STATISTICAL ANALYSIS PLAN

PROTOCOL ONX-2012-001

Phase 1b/2, Multicenter, Open–label Study of Oprozomib and Dexamethasone in Subjects with Relapsed and/or Refractory Multiple Myeloma

Sponsor: Onyx Pharmaceuticals, an Amgen subsidiary

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition
AE	adverse event
CRF	case report form
CBR	clinical benefit response
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
MM	multiple myeloma
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MTD	maximum tolerated dose
N	number of subjects
nCR	near complete response
ORR	overall response rate
PD	progressive disease
PDn	pharmacodynamic

Abbreviation or Term	Definition
PFS	progression-free survival
PK	Pharmacokinetic
PR	partial response
PT	MedDRA preferred term
SAE	serious adverse event
SAP	statistical analysis plan
sCR	stringent complete response
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) was prepared for an abbreviated clinical study report (aCSR) in accordance with Protocol ONX-2012-001, dated 26June2014 (amendment 3), and describes the analyses of data collected within the scope of the study. 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 the abbreviated clinical study report 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 Overall Study Design

This study is an open–label, Phase 1b/2, multicenter study in which subjects will receive oprozomib (OPZ) administered orally once daily in combination with dexamethasone (DEX) on 2 different treatment schedules. Subjects will receive OPZ on Days 1–5 of a 14–day cycle in combination with 20 mg DEX on Days 1, 2, 8, and 9; or OPZ on Days 1, 2, 8, and 9 of a 14–day cycle in combination with 20 mg dexamethasone on Days 1, 2, 8, and 9. Both the Phase 1b and Phase 2 portions of this trial will be open to subjects with relapsed and/or refractory multiple myeloma.

Treatment will be administered in 14–day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Disease response assessments will be performed every 4 weeks for the first year through Cycle 26 and then every 8 weeks thereafter according to the IMWG–URC. In addition, nCR and MR will be assessed per the modified EBMT criteria.

A minimum of 3 subjects will be entered within each dose cohort, to be expanded up to 6 subjects if DLTs are observed. Assessment of DLTs will occur during the first 14 days of treatment (or Cycle 1) or the first 14 days of treatment with the step-up dose to be

studies (Cycle 2). Any subject who develops a DLT after receiving at least 1 dose of OPZ will be considered evaluable. Any subject who does not develop a DLT, but has not received all planned doses of OPZ and DEX will be considered unevaluable for the dose escalation decision and will be replaced.

If none of the first 3 subjects in a cohort experiences a DLT in the first cycle, enrollment will commence at the next planned dose level. If 1 of 3 subjects enrolled in a cohort experiences a DLT during the first treatment cycle, the same cohort will be expanded up to 6 evaluable subjects. If 1 of 6 subjects experiences a DLT during the first treatment cycle, the next cohort will enroll at the next higher dose level. If 2 or more subjects in a cohort experience a DLT in the first treatment cycle, the MTD will have been exceeded, additional enrollment within the cohort will cease, and dose escalation will stop.

If 2 or more subjects experience a DLT at a given dose, additional subjects will be added to the preceding dose group if there are fewer than 6 subjects in that cohort, for a minimum of 6 subjects treated at that dose in order to determine the MTD. The MTD will be defined as the highest dose in which a DLT is observed in less than 2 of 6 subjects At least 6 subjects must be treated at the MTD for a minimum of 1 cycle to establish this dose as tolerated.

The initial cohort will be entered at a dose level of 210 mg. All subsequent cohorts will be escalated by 30 mg until the MTD is determined. There will not be a predefined maximum dose to be studied.

2.2 Study Objectives

2.2.1 Primary Objectives

Phase 1b:

- To determine the MTD and recommended Phase 2 dose (RP2D) of OPZ given orally, once daily, on 2 different schedules: 5 consecutive days every 14 days (bimonthly; 5/14) or 2 consecutive days every 7 days (weekly; 2/7) for a 14–day treatment cycle, both schedules given in combination with DEX.

