STATISTICAL ANALYSIS PLAN
PROTOCOL PX-171-010 (20130394)

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

Sponsor: Onyx Pharmaceuticals Inc., an Amgen Inc. subsidiary
One Amgen Center Drive
Thousand Oaks, CA 91320 USA

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Prepared by: PPD

Date: _22 Aug 2017_

Study Statistician: PPD

Reviewed by:

PPD

Digitally signed by PPD
PPD

Date: 2017.08.22 14:02:49 -07'00'

Date: _____

Clinical Research Medical Director: PPD

PPD

Date: _8/23/2017_

Global Statistical Leader: PPD

_____ **Date:** _____

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition
AE	adverse event
BSA	body surface area
CRF	case report form
CBR	clinical benefit response
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
FAS	Full Analysis population
M	meter
MM	multiple myeloma
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram
N	number of subjects
NCI	National Cancer Institute (US)
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PR	partial response
PT	MedDRA preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
sCR	stringent complete response

Abbreviation or Term	Definition
SD	stable disease
SOC	MedDRA system organ class
TEAEs	treatment emergent adverse events
TTP	time to progression
VGPR	very good partial response

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1   INTRODUCTION

This Statistical Analysis Plan (SAP) covers a number of sections that describe how the data from the trial is going to be analyzed to assess the clinical safety and efficacy associated with the treatment under consideration.

This SAP was prepared in accordance with Protocol Amendment 3, dated March 25, 2011.   Any changes that are made to the planned analyses after the SAP is finalized, along with an explanation as to when and why they occurred, will be noted in any Clinical Study Report (CSR) produced for the study.   Any changes made to the planned analyses that are in the protocol will be identified and documented in this document.

2   STUDY OVERVIEW

2.1   Study Design

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

2.2   Study Objective

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

2.3   Sample Size Considerations

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

3   ANALYSIS ENDPOINTS

3.1   Primary Endpoints - Safety

- Reported peripheral neuropathy AEs (All Grades)

- Reported Grades 3 and 4 AEs

- SAEs

- Grade 1 through Grade 4 AEs leading to a missed carfilzomib dose or a carfilzomib dose reduction, or discontinuation

3.2   Secondary Endpoints - Efficacy

- Overall Survival (OS)

- Progression Free Survival (PFS)

- Time to Progression (TTP)

Tumor measurements and efficacy assessments will be in accordance with the methods employed in the subject's prior carfilzomib study. For subjects participating in a carfilzomib trial without prior tumor measurements and efficacy assessments (eg, PX-171-008), tumor assessments will be conducted at the time of screening for the current study using the appropriate method (eg, RECIST criteria for solid tumors); these assessments will be used as the subjects' baseline disease assessments for determining response and progression while on the current protocol, PX-171-010.

4   ANALYSIS POPULATIONS

The analysis and reporting of the data from this study will be performed using the following populations.

4.1   Safety Population

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

4.2   Full Analysis Set Population

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

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

- Lack of baseline data for those analyses that require baseline data

5   ANALYTIC DEFINITIONS

5.1   Study Day 1

Study Day 1 corresponds to the date of the first dose of carfilzomib in this study. For subjects who receive at least one dose of carfilzomib, the earliest dosing date recorded on the Study Drug Administration case report form (CRF) will be used to determine Study Day 1.

5.2   Study Day

Study Day represents the elapsed number of days from Study Day 1, inclusive. Unless otherwise specified, the timing of all study-related events, assessments, and interventions will be calculated relative to Study Day 1. If assessment date is after date of study day 1, study day will be calculated as:

Study Day n = (Date of assessment – Date of Study Day 1) + 1 day

If assessment date is before date of study day 1, study day will be calculated as:

Study Day -n = Date of assessment – Date of Study Day 1

5.3   Cycle 1 / Cycle Day 1

The first 28-day treatment cycle will begin with the first dose of carfilzomib, and will be denoted as "Cycle 1 / Cycle Day 1". In general, the start date of each cycle (i.e., Cycle Day 1 of Cycle k, where k=1 to last cycle) equals the date of the first dose of carfilzomib administered in the corresponding cycle. If carfilzomib is permanently discontinued,

then the cycle and cycle day for study-related assessments done after the last cycle of carfilzomib will be replaced in the tables, figures, and listings with the visit label (e.g., end of study assessment). The visit date and study day also will be used to identify the timing of such assessments.

