STATISTICAL ANALYSIS PLAN

PROTOCOL OPZ007

Phase 1b/3 Multicenter Study of Oprozomib, Pomalidomide, and Dexamethasone in Primary Refractory or Relapsed and Refractory Multiple Myeloma Subjects

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
ORR	overall response rate
PD	progressive disease
PDn	pharmacodynamic
PFS	progression-free survival

Abbreviation or Term	Definition
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) for the Part 1 of the study in accordance with Protocol OPZ007, dated 08 July 2014 (amendment 2), and describes the analyses of data collected within the scope of the Part 1 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 aCSR 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 is a Phase 1b/3 study of oprozomib (OPZ) in combination with pomalidomide (POM) and dexamethasone (DEX) in subjects with primary refractory or relapsed and refractory multiple myeloma. There are 2 parts to this study. Part 1 includes an open-label, Phase 1b, dose-escalation and dose-expansion portion (the equivalent of a small Phase 2) during which the RP3D will be identified. Further evaluation of safety and efficacy will be assessed during the dose-expansion portion. During the Phase 1b portion of the study, subjects will receive Oprozomib ER Tablets according to their assigned dose cohort. Part 2 will consist of a placebo-controlled, double-blind, randomized Phase 3 component where subjects will be randomized to receive the RP3D of oprozomib or placebo administered orally in combination with pomalidomide and dexamethasone in 28-day cycles until disease progression or unacceptable toxicity.

This study will include subjects with primary refractory or relapsed and refractory multiple myeloma, i.e., those who have demonstrated disease progression on or within 60 days of their last therapy, and who have received at least 2 prior lines of therapy (including bortezomib and lenalidomide and/or thalidomide, and in the dose-expansion and Phase 3 portions of the study only, been treated with adequate alkylator therapy).

Subjects whose last therapy was bortezomib and who were not refractory but developed bortezomib intolerance, as defined by the development of Grade 2 peripheral neuropathy with pain or ≥ Grade 3 peripheral neuropathy after ≥ 2 consecutive cycles, are eligible.

Treatment cycles are 28 days in duration. Two (2) oprozomib dosing schedules will be assessed during dose escalation. Subjects will receive oprozomib once daily either on Days 1–5 and 15–19, referred to hereafter as the 5/14 schedule, or an alternate schedule of once daily on Days 1, 2, 8, 9, 15, 16, 22, and 23, referred to hereafter as the 2/7 schedule. Pomalidomide will be given on Days 1–21 and dexamethasone will be given on Days 1, 2, 8, 9, 15, 16, 22, and 23 of every 28-day cycle.

During Part 2 of the study, subjects will be randomized to oprozomib in combination with pomalidomide and dexamethasone (OPomd) at the RP3D and schedule determined during Part 1 of the study or placebo in combination with pomalidomide and dexamethasone (Pomd).

Approximately 35 study sites will participate in Part 1 of the study (15 sites for the Phase 1b dose-escalation and 20 additional sites for the dose-expansion portions of the study). An additional 35 sites, for a total of approximately 70 sites, will participate in Part 2 of the study (Phase 3 portion of the study).

Treatment cycles for both parts of the study will last 28 days. Disease assessments will be performed every 4 weeks for subjects in both arms for 18 months. Further disease assessments will be conducted every 8 weeks after this period, beginning with Month 20. Details of the study assessments required for both parts of this study are provided in Appendices A1, A2, B1, B2, C1, and C2 of the protocol.

The readiness of Phase 3 portion (Part 2) of the study was assessed after Part 1 was completed and three areas of concern were identified below:

- GI tolerability profile, though acceptable in relapsed/refractory disease, needed improvement
- Formulation determined not to be robust

- High intrapatient PK variability discovered in Clinical Pharmacology Study

A decision was made to reformulate, and determine if a new, robust formulation could improve PK variability and GI tolerability. Therefore the Part 2 of the study was cancelled and an aCSR would be produced for the Part 1 of the study.

2.2 Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study

In Part 1 of the study, the safety, MTD, PK/PDn, and RP3D of oprozomib when given in combination with pomalidomide and dexamethasone will be assessed using a standard 3 + 3 dose-escalation design. For each of the 2 schedules being studied, groups of 3 to 6 subjects will be enrolled into dose-escalation cohorts. As long as fewer than 33% of subjects experience a DLT in a given cohort, escalation will continue by 30-mg increments of oprozomib onto the next designated cohort(s). A minimum of 6 subjects must be treated at the MTD to establish the dose as the MTD. If the starting dose of oprozomib cannot be safely administered with the labeled pomalidomide dose or at sponsor discretion, then up to 2 possible alternative dose-escalation paths for oprozomib with lower pomalidomide doses will be explored (See tables below for primary and alternative dose-escalation paths). Dose escalation will continue until sponsor discretion, the maximum planned dose of pomalidomide is reached, or ≥ 2 DLTs occur in a cohort, whichever occurs first. The prior cohort will be expanded to at least 6 subjects if not previously done to establish it as the MTD. There may be more than 1 MTD of oprozomib if more than 1 dose level of pomalidomide is studied. The MTD for oprozomib associated with each dose level of pomalidomide assessed will be the dose level where < 2 DLTs in 6 subjects are observed.