- To evaluate safety and tolerability

Phase 2:

- To estimate the overall response rate (ORR), defined as the proportion of subjects with the best overall response of stringent complete response (sCR), complete response (CR), near complete response (nCR), very good partial response (VGPR), and partial response (PR) as defined by the International Myeloma Working Group–Uniform Response Criteria (IMWG–URC) and modified European Group for Blood and Marrow Transplantation (EBMT) criteria.
- To evaluate safety and tolerability

2.2.2 Secondary Objectives

- To evaluate PK of OPZ tablet and OPZ ER tablet
- To estimate clinical benefit rate (CBR), defined as ORR plus minimal response (MR), as defined by the EBMT criteria
- To estimate the duration of response (DOR)
- To estimate progression–free survival (PFS)
- To estimate time to progression (TTP)

2.3 Sample Size Justification

For the Phase 1b portion of the study, it is estimated that up to approximately 60 subjects (approximately 30 subjects per treatment schedule) will be required to determine the recommended Phase 2 dose for each treatment schedule. This is based on an estimate that up to 5 cohorts will be enrolled per treatment schedule, with up to 6 evaluable subjects per cohort.

For the recommended dose group (dose escalation cohort plus Phase 2 cohort), the null (H_0) and the alternative (H_A) hypotheses are as follows:

$$H_0: \ ORR_{Cd} \leq 15\%$$

$$H_A: ORR_{Cd} > 15\%$$

With a sample size of 46 subjects (6 evaluable dose escalation subjects + 40 Phase 2 subjects enrolled at the recommended dose), a 1–sample exact binomial test with a 1–sided significance level of 5% will have 77% power at an ORR of 30%. If at least 12 of the 46 subjects have a best overall response of PR or better, then the null hypothesis will be rejected and it will be inferred that the ORR is > 15%.

The total study sample size will depend on the number of dose levels required to establish the recommended dose for each schedule and the number of schedules initiated in the Phase 2 portion of the study. The study will enroll approximately 140 subjects.

3 STUDY ENDPOINTS

3.1 Primary Endpoints

Phase 1b:

- Dose–limiting toxicities identified to determine the MTD and RP2D, defined as the highest dose at which < 33% of subjects experience DLTs after 1 cycle (14 days) of treatment.
- Safety and tolerability

Phase 2:

- Overall response status, to determine whether a subject has a best response of sCR, CR, nCR, VGPR, or PR, as defined by IMWG–URC and EBMT criteria (nCR)
- Safety and tolerability

3.2 Secondary Endpoints

Phase 1b/2:

- Pharmacokinetics of OPZ tablet and OPZ ER tablet

Phase 2:

- Clinical benefit response status, to determine whether a subject has a best response of sCR, CR, nCR, VGPR, or PR, as defined by IMWG–URC and EBMT criteria (MR and nCR)
- Duration of response
- Progression–free survival
- Time to progression

4 ANALYSIS POPULATIONS

All subjects who receive at least 1 dose of study treatment will be considered evaluable for both the efficacy and safety analyses (Safety Population). The Safety Population will be the primary population for all safety and efficacy data presented (Phase 1 and Phase 2).

5 ANALYTIC DEFINITIONS

5.1 Study Day 1

Study day 1 corresponds to the date of the first dose of study drug.

5.2 Study Day

For events, assessments, and interventions after study day 1, study day represents the elapsed number of days from study day 1, inclusive:

$$\text{Study Day } n = (\text{Date of assessment} - \text{Date of Study Day 1}) + 1 \text{ day}$$

Unless otherwise specified, the timing of all study-related events, assessments, and interventions will be calculated relative to study day 1. Study day −1 will be the day before study day 1, and in general for assessments prior to study day 1, study day is defined as:

$$\text{Study Day } n = (\text{Date of assessment} - \text{Date of Study Day 1})$$

For listings (such as for adverse events) that include the derivation of "days since last dose," this is defined as event date – date of last dose. Events that occur on the same day

as the last dose of study drug will therefore be described as occurring zero days from the last dose of study drug.

5.3 Baseline

Unless otherwise specified, the baseline value is defined as the last assessment prior to the first dose of OPZ and DEX.

6 INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES

There are no formal interim analyses planned for this study. A Cohort Safety Review Committee (CSRC) will review the clinical and laboratory data of each dose cohort before escalating the OPZ dose to the next dose cohort.

