS:

“Nonclinical studies with carfilzomib demonstrated clinically significant dyspnea leading to death in some animals, and severity depended on the method of administration. In rats treated with IV bolus (< 20 seconds) administration carfilzomib at 8 mg/kg (48 mg/m²), lethality was noted in 44% of animals, and severe pulmonary findings, including dyspnea and tachypnea, were noted in the surviving animals at approximately 18 hours postdose (Report [TR-0356-171](#)). These clinical signs were not seen in animals receiving the same dose as a 30-minute infusion despite equivalent and near complete proteasome inhibition in lung tissue. Dyspnea, tachypnea, and/or respiratory distress were noted in the repeat-dose administration toxicity studies in rats and monkeys at doses that also resulted in mortality in both species (Reports [TR-0014-171](#), [TR-0017-171](#), [TR-0072-171](#), and [TR-0073-171](#)). The pulmonary changes were usually characterized by edema, hemorrhage, and interstitial inflammation, and some were considered severe enough to have contributed to the early deaths of some animals in these studies. These pulmonary changes may have been secondary to the heart lesions described in Section 7.4.1.1. Pulmonary changes in animals recovered during nondosing periods of 2 to 8 weeks. In chronic toxicity studies of bortezomib, labored breathing was noted in monkeys; and pulmonary lesions of necrosis, histiocytosis, and inflammation were noted in rats at the highest tested doses ([Bortezomib Summary Basis of Approval](#)). These preclinical pulmonary findings

found with both bortezomib and carfilzomib may be indicative of a proteasome inhibitor class effect.

Clinical Safety

In assessing cardiac safety from carfilzomib trial data, it must be borne in mind that there are no controls in any of the Phase 2 trials – all were cancer patients who received active therapy. Cross-trial comparisons of cardiac event rates with bortezomib trials are thus made particularly difficult, but it is important to keep in mind that this is a group of patients who have failed bortezomib already, so are further down the path of their cancers' clinical courses.

The ISS includes data from 768 patients treated with carfilzomib in nine Phase 1 and Phase 2 clinical studies. Of these 768 patients, the majority (612 [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. In addition to the 768 patients included in the ISS safety database, 135 patients were treated in non-Onyx-sponsored studies (i.e., Investigator-Sponsored Trials and Single-Patient INDs), and a line listing of the SAEs reported for these patients is included in the ISS.

Assessments for potential cardiovascular toxicity included ECGs, blood pressure, and heart-rate. Troponin T and I were assessed only in the initial Phase 1 [PX-171-001](#) and [PX-171-002](#). In all the other studies, cardiac-specific laboratory assessments, such as troponin or atrial/brain natriuretic peptide, or other assessments, such as echocardiography or cardiac multigated acquisition scans, were not required to evaluate study eligibility or to evaluate study drug safety.

In the pivotal safety data, the most frequently reported serious adverse events (SAEs) (excluding progressive disease) were pneumonia, renal failure acute, pyrexia, cardiac failure congestive, and pathologic fracture. The cause of on-study death was progressive disease in the majority of patients (14 of 24) who died. Other causes of death or AEs thought to contribute to death included cardiac events (acute coronary syndrome, cardiac arrest, congestive cardiac failure), infection (sepsis, pneumonia), hepatic failure, dyspnea, hemorrhage intracranial (without thrombocytopenia), and tumor lysis syndrome (TLS). AEs most commonly leading to discontinuation of carfilzomib included cardiac failure congestive (1.5%) and cardiac arrest (1.5%).

In its safety profile summary and recommendations, the sponsor notes the following with respect to cardiac and pulmonary events:

“Cardiac events of acute congestive heart failure (CHF), ischemic cardiac events, and arrhythmias were reported and in some instances were serious or fatal. While patients with New York Heart Association (NYHA) Class I-II CHF may be

treated, patients with risk factors for, or evidence of, existing heart disease should be closely monitored with routine clinical examination throughout their treatment with carfilzomib. Carfilzomib should be held if clinically significant cardiac events such as arrhythmias, including QTc prolongation, develop or appear to be exacerbated by treatment or if myocardial ischemia or infarction or CHF are manifested. Once the event resolves or returns to Baseline, carfilzomib treatment may be resumed at a reduced dose, with a return to full dose if tolerated. Dyspnea, either of cardiac or pulmonary origin, was a commonly reported AE that was typically of low severity, but in some cases it was serious; in such cases, cardiopulmonary assessment should be performed to determine the etiology.”

To place these high cardio-pulmonary event rates into context, the sponsor rightly points out that MM patients are especially prone to cardiac events, due to myocardial infiltration with amyloid leading to dilated/restrictive cardiomyopathy and CHF, hyperviscosity limiting coronary flow, anemia exacerbating ischemia, toxicity from prior anthracycline therapy presenting as arrhythmia, LV dysfunction, or pericarditis-myocarditis syndrome, bone involvement leading to high output CHF, and the reality that the median age of the MM patient at diagnosis is approximately 70 years.

Analysis of Cardiac Events

A medical history of events in the cardiovascular system was reported for 73.6% and 62.8% of patients in the Phase 2 and Phase 1 MM Studies, respectively. Importantly, in the Phase 2 MM Studies, 52.5% of patients had previously been treated with anthracycline-based chemotherapy, and 75.5% had previously received bortezomib, 88.4% had received alkylating agents, 80.6% had received lenalidomide, and 73% received thalidomide, while 70.7% had received other chemotherapeutic agents that may have cardiovascular effects. In addition, 74.5% of patients in the Phase 2 MM Studies had received stem-cell transplantations, which also may have cardiovascular effects. Similar summaries regarding prior treatment for multiple myeloma are not available for patients in the Phase 1 MM Studies.

Of the 526 patients in the Phase 2 MM Studies, 22.4% (118 patients) reported 1 or more events in the Cardiac Disorders SOC (ISS Post-text [Table 2.2.2](#)). The most frequently reported events were cardiac failure congestive (23 patients, 4.4%), tachycardia (22 patients, 4.2%), and palpitations (14 patients, 2.7%). Cardiac failure congestive was most often classified as a Grade 3 event (19 of 23 patients), whereas all tachycardia and palpitations events were categorized as maximum Grade 1 or 2 events (22 and 14 patients, respectively) (ISS Post-text [Table 2.2.5](#)). SAEs in the Cardiac SOC were reported by 41 patients (7.8%) (ISS Post-text [Table 3.2.2](#)). The most frequently reported SAEs were cardiac failure congestive (18 patients, 3.4%), cardiac arrest (5 patients, 1.0%), atrial fibrillation (4 patients, 0.8%), and myocardial ischemia (3 patients, 0.6%). Other SAEs included atrial flutter and cardiac failure (2 patients each), and acute coronary syndrome, acute myocardial infarction, aortic valve stenosis, arrhythmia, cardiac disorder, cardiomyopathy, congestive cardiomyopathy, mitral valve

incompetence, right ventricular failure, supraventricular tachycardia, and ventricular dysfunction (1 patient each).