5.4   Cycle k / Cycle Day j

Cycle Day j represents the elapsed number of days since the first dose of carfilzomib in Cycle k.

Cycle Day j = (Date of assessment – Date of Day 1 in Cycle k) + 1 day

Unless otherwise specified, the timing of study-related visits and assessments will be calculated relative to Cycle Day 1 in each cycle.

As noted previously, if carfilzomib is permanently discontinued, then the cycle and cycle day for study-related assessments done after the last cycle of carfilzomib will be replaced in the tables, figures, and listings with the visit name (e.g., End of Study assessment). The visit date and study day also will be used to identify the timing of such assessments.

5.5   Baseline

If subjects had not received other anti-cancer therapies and not reached progressive disease when they enrolled in study 010, baseline disease assessments from the initial study will be used for baseline values for determining response and progression unless no prior assessments were collected (eg, PX-171-008). For those subjects who didn't have baseline collected in prior study, tumor assessments will be conducted at the time of screening for the current study using the appropriate method. And for those who received other anti-cancer therapies and/or progressive disease when they enrolled in study 010, baseline values from current study will be used.

During the study, the addition of certain approved agents with known antitumor activity or increase of carfilzomib dose and/or frequency is permitted if there is concern for disease progression and per Investigator discretion in consultation with the Onyx Medical Monitor. If it happens, measurements at the time of addition of new agents will be used as new baseline.

5.6   Age at Enrollment

Age will be calculated in years relative to the subject's carfilzomib study enrollment date and based on the following SAS programming statement:

$$AGE = FLOOR((INTCK('MONTH', DOB, CONDT) - (DAY(CONDT) < DAY(DOB))) / 12);$$

where DOB=date of birth; CONDT=consent DATE

6   INTERIM ANALYSIS and EARLY STOPPING GUIDELINES

No interim analysis is planned for this study.

7   STATISTICAL METHODS

7.1   General Considerations

All statistical analyses will be performed in SAS® version 9, or later (SAS Institute Inc., Cary, NC, USA).

Summary statistics will be provided for all endpoints involved. For continuous variables, the number of subjects with non-missing data (n), mean, standard deviation, median, minimum, and maximum will be presented. For discrete data, the frequencies and percentages will be provided. Unless otherwise indicated, percentages will be calculated based on the number of subjects with non-missing data as the denominator.

For the efficacy analyses, point estimates will be accompanied by a two-sided 95% confidence interval.

The efficacy analyses will be performed separately by disease cohort (MM or solid tumor). All other analyses will be presented by disease cohort and overall unless otherwise specified.

7.2   Subject Accountability

The number of subjects treated will be presented by disease cohort and overall.

The number and percent of subjects who terminated from the study and reasons for termination will be summarized. In addition, the number and percent of subjects who had a final visit and reasons for subjects who had no final visit will be presented.

7.3   Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized by both disease cohorts and overall unless otherwise indicated. Summary statistics will be tabulated based on the Safety population.

- Both Disease Cohorts

  - Age at the entry of PX-171-010: <65, ≥65

  - Sex: female, male

  - Race: Caucasian, African American, Hispanic, Asian/pacific islander

  - Time since diagnosis (years) in PX-171-010

  - Clinical response assessment at entry of PX-171-010

- MM Cohort

  - Height (cm), weight (kg), body surface area (BSA), ECOG performance status, Neuropathy Grade (All data from time of entry in PX-171-010 except ECOG which is from the time of entry in initial study and entry in PX-171-010.)

  - Number of prior regimens (initial study)

  - Prior Bortezomib (initial study)

  - M-protein light chain isotype and heavy chain iostype (initial study and PX-171-010)

  - Measurable disease category (initial study)

  - Refractory status (initial study)

- Plasma cell involvement (<50%, >=50%) (initial study)

- Cytogenetics (initial study): normal/favorable, poor prognosis, unknown or not done

- FISH (initial study): normal/favorable, poor prognosis, unknown or not done

- Cytogenetics or FISH (initial study): normal/favorable, poor prognosis, unknown or not done

- Serum Beta-2 Microglobulin (mg/L) (initial study)

- Durie-Salmon Staging and Subclassification (initial study)
- Did the subject maintain the parent study's response until PX-171-010 enrollment?
- Did the subject meet IMWG criteria for disease progression until PX-171-010 enrollment?