7 STATISTICAL METHODS

7.1 General Considerations

This statistical analysis plan is being generated prior to locking the study database. It specifies the main efficacy and safety analyses to be performed.

All statistical summaries and analyses will be performed in SAS® version 9.3 or higher (SAS Institute Inc., Cary, NC, USA) on a PC platform.

In general, summaries of all data will be presented by schedule and dose groups, defined as initial dose level cohort for phase 1 and recommended dose cohort for phase 2. In addition, some summaries will include the combined recommended dose cohort from phase 1 and 2 and total cohorts (all subjects by schedule).

Summary statistics will be provided for selected endpoints. 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 frequency and percent distribution will be presented. Unless otherwise indicated, percentages will be calculated

based upon the number of subjects in the Safety Population in each dose group as the denominator.

Confidence intervals, when presented, will be constructed at the 95% level. For binomial variables, exact distribution methods will be employed. The distribution of time-to-event endpoints will be summarized by Kaplan-Meier method. Quartiles including median will be estimated by Kaplan-Meier method along with their 95% confidence intervals.

Individual subject data recorded on the electronic case report forms (eCRFs) and any derived data will be presented by dose cohort and subject in data listings.

7.2 Disposition of Subjects

The following subject disposition information will be summarized for all subjects by each of the schedule and dose group and for the combined dose groups (total group).

- number of treated subjects
- number (%) of subjects who discontinue from the study drug
- primary reason for study drug discontinuation
- number (%) who had an End of Study visit
- reason for no End of Study visit

7.3 Demographic and Baseline Characteristics

7.3.1 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized for the Safety Population.

- Age (years) and age categorized (years) as <65, 65 - <75, and ≥ 75
- Sex

- Ethnicity
- Race
- Baseline ECOG performance status
- Baseline fertility status
- Baseline weight (kg)
- Baseline height (cm)

7.3.2 Medical History

The number (%) of subjects who experienced a prior disease or disorder will be summarized by body system for the Safety Population.

7.3.3 Disease Characteristics

The following disease characteristics will be summarized for the Safety Population.

- ISS at initial diagnosis and at Screening
- Time (years) since initial diagnosis, defined as date of informed consent signed minus date of diagnosis
- Category of multiple myeloma
- Heavy chain and light chain status
- Plasma cell involvement (%) as assessed with bone marrow assessment ($< 50\%$, $\geq 50\%$, unknown or missing)
- FISH (standard risk, high risk, unknown or not done)
    - High risk: with one of the following abnormalities: t(4;14), t(14;16), del(17p;13), or 1q21 amplification
    - Standard risk: none of the high risk finding
- Baseline β2 microglobulin (mg/L) (< 5.5 mg/L versus ≥ 5.5 mg/L)

7.3.4 Prior Cancer Therapies

The following prior cancer therapy data will be summarized for the Safety Population:

- Number (%) of subjects with at least one prior:
    - Chemotherapy
    - Transplant
    - Radiotherapy
    - No prior therapy
- Number of regimens of prior treatment (1, 2, etc) for multiple myeloma and number of prior drugs

7.4 Treatments and Medications

7.4.1 Study Drug Administration

The overall extent of study treatment exposure and dose information will be summarized for the Safety Population for both OPZ and DEX.

- Duration of treatment (weeks), defined as (date of last dose – date of first dose + 1) divided by 7 for OPZ and DEX
- Total number of treatment cycles during which one full daily dose of OPZ and DEX was taken by the subject.
- Number (%) of subjects dosed by cycle, where a subject will be considered to have been dosed in a cycle if the subject receives at least one full daily dose of OPZ and DEX.
- Total doses received across all cycles of OPZ and DEX
- Dose modifications of study drug based on AE action taken data

7.5 Efficacy Analyses

All efficacy analyses will be based on the Safety Population. Disease progression as collected at the end of treatment (end of study visit) as determined by the investigator will be used for the analysis for PFS, TTP, and DOR.

7.5.1 Overall Response Rate

The overall response rate (ORR) is defined as proportion of subjects for whom the best overall confirmed response is stringent complete response (sCR), complete response (CR), near complete response (nCR), very good partial response (vGPR), or partial response (PR) as defined by International Myeloma Working Group Uniform Response Criteria (IMWG-URC) and modified European Group for Blood and Marrow Transplantation (EBMT) criteria (nCR). An estimate of the ORR and its 1–sided 95% exact binomial confidence interval for each of the recommended dose groups will be determined. Additionally, the ORR and CBR along with the associated 2–sided 95% exact binomial confidence intervals will be determined including the recommended dose group (dose escalation cohort + Phase 2 cohort).