Assessing CV events by four SMQ groups (Arrhythmias, CHF, Cardiomyopathy, and Ischemic Heart disease) from the phase 2 data demonstrated the following breakdown of these CV AE subtypes:

SMQ	All Patients (N=526) n (%)
Arrhythmias	70 (13.3)
Cardiac Failure	38 (7.2)
Cardiomyopathy	9 (1.7)
Ischemic Heart Disease	18 (3.4)

CHF was reported in 4.4% of those treated in Phase 2 MM Studies, and additional patients had clear signs and symptoms of HF, including pulmonary edema and ejection fraction decreased. In addition, cardiomyopathy and congestive cardiomyopathy were reported for 1.0% of patients treated in the Phase 2 MM Studies. Pretreatment with anthracyclines was documented in more than 60% of patients in the Phase 2 MM Studies who developed overt HF or its signs, and nearly 90% of those patients had documented cardiac comorbidities associated with the development of HF.

Angina, myocardial ischemia and infarctions, and CAD were reported in patients treated with carfilzomib. Nearly 90% of patients with cardiac AEs in these studies had documented cardiac comorbidities, including 55.6% with pre-existing CAD. Ischemic heart disease presented in patients across all treatment cycles.

The Preferred Terms of hypotension, orthostatic hypotension, syncope, and syncope vasovagal were used to search for patients with AEs consistent with clinically relevant hypotension. Some patients may have experienced one or more of these AEs. The Preferred Term of hypotension was reported in 5.9% (31 patients) in the Phase 2 MM Studies. Orthostatic hypotension was reported by 0.6%, and syncope and syncope vasovagal were reported by 2.3% of those in the Phase 2 MM Studies.

In the clinical studies to date, QT-interval prolongation has been reported as an AE in 7 patients, including 6 patients in the Phase 2 MM Studies (ECG QT prolonged, 3 patients, and ECG QT corrected interval prolonged, 3 patients) and for 1 patient in the Phase 1 studies (ECG QT corrected interval prolonged). All of these reports were nonserious, one led to dose reduction, and none led to permanent discontinuation of carfilzomib. None of the 7 patients had a reported medical history of QT prolongation.

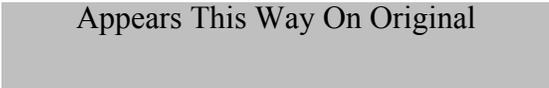
Serious adverse cardiac events were most commonly reported for cardiac failure events (30 events in 26 patients, of 612 patients evaluated in the Phase 1 and 2 MM Studies), which typically resolved and did not require study drug discontinuation. Five SAEs in 5 patients related to ischemic heart disease were reported: 1 patient died as a result of acute

coronary syndrome (and disease progression), study drug was discontinued for 3 patients, and the dose was reduced and later re-escalated for 1 of the patients with myocardial ischemia. SAEs of cardiomyopathy led to study drug discontinuation for 2 patients. However, cardiac disease appeared to contribute to the death of 9 patients in the Phase 1 and 2 MM Studies, including a single event of acute coronary syndrome, 5 events that have either been reported or described as a cardiac arrest, 2 deaths that were temporally associated with events of CHF, and 1 death attributed to hypotension. The onset of events leading to death which appear to be due to cardiac disorders has occurred within a day of administration of carfilzomib in 6 of these 9 cases.

Integrated ECG Safety – Studies 005 and 007

No TQT study has been performed for carfilzomib because the drug induces chromosomal aberrations, and there would be ethical considerations for running placebo controlled studies in the treatment of relapsed/refractory MM. However, ECGs were systematically collected from two clinical studies at multiple times post-dosing (study 005 in MM patients with varying degrees of renal dysfunction, and study 007 in patients with relapsed solid tumors). Though central lab analysis was not done during the trials, ECGs from these two studies were subsequently sent to a central lab for reading, and data integrated across studies based on the dose of carfilzomib that the patient received. The ECG acquisition times were somewhat different across the two studies, and this is reflected in the graphical displays of the integrated data. Time averaged analyses, as well as outlier analyses were also performed.

Figure 4,



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Figure 5,

Figure 6, and **Figure 7** below show analyses of change from baseline to each of the timepoints with ECG information, by dose, for heart rate, PR interval, QRS interval, and QTcF interval, respectively:

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Figure 4. Change in HR vs Time, 005 + 007

Figure 14.5.1.1
 Change in HR [bpm] versus Time - Mean +/- 90% C.I.