- Solid Tumor Cohort

  - Tumor type (initial study)

7.4 Regimen Change

The number and percent of subjects who had regimen change during the study and reasons for regimen changes will be summarized as collected on regimen change case report form. In addition, type of regimen changes: carfilzomib dose level increased/decreased, dose frequency increased/decreased, or other anti-myeloma drugs added will be summarized .

7.5 Study Treatment Exposure and Compliance

The overall extent of study treatment exposure and dose information will be presented by disease cohort and overall in the Safety population using descriptive statistics:

- Study drug dose administered in initial study
- Duration of exposure, calculated as (last dose date in PX-171-010 – first dose date in the initial study + 1), for subjects with less than or equal to 60 days between the end of the initial study and enrollment in PX-171-010. For subjects with great than 60

days between the initial study and enrollment in PX-171-010, duration of exposure is the sum of the exposure during the initial study and the exposure during PX-171-010.

- Categorical summary of duration of exposure by number of weeks.

- Total number of treatment cycles (PX-171-010 only and initial study + PX-171-010) during which one or more doses of carfilzomib was administered per subject. Categorical summary of the number of cycles received per subject (PX-171-010 only and initial study + PX-171-010)

- Overall treatment duration in weeks, calculated as weeks from first dose administration to last dose administration in PX-171-010, and treatment duration by regimen

- Number of weeks between last day of initial study and PX-171-010 enrollment

- Categorical summary of the number of weeks between last day of initial study and PX-171-010 enrollment

- Number of doses received per subject

- Average dose of carfilzomib (in mg/m²) administered across all cycles and average dose of carfilzomib (in mg/m², mg) by regimen

- Cumulative dose (mg) administered across cycles and cumulative dose (mg, mg/m²) by regimen

Summary of study drug administration will be summarized categorically as follows:

- First dose administered (mg/m^2)

- Highest dose administered (mg/m^2)

- Method of administration (IV bolus, IV infusion)

- Dose frequency

- Drug product administered (Lyophilized or not)

- Dose level reduced at least once due to AE
  - Number of dose level reduction due to and AE
  - AEs resulting in dose level reduction

- Dose level increased at least once

- Dose frequency reduction due to an AE
    - AEs resulting in dose frequency reduction
- Dose frequency increased at least once

Study drug administration data by cycle and cycle day and cumulative data (initial study and PX-171-010) will be listed for all subjects.

7.6   Safety Analysis

The safety analysis will be based on the Safety population (Section 4.1) and will presented by disease cohort (MM and solid tumor) and overall.

This analysis will be focused on assessing the extent of all reported Grades 3 and 4 adverse events (AEs), all reported peripheral neuropathy AEs (Grades 1-4), all serious adverse events (SAEs), and Grades 1-4 AEs leading to either a missed carfilzomib dose, carfilzomib dose reduction, or discontinuation.

The analysis will remain descriptive in nature.

7.6.1   Adverse Events (AEs)

Treatment emergent adverse events (TEAEs) are defined as AEs that start on or after the first administration of study drug and within 30 days of the last infusion of study treatment. An AE that is present before the first administration of study treatment and subsequently worsens in severity during treatment is also considered to be treatment emergent.

Missing and partially missing AE start dates will be imputed according to the specifications described in Section 7.7.2 of the SAP. Each reported AE term will be mapped to a preferred term (PT) and a system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA, version 8.1).

Adverse events will be summarized based on the number and percentage of subjects experiencing events by MedDRA SOC and PT. The denominator for the percentage will be based on the number of subjects at risk (i.e., those that received at least one dose of

carfilzomib). The causal relationship of the AE to the study drug will be judged by the investigator as none, unlikely, possible, or probable.

 A subject reporting the same AE more than once will be counted only once when calculating 1) within a given system organ class, and 2) within a given system organ class and preferred term combination. For such cases, the maximum National Cancer Institute (NCI; US)-Common Terminology Criteria for Adverse Events (CTCAE. Version 3) toxicity grade and strongest causal relationship to study treatment for the event will be used in the incidence calculations. AEs will also be summarized by severity and by relationship to carfilzomib.

Tabular summaries of the following AEs will be provided by SOC and/ or PT:

- Overall summary of treatment emergent adverse events
- Treatment emergent adverse events
- Treatment emergent adverse events by maximum severity
- Treatment emergent adverse events grade 3 or higher
- Treatment emergent adverse events by relationship to study drug
- Serious treatment emergent adverse events
- Treatment emergent adverse events that led to dose reduction
- Treatment emergent adverse events that led to permanent discontinuation of study drug

All AEs, including treatment emergent events, will be included in listings by subject.