7.5.2 Progression Free Survival

Progression free survival (PFS) is defined as number of months (one month = 30.4 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 using IMWG-URC and will be determined by the investigator.

PFS = Earliest date of disease progression, death, or censoring – Date of first dose + 1 and expressed in months

The duration of PFS will be right–censored for subjects who meet 1 of the following conditions: 1) starting a new anticancer therapy before documentation of disease progression or death; 2) death or disease progression immediately after more than 1 consecutively missed disease assessment visit or; 3) alive without documentation of

disease progression before the data cutoff date. For such subjects, the analysis of PFS will be right–censored according to the conventions described in Table 1.

Table1: Date of Progression or Censoring for PFS and DOR

Situation	Date of Progression or Censoring	Outcome
No baseline disease assessments	Date of first dose	Censored
New anticancer therapy started before documentation of PD or death	Date of last disease assessment prior to start of new anticancer therapy	Censored
Death or PD immediately after more than 1 consecutively missed disease assessment visit	Date of last disease assessment visit without documentation of PD that is before the first missed visit	Censored
Alive and without PD documentation	Date of last disease assessment	Censored
Death or PD between planned disease assessments	Date of death or first disease assessment showing PD, whichever occurs first	Progressed
Death before first disease assessment	Date of death	Progressed

PD = progressive disease

Kaplan-Meier method will be used to estimate the distribution of PFS and the median and other quartiles in addition to the corresponding two-sided 95% confidence intervals.

Duration of follow-up for PFS will be summarized according to the Kaplan-Meier estimate of potential follow-up also termed “reverse Kaplan-Meier” (Schemper 1996).

7.5.3 Time to Progression

Time to progression (TTP) is defined as number of months between start of treatment to the first documentation of disease progression. Disease progression will be determined using IMWG-URC as assessed by the investigator:

TTP = Earliest date of disease progression or censoring – Date of first dose + 1 and expressed in months

The same censoring rules, except for death, as in analysis of PFS will be applied in calculation of TTP. Subjects who die prior to progressive disease will be censored at the date of last evaluable response assessment.

7.5.4 Duration of Response

Duration of response (DOR) will be calculated for subjects who achieve a sCR, CR, nCR, VGPR, or PR. For such subjects, the duration of overall response is defined as the time from first evidence of PR or better to disease progression or death due to any cause.

DOR = Earliest date of disease progression, death, or censoring - Date of first observation of PR or better before confirmation + 1 and expressed in months

Duration of response will be right–censored for subjects who at least achieve a PR based on the censoring conventions defined previously for PFS. Analysis of DOR will be performed using the Kaplan–Meier method. Medians and other quartiles for DOR will be estimated in addition to the corresponding 2–sided 95% confidence intervals.

7.5.5 Duration of Clinical Benefit Response

Duration of clinical benefit response (CBR) will be calculated for subjects who achieve a MR or better. For such subjects, the duration of CBR is defined as the time from first documentation of MR or better to disease progression or death due to any cause. Dates of progression and censoring will be determined as described for the analysis of PFS.

Duration of CBR = Earliest date of disease progression, death, or censoring - Date of first observation of MR or better before confirmation + 1 and expressed in months

The duration of CBR will be summarized descriptively using the Kaplan-Meier method. The quartiles of the Kaplan-Meier distribution will be used to estimate the median duration of CBR.

7.6 Safety Analysis

All safety analyses will be based on the Safety population.

7.6.1 Adverse Events

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).

Treatment-emergent adverse events (TEAEs) are defined as AEs that start on or after the first day of study treatment and within 30 days of the last day 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.

Adverse events will be summarized based on the number (%) of subjects experiencing events by MedDRA system organ class and preferred term. The denominator for the percentage will be based on the number of subjects at in the Safety Population (i.e., those that received at least one dose of study drug).

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 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 study drug.