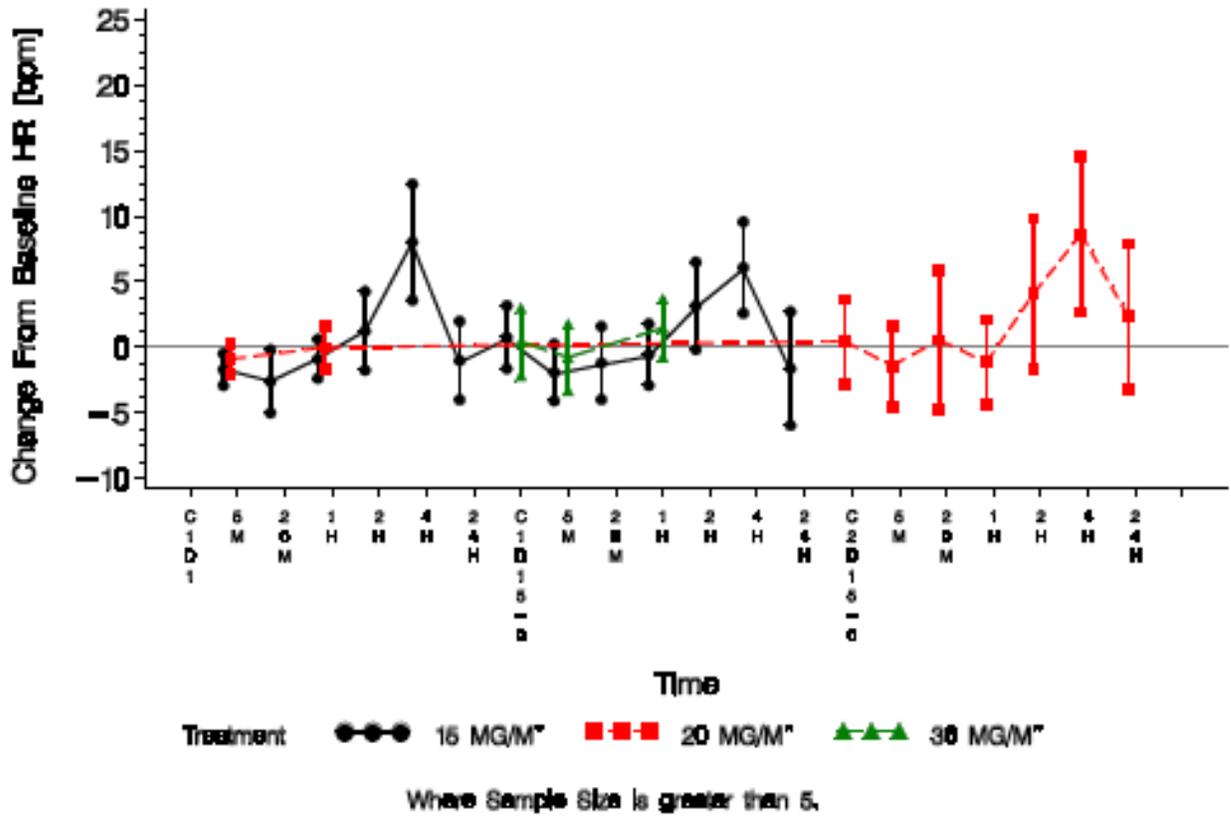
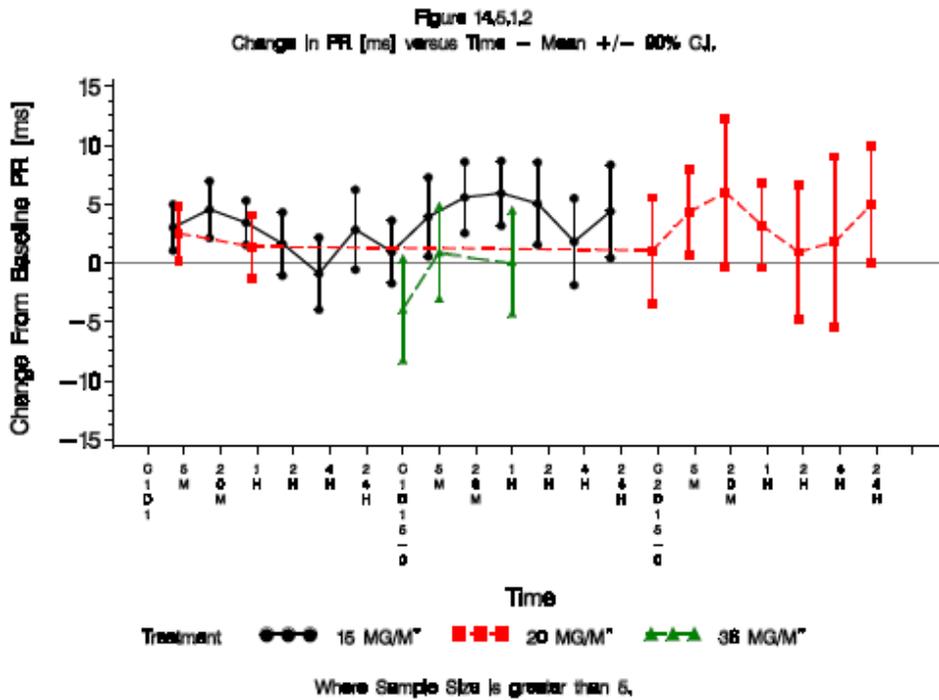


Figure 5. Change in PR vs Time, 005 + 007

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Figure 6. Change in QRS vs. Time, 005 + 007

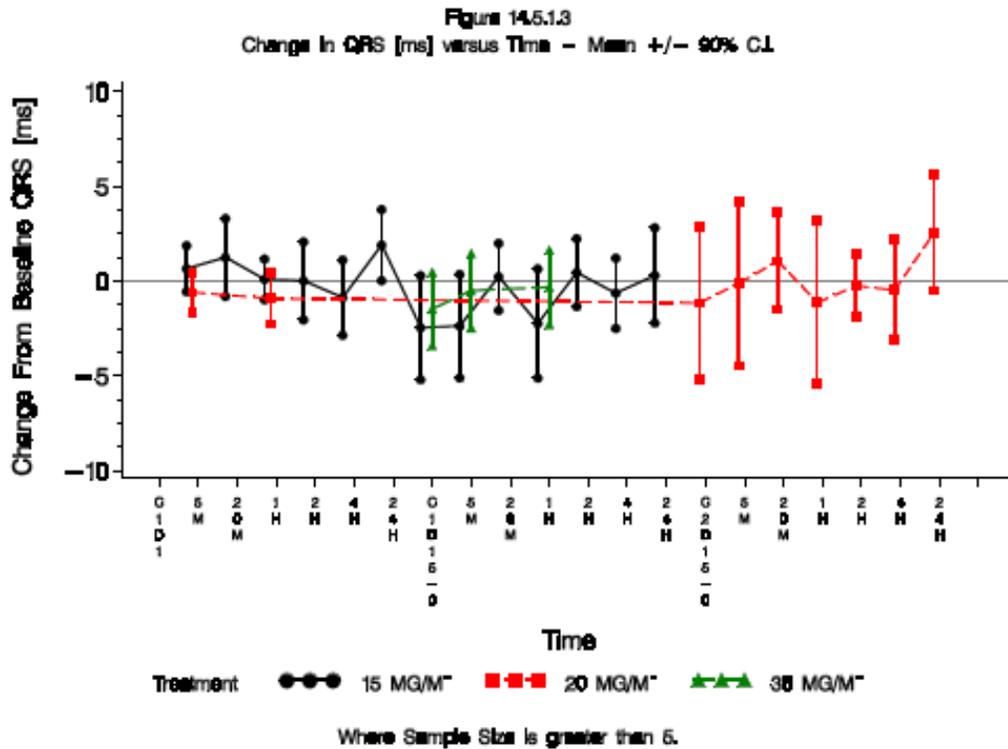
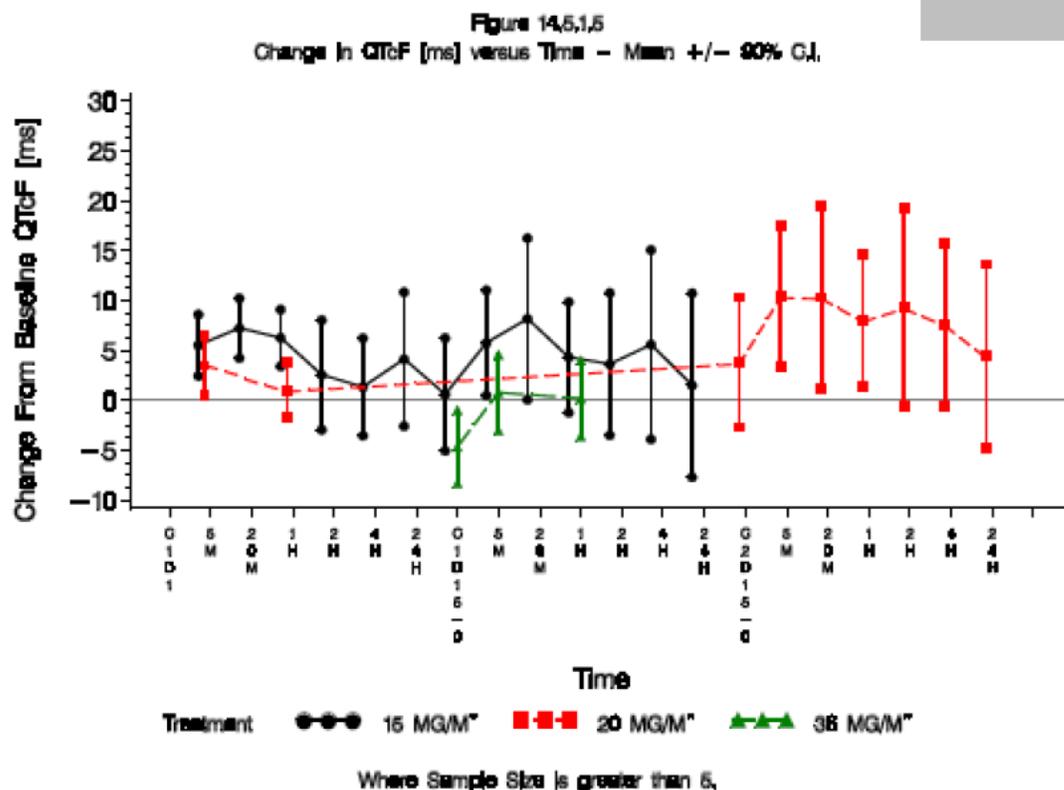