7.6.2   Concomitant Medications

Concomitant chemotherapies will be collected and coded using WHODDE version March 1, 2010. All chemotherapy agents will be listed individually and summarized by anatomical therapeutic class and generic name.

7.7   Efficacy Analyses

The efficacy analyses will be performed by disease cohort and will be based on investigator's assessment recorded on the CRF page.

All efficacy analyses will be based on the FAS population.

7.7.1   Overall Survival (OS)

Duration of OS is defined as the days from the start of treatment (initial study) to death due to any cause. For subjects who are alive at the time of the data cut-off, duration of OS will be censored as of the date the subject was last known to be alive.

Since the subjects will be followed up till 30 days after administration of last dose of study drug only per protocol, OS will be calculated and presented in a listing, no Kaplan-Meier estimates will be provided. Number and percentage of subjects who died within 30 days after administration of last dose of study drug will be calculated and death reason will be summarized.

7.7.2   Progression Free Survival (PFS)

PFS is defined as number of days between start of treatment and first evidence of documented disease progression or death (due to any cause), whichever occurs first. Disease progression will be determined by the local investigator for regimens with the same baseline using the International Uniform Response Criteria (Durie et al. 2006, with corrections) (IMWG-URC) for multiple myeloma subjects and RECIST criteria (Therasse et al. 2000) for solid tumor subjects. PFS will be re-calculated whenever the baseline is reset due to addition of new anti-cancer therapy or increase of carfilzomib dose/frequency:

1)   For regimens that continue from initial study without baseline being reset, if subjects didn't progress before PX-171-010, then PFS for the period from initial study to PX-171-010 study will be calculated as Disease Progression /Death Date – Date of first dose in initial study + 1 day, and PFS for the period of PX-171-010 study only will be calculated as Disease Progression /Death Date – Date of first dose in PX-171-010 + 1 day.

2)   For regimens that start in PX-171-010 study with baseline being reset from initial study or previous regimens, PFS will be calculated as Disease Progression /Death Date –

Date of first dose in the first regimen among the regimens with common baseline + 1 day.

PFS will be right-censored for subjects who met one of the following conditions: 1) no baseline disease assessments or any post-baseline assessments, 2) alive and does not have documentation of disease progression before a data analysis cutoff date. The PFS censoring rules are described in Table 1.

Table 1. Censoring Rules for PFS Analysis

Situation	Date of Progression or Censoring	Outcome
No baseline disease assessments or any post-baseline assessments	Date of first dose	Censored
Alive and without documentation of disease progression	Date of last disease assessment	Censored
Death or disease progression between planned disease assessments	Date of death or first disease assessment showing disease progression, whichever occurs first	Progressed
Death or PD immediately after more than 1 consecutively missed disease assessment visit*	Date of last disease assessment before the first missed visit	Censored
Death before first disease assessment	Date of death	Progressed

* If death or PD is more than 168 days after previous disease assessment, or the first dosing date if there is no previous disease assessment.

The number and percentage of subjects with events, the number and percentage of subjects censored will be calculated for each disease cohort (MM, solid tumor) by regime. The denominator for each regimen will be subjects who had the regimen. Kaplan-Meier method will be used to estimate the distribution of PFS. The 25%, 50% and 75% KM quartiles will be provided along with a two-sided 95% confidence interval (Klein and Moeschberger, 1997).

7.7.3 Time to Progression (TTP)

TTP is defined as number of days between start of treatment to the first documentation of disease progression. TTP will be re-calculated whenever the baseline is reset due to addition of new anti-cancer therapy or increase of carfilzomib dose/frequency:

1) For regimens that continue from initial study without baseline being reset, if subjects didn't progress before PX-171-010, then TTP for the period from initial study to PX-171-010 study will be calculated as Date of Disease Progression– Date of first dose in initial study + 1 day, and TTP for the period of PX-171-010 study only will be calculated as Date of Disease Progression – Date of first dose in PX-171-010 + 1 day.

2) For regimens that start in PX-171-010 study with baseline being reset from initial study or previous regimens, TTP will be calculated as Date of Disease Progression – Date of first dose in the first regimen among the regimens with common baseline + 1 day

The same censoring rules, except for death, as in analysis of PFS (Section 7.7.2) will be applied in calculation of TTP. Subjects who die before disease progression will be censored at death date.