An overall summary of TEAEs will summarize the number (%) of subjects

- with at least one TEAE
- with at least one treatment-related TEAE, defined as related to OPZ or DEX
- with at least one grade 3 or higher TEAE
- with at least one treatment-related grade 3 or higher TEAE, either OPZ or DEX
- with at least one serious AE
- with TEAE leading to discontinuation of study drug, either OPZ or DEX
- with TEAE leading to discontinuation of OPZ

- who died within 30 days of last dose of study drug

Summaries of the following TEAEs will be provided by SOC and/ or PT unless otherwise noted:

- all TEAEs
- all TEAs (PT)
- TEAEs by maximum severity
- treatment-related adverse events (OPZ, DEX, and study drug [OPZ/DEX])
- serious TEAEs
- TEAEs that led to permanent discontinuation of study drug (OPZ, DEX and study drug [OPZ/DEX])

Summaries that are displayed by system organ class and preferred terms will be ordered by descending order of incidence of system organ class and preferred term within each system organ class for the total group. Summaries of TEAEs, treatment-related AEs will also be provided by descending order of incidence of preferred terms in the total group.

All AEs, including TEAEs, will be included in listings by subject.

Listings of AEs determined to be DLTs during the first cycle of Phase 1, serious AEs, and AEs leading to discontinuation of study drug will be provided.

A summary of the number of deaths and the cause of death, classified by deaths within 30 days of last dose of study drug and deaths more than 30 days after the last dose, will be provided.

7.6.2 Laboratory Data

All available laboratory results will be included in the subject data listings.

Selected laboratory test results will be assigned toxicity grades using CTCAE 4.03. A summary of post-baseline grade 3 or higher laboratory toxicities will be provided. The laboratory parameters of interest for these summaries are:

Hematology (all decrease)	**Serum Chemistry (increase except where noted)**	
Hemoglobin	ALT	Albumin
Platelets	AST	Uric Acid
WBC	Alkaline Phosphatase	Sodium (increase, decrease)
Neutrophils (absolute)	Total Bilirubin	Phosphorus (decrease)
Lymphocytes (absolute)	Creatinine	Potassium (increase, decrease)
	Calcium (increase, decrease)	Magnesium (increase, decrease)
	Glucose (increase, decrease)	

7.6.3 Vital Signs and Weight

Vital sign results including blood pressure, pulse, and temperature will be included in the subject data listings.

7.6.4 12-Lead Electrocardiogram

Maximum post-baseline and maximum increase from baseline categories of corrected QT interval results will be summarized.

7.6.5 Prior and Concomitant Medications

All prior and concomitant medications will be coded using WHO Drug Dictionary. Concomitant medications are defined as medications with start date or end date on or after the date of first dose and before the date of the last dose + 30 days or are ongoing at the time of first dose. Prior medications are defined as medications with a stop date before the date of first dose.

Concomitant medications will be summarized by generic name.

7.6.6 Protocol Deviations

Protocol deviations will be included in the subject data listings. Major protocol deviations will be either captured on the designated eCRF (e.g., eligibility violations) or identified through data review and surveillance.

8 Statistical/Analytical Issues

8.1 Handling of Dropouts or Missing Data

The handling of dropouts and missing disease status assessments for the efficacy variables is described in their definitions.

Missing or partially missing dates will not be imputed at data level. However, assumptions for missing or partially missing dates for important variables will be made to allow inclusion of appropriate data records in the analyses.

If a medication date or time is missing or partially missing, so it cannot be determined whether it was taken prior or concomitantly, it will be considered as a prior, concomitant, and a post-treatment medication.

If the partial AE onset date information does not indicate whether the AE started prior to treatment or after the TEAE period, the AE will be classified as TEAEs.

If the start day of subsequent anti-cancer therapy is missing, it will be assumed to be the first day of the month.

8.2 Interim Analysis and Data Monitoring

The CSRC will review the clinical data of each dose cohort after three subjects have been treated for at least one cycle during phase 1 of the study. Based on the number of subjects with dose-limiting toxicity, escalation to the next higher OPZ dose may occur, the cohort may be expanded to six subjects, or dosing at that dose level may stop and the

next-lower dose cohort may be expanded. The committee must agree that dose escalation to the next cohort is appropriate before it proceeds.