Figure 7. Change in QTcF vs Time, 005 + 007



The numbers of patients in each dose group at each time point are small and the confidence intervals of some reading wide. However, the following trends are noted:

- A reproducible rise in the point estimate of the change in heart rate from baseline between hours 2 and 4 post-dosing
- A tendency for higher post-dosing PR intervals compared to baseline
- No impact on QRS duration
- A trend to higher post-dose QTcF values for the two lower doses for which there is the most information. The upper bound of the 95% CI for the change from baseline exceeds 10 msec for the two lower dose groups.

The sponsor made an attempt to generate PK-PD models for predicting concentration-based changes on QTcF per [Table 1](#) and [Figure 8](#) below. These modeled outputs indicate no effect of drug concentration on QTc/QTcF. However, this conclusion is not robust because of the small numbers of patients in the dataset, as well as the fact that the PK/PD model has insufficient range across the PK profile. On Day 1 of Cycle 1, average maximum concentration (C_{max}) values were 2,546 ng/mL and 3,060 ng/mL following administration of 15 and 20 mg/m², respectively. On Day 16 of Cycle 1, average C_{max} was 4564 ng/mL following administration of 27 mg/m².

Table 1. Change from Baseline vs Plasma Concentration - Estimates from Linear Mixed Model

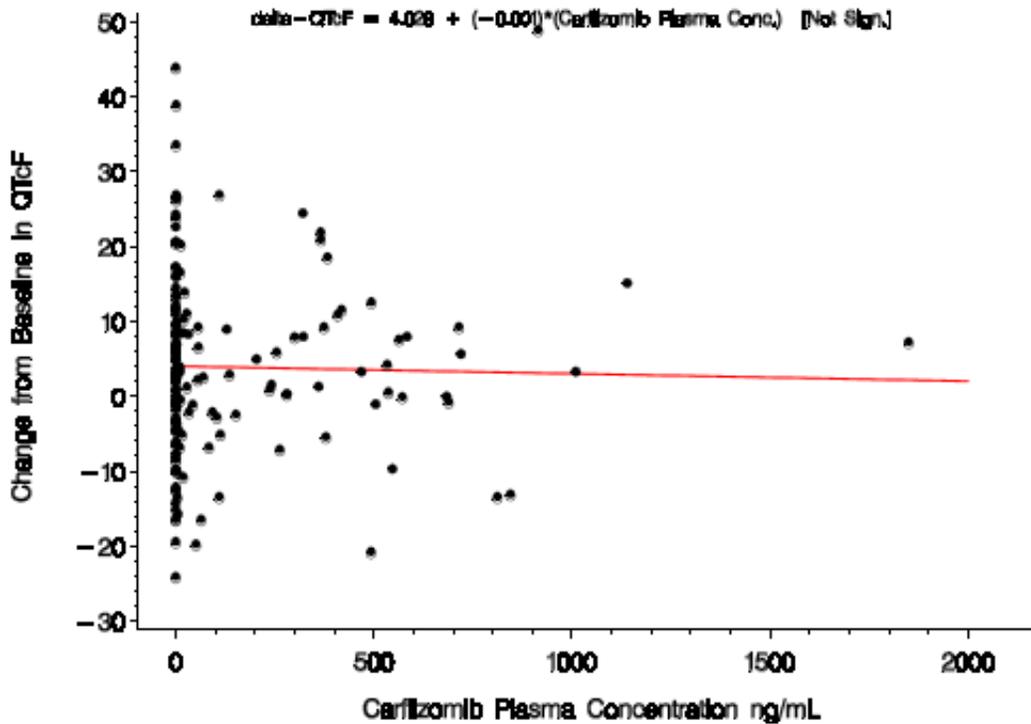
QT Parameter	Slope of Plasma Conc. Effect on Δ QTc	Standard Error of Slope of Plasma Conc. Effect on Δ QTc	p-value	Overall Model Fit	Carfilzomib	
					Predicted QTc at Average C _{max} 448.31 ng/mL	One-sided Upper 95% Confidence Bound of Predicted QTc [2]
QTcF	-0.0012	0.0028	0.6731	<.0001	3.4959	6.0839
QTcB	-0.0029	0.0031	0.3649	<.0001	3.3802	6.1453

[1] Linear Mixed Model is fit for change from baseline versus the plasma concentration as a fixed effect with subject included in the model as a random effect.

[2] Lower/Upper Bound = lower/upper one-sided 95% linear mixed model based confidence limit.

Concentration for prediction of QTc effect was chosen as the mean C_{max} despite abbreviated range.