The number and percentage of subjects with events, the number and percentage of subjects censored will be calculated. Kaplan-Meier method will be used to estimate the distribution of TTP for each disease cohort by regimens. The 25%, 50% and 75% KM quartiles will be provided along with a two-sided 95% confidence interval (Klein and Moeschberger, 1997).

7.7.4   Additional Efficacy Analyses

7.7.4.1   Objective Response Rate (ORR)

Best overall response will be determined by the local investigator for regimens with the common baseline using the International Uniform Response Criteria (Durie et al. 2006, with corrections) (IMWG-URC) and the European Group for Blood and Marrow Transplant (EBMT) criteria (Bladé et al. 1998) for multiple myeloma subjects and RECIST criteria (Therasse et al. 2000) for solid tumor subjects.

Objective response rate (ORR) is defined according to disease cohort:

- MM - ORR is defined as proportion of subjects for whom the best overall response is stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR).

- Solid Tumor – ORR is defined as the proportion of subjects for whom the best overall response is confirmed PR or confirmed CR.

Point estimates for ORR will be accompanied by 2-sided 95% confidence intervals (Clopper CJ and Pearson, 1934).

7.8   Handling of Data

7.8.1   Data Management

The data management for this study will be provided by Synteract. All data reported on case report forms will be double-entered into a clinical database system. A series of computerized edit checks will be run to identify missing data, inconsistent data, and errors in the clinical database. A description of these procedures is provided in the Data Management and Data Quality Plan (document on file).

7.8.2   Incomplete Adverse Event Start Dates

Missing and incomplete AE start dates will be imputed based on the algorithm described below. The algorithm will be used only if the end date of the AE (if reported) indicates the event was not resolved before the first administration of study drug. The purpose of the imputation is to determine for purposes of analysis if an AE with missing or incomplete start date is treatment emergent (as defined in Section 9.6.1). Imputed AE dates will not be used to calculate the duration of AE episodes.

A list of incomplete and imputed dates will be prepared by the statistical programmer and will be submitted to the statistician for review. Missing and incomplete AE end dates will not be imputed.

Algorithm for Imputation of Incomplete/Missing Adverse Event Start Dates

Case 1:

IF YEAR PORTION OF AE START DATE = MISSING THEN MISSING AE START DATE = FIRST DOSE DATE;

Case 2:

     IF YEAR PORTION OF AE START DATE = YEAR PORTION OF FIRST DOSE DATE THEN DO;

     IF MONTH PORTION OF AE START DATE = MISSING THEN MISSING AE START DATE = FIRST DOSE DATE;
     ELSE

     IF MONTH PORTION OF AE START DATE = MONTH PORTION OF FIRST DOSE DATE THEN MISSING AE START DATE = FIRST DOSE DATE;

     ELSE
     IF MONTH PORTION OF AE START DATE ≠ MONTH PORTION OF FIRST DOSE DATE THEN MISSING AE START DATE = MDY(AE START MONTH, 1, AE START YEAR);
     END;

Case 3:

     IF YEAR PORTION OF AE START DATE > YEAR PORTION OF FIRST DOSE DATE THEN DO;

     IF MONTH PORTION OF AE START DATE = MISSING THEN MISSING AE START DATE = MDY(1, 1, AE START YEAR);

     ELSE
     IF MONTH PORTION OF AE START DATE ^= MISSING THEN MISSING AE START DATE = MDY(AE START MONTH, 1, AE START YEAR);
     END;

7.8.3 Prior and Concomitant Medication Start Dates

Incomplete start dates for concomitant medications will be imputed in the same manner as AEs.

In determining if a medication is prior or concomitant, the following code will be used:

```
    *IF STARTED BEFORE TRTSTDT;
     IF STRDT_S < TXST_S THEN PRIOR = 'Y';


    *IF STOPPED BEFORE TRTSTDT OR NO DATE REPORTED AND
     CONTINUED.;
     IF STPDT_S < TXST_S AND CONT = ' ' THEN PRIOR = 'Y';


    * IF STARTED ON/AFTER TRTSTDT;
     IF STRDT_S >= TXST_S THEN PRINT= 'N';


    * IF STOPPED ON/AFTER TRTSTDT OR CONTINUED.;
     IF STPDT_S >= TXST_S OR CONT = 'Y' THEN PRIOR= 'N';
```

NOTE: STRDT_S=START DATE FOR MEDICATION

         TXST_S = treatment start date

         CONT='Y' = medication is continuing

8   REFERENCES

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