Figure 8. QTcF Change vs Concentration - PK/PD Analysis



The time averaged data, though limited in usefulness, did demonstrate that only 2 patients demonstrated new QTcF values > 500 msec, as shown in [Figure 9](#) below:

Figure 9. Time-Averaged Mean Change and New Outliers

Treatment Group				
Carfilzomib dose in mg/m ² received:	Cycle 1 15mg/m ²	Cycle 2 15mg/m ²	Cycle 1 *20/36 mg/m ²	Cycle 2 20 mg/m ²
Total N	49	5	37	27
Heart Rate in bpm ^a	-0.2	-0.7	+0.2	+0.1
Heart Rate tachycardic outliers N (%)	0	0	0	0
Heart Rate bradycardic outliers N (%)	0	0	1 (3%)	1 (2%)
PR in ms ^a	+3.2	+7.3	-0.4	+2.7
PR outliers N (%)	1 (2%)	0	0	0
QRS in ms ^a	-1.4	-4.7	-0.9	-1.1
QRS outliers N (%)	0	0	0	0
QT in ms ^a	+4.2	+3.2	+0.9	+6.9
QT new >500 ms N (%)	1 (2%)	0	0	0
QTcF in ms ^a	+4.1	+1.8	+1.0	+7.1
QTcF new >500 ms N(%)	2 (4%)	0	0	0
QTcF new >480 ms N (%)	4 (8%)	0	1 (3%)	1 (4%)
QTcF 30-60 ms inc N (%)	8 (16%)	0	0	5 (19%)
QTcF >60 ms inc N (%)	1 (2%)	0	0	0
QTcB in ms ^a	+4.0	+1.0	+1.2	+7.1
QTcB new >500 ms N(%)	3 (6%)	0	1 (3%)	1 (4%)
QTcB new >480 ms N (%)	8 (16%)	0	1 (3%)	3 (11%)
QTcB 30-60 ms inc N (%)	12 (24%)	0	1 (3%)	6 (22%)
QTcB >60 ms inc N (%)	1 (2%)	0	0	1 (4%)
New abnormal U waves N (%)	0	0	0	0
New ST segment depression changes N (%)	0	0	0	0
New ST segment elevation changes N (%)	0	0	0	0
New T wave inverted N (%)	0	0	0	0
New AF N (%)	0	0	0	0
New 2 nd Degree Heart Block N (%)	0	0	0	0
New 3 rd Degree Heart Block N (%)	0	0	0	0
New Complete RBBB N (%)	0	0	1 (3%)	0
New Complete LBBB N (%)	0	0	0	0

Assessments

- Mechanism of Cardiotoxicity. Follow-on data requirements for longer term assessment of cardiac toxicity depend on the mechanism of the toxic cardiac side effects. There are four basic choices here, which are not mutually exclusive:
 - Amyloid heart disease in patients whose disease progression is further along than patients who have not already failed bortezomib, with progressively worsening LV systolic function, rhythm destabilization, and thus increased risk for sudden death
 - Exacerbation of underlying atherosclerotic coronary disease by sludging from a hyperviscosity syndrome in patients with end-stage MM, possibly aggravated by a tendency to anemia in these patients
 - Cell surface sodium and/or potassium channel blockade that could predispose to drug-induced Brugada's type syndrome or long QT syndrome, either one of which could increase arrhythmic sudden death and/or CHF due to decreased calcium transients in an elderly population with a lot of underlying structural heart disease and possibly superimposed amyloid infiltration
 - Drug induced metabolic poisoning, potentially worsened for patients having undergone prior anthracycline therapy.

Certainly, the worst of amyloid heart disease would be expected to occur in those patients with the most advanced MM. Likewise, the worst of the hyperviscosity states and most severe anemias would be expected in this population. Given that the patients in this phase II program have failed both bortezomib and an immunomodulator, these are by definition the sickest MM patients with probably the highest risk for amyloid/hyperviscosity/anemia driven cardiac events. However, it is our opinion that these factors are exacerbators, but not the root mechanisms/causes of the observed high cardiac event rates.

With respect to the potential for carfilzomib to induce cardiac toxicity through cell-surface ion channel blockade, it is noted that no formal ICH S7B trials have been conducted, and that a TQT study is not possible for ethical reasons. There are suggestions of a tendency for increased QTcF intervals in the middle of the treatment cycle as opposed to just before its beginning, with upper bound QTcF prolongation being in the range of 10 to 20 msec. However, there were only two patients with QTcF > 500 msec in the integrated 005 + 007 database, and the overall change in QTcF with time from the integrated data is not impressive. Furthermore, non-specific increases in QTcF can occur as a consequence of metabolic/ischemic disease or the progression of conduction system deterioration. For these reasons, a primary drug-induced "channelopathy" syndrome does not appear to be the major contributor to the excess cardiac risk.

This brings us to the most likely culprit here – drug induced metabolic poisoning. The data from Nowis et al reviewed above is quite clear – proteasome inhibitors reduce survival of mammalian cardiomyoblasts, and bortezomib causes a marked

time-dependent decrement in LV systolic function over a period of days that is reversible when the drug is stopped. Commensurate with the drug's known mechanism of action, these investigators directly visualized with immunofluorescence the accumulation of polyubiquitinated proteins inside treated myoblasts, with evidence of ER stress and autophagy, as seen in **Figure 10** below (from Nowis et al, 2010):

Figure 10. Accumulation of Polyubiquitinated Proteins and ER Stress in Rat Myoblasts

Copyright Material Withheld



That myocellular contractile dysfunction and even cell death would accompany the intracellular buildup of polyubiquitinated proteins comes as no surprise, given that we know that these are capable of activating a cell's apoptosis genetic program in experimental models.

With respect to QTcF, a trend to elevations as therapy progresses (point estimates in the 10-15 msec range) is noted from the integrated analysis of studies 005 and 007 as presented above. Data is limited by the lack of placebo control, and these temporal effects may reflect direct myocellular toxicity as discussed, as opposed to channel-blocking activity. In the clinical studies to date, QT-interval prolongation has been reported as an AE in 7 patients, including 6 patients in the Phase 2 MM Studies (ECG QT prolonged, 3 patients, and ECG QT corrected interval prolonged, 3 patients) and for 1 patient in the Phase 1 studies (ECG QT corrected interval prolonged). All of these reports were nonserious, one led to dose reduction, and none led to permanent discontinuation of carfilzomib.

- Pulmonary Hypertension. We agree with the sponsor that pulmonary toxicity is likely a class effect of proteasome inhibitors based on the preclinical data presented above. Furthermore, we would anticipate the high likelihood that acute pulmonary interstitial inflammatory responses noted in animal models could evolve to interstitial fibrosis with long-duration exposure. Review of the ISS suggests that the additional cases of pulmonary hypertension that were noted to be severe but not counted as adverse events were diagnosed within the text of an echo report, calculated from continuous wave dopler velocities of tricuspid regurgitation jets. I do not think this indicates an intentional or systemic undercounting effort on the part of the sponsor, but it does raise a very important question about the drug's potential role in causing or exacerbating this condition acutely, versus causing pulmonary hypertension due to chronic exposure. It is interesting that some of these people have depressed LV systolic function (with high pulmonary backpressures being at least worsened, if not caused by, high left sided pressures). However, there are others with isolated right-sided cardiac dilatation, pulmonary hypertension by dopler, but preserved LV systolic function, suggesting that there is specific pulmonary and pulmonary vascular toxicity in play that is causing isolated elevations of right sided pressures in some patients. Given that there are concomitant myopathic processes in progress (see number one above), it is not surprising that these elevated pulmonary pressures might be poorly tolerated in some patients.

The sponsor notes that respiratory symptoms are common with carfilzomib infusion. In fact, dyspnea is one of the most commonly reported AEs, and cardiac failure one

of the most common SAEs. Furthermore, the currently approved label for bortezomib warns that "...there have been reports of acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration and Acute Respiratory Distress Syndrome (ARDS) in patients receiving VELCADE. Some of these events have been fatal. In a clinical trial, the first two patients given high-dose cytarabine (2g/m² per day) by continuous infusion with daunorubicin and VELCADE for relapsed acute myelogenous leukemia died of ARDS early in the course of therapy. There have been reports of pulmonary hypertension associated with VELCADE administration in the absence of left heart failure or significant pulmonary disease."

Thus, we are seeing the very same phenomenon here with carfilzomib. However, due to its MOA, it is distinctly possible that pulmonary, as well as cardiac toxicities, may be worse with carfilzomib.

- Severity of Cardiac and Pulmonary Toxicities. Relative to bortezomib, these may be more severe with carfilzomib because inhibition of the proteasome is reversible with bortezomib, but irreversible with carfilzomib. This results in longer periods of more complete proteasome inhibition with carfilzomib. While this characteristic undoubtedly contributes to the therapeutic benefits of the drug in relapsing, drug-resistant MM, we expect that it would likewise contribute to more aggressive cardiopulmonary toxicity. Indeed, we may be seeing this in the Phase II carfilzomib MM data, where treatment emergent adverse events in the "cardiac disorder" SOC were reported by 22.4% of subjects, whereas the bortezomib label states that in the relapsed MM study, "...the incidence of any treatment-emergent cardiac disorder was 15% and 13% in the VELCADE and dexamethasone groups, respectively. The incidence of heart failure events (acute pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock, pulmonary edema) was similar in the VELCADE and dexamethasone groups, 5% and 4%, respectively."

Unfortunately, study PX-171-003, the pivotal approval study, was a single-arm open-label study (N=266), so comparing carfilzomib cardiopulmonary event rates with dexamethasone is not possible from the pivotal dataset.

- Hypertension. In Phase 2 MM studies, (N=526), hypertension was reported in the medical history of 53.2% of patients. In this population, BP elevations adverse events occurred in 75 of 526 patients (14.7%), of which 15 (2.9%) were considered Grade 3 and 2 (0.4%) considered to be Grade 4 adverse events. For the most part, BP elevations appeared to have been manageable, in that only 3 of these cases required dose delays because of hypertension. No events of hypertension resulted in death, but 2 patients of these patients discontinued from the study with multiple ongoing AEs.

Of note, multiple prior MM therapies that the patients had been exposed to can increase the risk of hypertension, and the degree to which there was any carryover affect is unknown.

Recommendations

In thinking about asking this sponsor for more data to define cardio-pulmonary safety, the possibilities are almost endless, given the remarkable cardiac and pulmonary toxicities of carfilzomab. For example, it would be optimal to have sequential echo data at the beginning and end of each treatment cycle to assess acute myopathy (LVEF, RVEF, recovery rates) and pulmonary toxicity (PA pressures, right sided chamber dimensions and pulmonary hemodynamics). Likewise, full pulmonary function testing with DLCO and oxymetry at the beginning and end of each treatment cycle would assist in defining the time course of acute pulmonary inflammation, the degree of its recovery during rest periods, and the degree to which progression of acute interstitial inflammatory progresses to chronic interstitial lung disease. Sequential chest MR could help correlate functional PFT testing with visual structural deterioration of the lungs, and assess the risk of chronic pulmonary embolization/thrombosis in these hypercoagulable patients.

However, we assume that it is the opinion of the review division that the potential benefit of a new salvage therapy for MM patients that have relapsed through bortezomib outweighs the known risks of proteasome inhibition (median overall survival (OS), which accounts for all deaths regardless of cause, for all enrolled patients of 15.4 months (95% CI: 12.5 to 19.0 months) in the pivotal Phase 2 carfilzomib study, versus the median OS between reported to be 6 to 9 months in a relapsed and refractory MM population on standard approved therapies). If this is indeed the case, then we feel that a more pragmatic approach is warranted. We know what the issues are here (early and late risks, and how these will manifest). Specifically, we would expect carfilzomib's cardiac and pulmonary toxicities to be similar in nature as those seen with bortezomib therapy, but potentially more severe, given carfilzomib's more intense, more prolonged, and irreversible inhibition of the proteasome (and from which non-nucleated red cells never recover, as they lack protein synthetic machinery to generate new proteasomes). The fact of the matter is that the sequential investigations on the "wish list" noted above were not acquired during the Phase II program, and the phase III program is already in progress to satisfy subpart H approval requirements, so they will not be available from the phase III program either. Furthermore, we assume that the above-noted potential survival benefits to relapsed and refractory MM patients demonstrated in the pivotal Phase 2 study would make the delay of holding approval for the acquisition of this information difficult, if not impossible, to justify. Therefore, our recommendations for additional data analyses are limited to basics that can be obtained from the currently available information from the Phase 1 and Phase 2 programs, and are focused toward further exploring the timing of what seems to be two different toxicity profiles:

1. Early toxicity – manifest as early death in animals with rapid drug infusion, as well as the onset of events leading to death in human patients which appear to be due to cardiac disorders occurring within one day of administration of carfilzomib in 6 of these 9 cases, the mechanism of which is not clear
2. Late toxicity – manifest in part as cardiomyopathy, pulmonary toxicity, and perhaps hypertension, as a consequence of the known MOA of the drug,

proteasome inhibition, buildup of intracellular polyubiquitinated proteins, and subsequent apoptosis and/or inflammation.

We recommend that consideration be given to performing the following analyses (i.e., none felt mandatory for the approval/non-approval decision):

- Analyze cardiac disorder SOC AEs and SEAs from the entire Phase 1 and Phase 2 integrated dataset (MM and non-MM) for the occurrence of these events as a function of total dose administered, and then repeat these analyses for pulmonary AEs/SAEs, and then all AEs/SAEs, in an attempt to define whether chronic carfilzomib toxicity behaves in a dose-related manner like anthracycline toxicity.
- Time to first event analyses from first dose of first cycle to any cardiac AE/SAE, pulmonary AE/SAE, and any AE/SAE (this is another way of looking at adverse outcomes as a function of total dose, since more dose is received over time)
- Time to first event analyses from first dose of any cycle to the first cardiac AE/SAE, pulmonary AE/SAE, and any AE/SAE within that cycle, in an attempt to delineate the degree to which these events are acute reactions to the infusion protocol, and whether consideration should be given to slowing this down (i.e. per the animal data, infusion prolonged from 10 min to 30 min), if that would not sacrifice important efficacy responses
- Tabulate the total death experience from the entire Phase I and Phase II MM dataset with columns for time from first dose of first cycle to any death, and time from first dose of most recent cycle to death
- Ask sponsor to assess their entire Phase I and Phase II dataset (MM and recurrent non-MM cancer) to:
 - i. See if they have baseline and follow up echo, PFT, or chest imagine data on anyone, and if they do, ask them to assess changes
 - ii. Pull any echo on all patients on-therapy to summarize diagnoses, to see what the incidence is of an echocardiographic diagnosis of pulmonary hypertension, and to assess how many of these were symptomatic.
 - iii. Pull any PFT information that they have on anyone on-therapy to summarize diagnoses, and correlate with echo findings if available
- K-M analyses from the entire Phase I and Phase II dataset (MM and non-MM cancer) for time to first blood pressure that is:
 - i. > 140/90
 - ii. > 160/100
- Shift tables from the entire Phase I and Phase II dataset (MM and non-MM cancer) for BP changing from < 140/90 to >140/90 to >160/90
- Shift tables from the entire Phase I and Phase II dataset (MM and non-MM cancer) for any available cardiac enzymes that might have been measured (CK, CK-MB, Troponins)
- If approved, consider labeling carfilzomib such that:
 - i. 12-lead ECGs should be obtained at the beginning and end of each treatment cycle to assess rhythm, morphology, and QTcF, so that drug

might be held for new onset arrhythmias, ischemic changes, or QTcF prolongations of clinical import

- ii. Full pulmonary function tests with DLCO should be obtained at baseline, at the end of each cycle where the dose has been escalated, or for clinical cause
- iii. Echocardiograms should be obtained at baseline to assess LVEF, RV systolic function, valve integrity (especially the mitral valve, which depends on papillary muscle function to maintain competence), and right sided hemodynamics. These should be repeated at the end of any cycle where dose has been escalated or for clinical cause.

Citations

1. Dasanu, CA. Complete heart block secondary to bortezomib use in multiple myeloma. *J Oncol Pharm Practice* 2010;17(3):282–284.
2. Hampton J, Dell K. Cardiac Arrest and Persistent Sinus Bradycardia after the Initiation of Bortezomib Therapy for Multiple Myeloma. *40th Critical Care Congress of the Society of Critical Care Medicine* January 18, 2011;Abstract#995.
3. Honton B et al. Direct involvement of Bortezomib in the occurrence of heart failure. *Archives of Cardiovascular Diseases Supplements* 2010;Abstract#090.
4. Jerkins JH, Suci A, Mazimba S, Calvo A. Bortezomib-induced Severe Congestive Heart Failure. *Cardiol. Res.* 2010;1(1):20-23.
5. Nowis D et al. Cardiotoxicity of the Anticancer Therapeutic Agent Bortezomib. *Am J Pathol.* 2010 June;176(6):2658–2668.
6. Yeh ETH, Bickford CL. Cardiovascular Complications of Cancer Therapy: Incidence, Pathogenesis, Diagnosis, and Management. *J. Am. Coll. Cardiol.* 2009;53:2231-2247.

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/s/

PRESTON M DUNNMON
12/16/2011

THOMAS A MARCINIAK
12/17/2011

NORMAN L STOCKBRIDGE
12/19/2011

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

Application: NDA 202714
Name of Drug: Carfilzomib for Injection
Applicant: Onyx Pharmaceuticals, Inc. (Onyx)

Labeling Reviewed

Material Reviewed: Package Insert (PI)
Supporting Document Number: 2
Submission Date: September 26, 2011
Receipt Date: September 27, 2011

Background and Summary Description

Onyx's carfilzomib drug product is a proteasome inhibitor for the treatment of patients with relapsed and refractory multiple myeloma who have received at least two prior therapies. Carfilzomib was granted orphan designation for the indication of multiple myeloma on January 18, 2008. On January 6, 2011, Onyx was granted Fast Track designation for carfilzomib. NDA 202714 was submitted as a rolling submission, the first part of which was received on January 31, 2011 and the final part received on September 27, 2011.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" section of this review. Labeling deficiencies are identified in the SRPI attachment with an "X" in the checkbox next to the labeling requirement. Any noted deficiencies are summarized in the comments below.

I. HIGHLIGHTS OF PRESCRIBING INFORMATION section

- A. The Highlights page should be in the portrait orientation, not landscape. After changing the orientation, the applicant should ensure that the Highlights do not exceed one-half page of standard-sized paper (8 ½ by 11 in.), in 8-point type, two-column format. [See 21 CFR 201.57(d)(8)].

- B.** The Applicant should ensure that white space precedes each major heading in the Highlights section.
- C.** Each summarized statement must cross-reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information.
- The applicant should add the cross-reference to the second bullet point under “Dosage and Administration.”
- D.** The Warnings and Precautions (WPs) in the Highlights should be listed in the same order as the WPs in the FPI section.
- The applicant should list “(b) (4) before (b) (4)”
- E.** Only known hazards and not theoretical possibilities (i.e. hypersensitivity to the drug or active ingredient) should be listed under “Contraindications.” If the contraindication is not theoretical, the applicant should describe the nature of the adverse reaction.
- (b) (4)
- F.** Only “Adverse Reactions” as defined in 21 CFR 201.57(a)(11) are to be included in the Highlights. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
- The applicant currently has the statement (b) (4)
- G.** A general customer service email address or general link to a company website cannot be used to meet the requirement to have an adverse reactions reporting contact information in HL. See 21 CFR 201.57(a)(11).
- The applicant lists an e-mail address as one of the methods to report suspected adverse events. “To report SUSPECTED ADVERSE REACTIONS, contact Onyx Pharmaceuticals, Inc. at 1-877-669-9121 or (b) (4) FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.”
- H.** The Revision Date for the most recent revision of the labeling, identified as such, must be placed at the end of the Highlights [see 21CFR 201.57(a)(15)]. For new applications, the revision date will be the month/year of application approval.
- The applicant needs to add the revision date to the end of the Highlights in one of the following formats using bold font: "Revised: Month Year" or "Revised Month/Year" (e.g., Revised: Month YEAR or Revised MM/YYYY).

II. FULL PRESCRIBING INFORMATION: CONTENTS section

- I.** The section headings and subheadings in the FPI: Contents must match the headings and subheadings in the FPI.
- The subheading listed for 2.4 does not match the FPI. Currently, they are listed as “Dose Modification” and “Dose Modifications,” respectively. The applicant should resolve this discrepancy.
- J.** A horizontal line is required that separates the “Full Prescribing Information: Contents” and the “Full Prescribing Information” (FPI) [*see 21 CFR 201.57(d)(2)*]. This applicant needs to add the horizontal line to the labeling.

III. FULL PRESCRIBING INFORMATION section

- K.** The applicant should remove the underline under the title “Full Prescribing Information.” The title must appear in UPPER CASE and bold type only.
- L.** The presentation for cross-references in the FPI should be the section heading followed by the numerical identifier. For example, instead of [*see Dose Modifications (2.4)*] the cross-reference should be presented as [*see Dosage and Administration (2.4)*]. Do not include the subsection headings or other headings within a subsection in the cross-references. The applicant should update cross-references within the FPI accordingly.
- M.** Only “adverse reactions” as defined in 21 CFR(c)(7) should be included in labeling. Other terms such as “adverse events” or “treatment-emergent adverse events” should be avoided.
- N.** The revision date at the end of Highlights replaces the “revision” or “issued” date at the end of the full prescribing information and should not appear in both places.
- The applicant should delete “Issued: [Date of Approval]” from the end of FPI.

Conclusions/Recommendations

All labeling deficiencies will be conveyed to the applicant. Comments A-D, H, I-L and N should be conveyed to the sponsor in the Day-74 letter. The applicant will be asked to resubmit labeling that addresses the identified labeling deficiencies by December 30, 2011. The resubmitted labeling will be used for further labeling discussions. Comments E-G and M should be addressed during labeling negotiations with input from the review team.

Regulatory Project Manager Date

Chief, Project Management Staff Date

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**
 - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”
- **Product Title**
 - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.
- **Initial U.S. Approval**
 - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.
- **Boxed Warning**
 - All text in the boxed warning is **bolded**.
 - Summary of the warning must not exceed a length of 20 lines.
 - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
 - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.
- **Recent Major Changes (RMC)**
 - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
 - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
 - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
 - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
 - Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

• General Format

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

• Boxed Warning

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

• Contraindications

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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

/s/

KAREN E BENGTON
12/07/2011

JANET K JAMISON
12/07/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 202714	NDA Supplement #:S- N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: TBD Established/Proper Name: carfilzomib Dosage Form: Reconstituted lyophilized powder for injection Strengths: 60 mg/vial (2 mg/mL after reconstitution)		
Applicant: Onyx Pharmaceuticals, Inc. Agent for Applicant (if applicable): Not Applicable		
Date of Application: September 26, 2011 Date of Receipt: September 27, 2011 Date clock started after UN: N/A		
PDUFA Goal Date: July 27, 2012	Action Goal Date (if different):	
Filing Date: November 26, 2011	Date of Filing Meeting: November 8, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1 – New Molecular Entity		
Proposed indication(s)/Proposed change(s): Relapsed and refractory multiple myeloma		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input checked="" type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>): Not Applicable				
List referenced IND Number(s): 071057				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X*			*Proprietary name is not currently entered in tracking system; the review is ongoing.
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>	N/A	N/A		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			Included in submission 1 of 2 (received 1/31/11) for the rolling submission.

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: <u>5 years</u></p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			Included in submission 2 of 2 (received 9/27/11) for the rolling submission.
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			Included in submission 2 of 2 (received 9/27/11) for the rolling submission.
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			Included in submission 1 of 2 (received 1/31/11) for the rolling submission.
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				

Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>		X		
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		Granted orphan designation for the indication of multiple myeloma.

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>			X	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i> QT-IRT – November 21, 2011 DCRP - November 17, 2011 OSE (Hepatology Consult) – November 16, 2011	X			

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): November 6, 2008 August 3, 2009 (CMC) <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): August 5, 2010 September 28, 2010 (CMC) <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): January 15, 2010 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 8, 2011

BLA/NDA/Supp #: 202714

PROPRIETARY NAME: TBD

ESTABLISHED/PROPER NAME: Carfilzomib

DOSAGE FORM/STRENGTH: Reconstituted lyophilized powder for injection, 60 mg/vial

APPLICANT: Onyx Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Relapsed and refractory multiple myeloma

BACKGROUND:

Onyx's carfilzomib drug product is a proteasome inhibitor for the treatment of patients with relapsed and refractory multiple myeloma who have received at least two prior therapies. Carfilzomib was granted orphan designation for the indication of multiple myeloma on January 18, 2008. On January 6, 2011, Onyx was granted Fast Track designation for carfilzomib. The application was submitted as a rolling submission, the first part of which was received on January 31, 2011 and the final part received on September 27, 2011.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Karen Bengtson	Y
	CPMS/TL:	Janet Jamison	N
Cross-Discipline Team Leader (CDTL)	Albert Deisseroth		Y
Clinical	Reviewer:	Thomas Herndon	Y
	TL:	Albert Deisseroth	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	N/A

	TL:	N/A	N/A
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Pharmacology	Reviewer:	Bahru Habtemariam	Y
	TL:	Julie Bullock	N
Biostatistics	Reviewer:	Kallappa Koti	Y
	TL:	Mark Rothmann	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer(s):	Todd Palmby Jessica Hawes Jeffrey Bray	N N Y
	TL:	Haleh Saber	Y
Statistics (carcinogenicity)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Product Quality (CMC)	Reviewer(s):	Mike Adams Josephine Jee	Y Y
	TL:	Janice Brown	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	John Metcalf	Y
	TL:	Brian Riley	N
CMC Labeling Review	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Facility Review/Inspection	Reviewer:	Vipul Dholakia	Y
	TL:	Tara Gooen	N
OSE/DMEPA (proprietary name)	Reviewer:	Kim Defronzo	Y
	TL:	Todd Bridges	N

OSE/DRISK (REMS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A

Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orenca	Y
	TL:	Susan Leibenhaut	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Other reviewers	N/A		
Other attendees	Richard Pazdur, Director – OHOP Ann Farrell, Acting Director - DHP R. Angelo de Claro, MO Tyree Newman, RPM Scott Goldie, Product Quality RPM		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: No comments provided in filing meeting</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input checked="" type="checkbox"/> YES Date if known: TBD <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p>BIOSTATISTICS</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Richard Pazdur, M.D., Director of OHOP</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>

ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Regulatory Project Manager

Date

Chief, Project Management Staff

Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

KAREN E BENGTSON
11/21/2011

JANET K JAMISON
11/22/2011