There is no planned maximum dose of oprozomib to be evaluated as it is being added to the FDA-approved regimen of pomalidomide/dexamethasone, however, this could be imposed at any time during the course of the study, based on sponsor discretion. The starting dose of oprozomib for the 5/14 schedule is 150 mg, 3 dose levels below the

established single-agent MTD of 240 mg. The starting dose of oprozomib for the 2/7 schedule is 210 mg, 3 dose levels below the established 2/7 single-agent MTD of 300 mg. The MTD will be determined as outlined in the protocol for each schedule. Following dose escalation, the sponsor has the option of expanding 1 or both schedules in order to establish the RP3D and schedule.

The sponsor, with input from the Cohort Safety Review Committee ([CSRC] consisting of investigators, sponsor's medical monitor, and sponsor's drug safety representative), will determine which dose and schedule of oprozomib in combination with pomalidomide and dexamethasone to use for the dose-expansion (i.e., the RP3D) portion of the study. The sponsor has the option of expanding 1 or both schedules in order to establish the RP3D and schedule. The RP3D may differ from the MTD, but will not be higher than the MTD, and will be selected based upon the assessment of the safety, tolerability, PK, PDn, preliminary activity, and other variables to be observed across multiple cycles of combination therapy.

2.3 Study Objectives - Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study (by Schedule)

2.3.1 Primary Objectives

- To determine the maximum tolerated dose (MTD) and identify the recommended Phase 3 dose (RP3D) and schedule of oprozomib in combination with pomalidomide and dexamethasone (OPomd) in subjects with primary refractory or relapsed and refractory multiple myeloma
- To evaluate the safety and tolerability of the OPomd combination in subjects with primary refractory or relapsed and refractory multiple myeloma

2.3.2 Secondary Objectives

- To estimate the overall response rate (ORR) of OPomd, defined as the proportion of subjects with an overall response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response

(PR) as determined by investigator according to the International Myeloma Working Group- Uniform Response Criteria (IMWG-URC)

- To estimate the clinical benefit rate (CBR) of OPomd, defined as the proportion of subjects with an overall response of minimal response (MR) or better as determined by investigator according to the IMWG-URC and modified European Group for Blood and Marrow Transplantation (EBMT) criteria
- To characterize the pharmacokinetics (PK) of oprozomib in the OPomd regimen

2.4 Sample Size Justification

Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study

A total enrollment of approximately 82 subjects is planned for Part 1 of the study. During the Part 1 Phase 1b dose-escalation portion of the study, approximately 21 subjects are expected to be enrolled for each schedule. The estimated sample size for the dose-escalation part of the study is based on standard 3 + 3 dose-escalation rules, with expectations that 2–3 dosing cohorts of 3–6 subjects per cohort will be required to establish the MTD. A minimum of 6 subjects must be treated at the MTD. For each schedule, more than 1 MTD for oprozomib may be established if additional dose levels of pomalidomide are assessed. The MTD for oprozomib in combination with each dose level of pomalidomide will be the dose(s) where < 2 DLTs in 6 subjects are observed.

The actual number of required subjects will depend on both the total number of cohorts, and the need to expand a given cohort from 3 to 6 subjects in order to identify the MTD. Properties of the dose-escalation rules for different underlying DLT rates are provided in Table 1.

Table 1 Properties of the Dose-Escalation Rules for Different Underlying DLT Rates

Underlying Rate of DLT	Probability of Enrolling 3 Additional Subjects	Probability that Dose is Determined to be

		Tolerated
0.10	0.24	0.91
0.20	0.38	0.71
0.33	0.44	0.43
0.40	0.43	0.31
0.50	0.38	0.17
0.60	0.29	0.08

DLT = dose-limiting toxicity.

The criteria for selecting the RP3D for each schedule at the sponsor's discretion will include assessment of the safety, tolerability, and preliminary activity of oprozomib observed across multiple cycles. In addition, both PK and PDn assessments to demonstrate adequate exposure and proteasome inhibition will be a key factor. The CSRC will review the data and provide guidance in selection of the RP3D. Therefore the RP3D may differ from the MTD, but will not be higher than the MTD. A minimum of 20 additional subjects are planned for enrollment and treatment for 1 or both schedules at the sponsor's discretion at the RP3D during the Phase 1b dose-expansion portion of Part 1 of the study. In the dose-expansion portion of the study, if the true ORR $\geq$ 40%, then the probability of seeing at least 7 responses among the 26 subjects (6 treated at the MTD during escalation + 20 in the expansion) is approximately 94%.

3 STUDY ENDPOINTS

3.1 Primary Endpoints

Part 1:

- DLTs
- Adverse events and laboratory abnormalities graded according to NCI-CTCAE, Version 4.03
- Vital signs and clinical laboratory results during and following study drug administration

3.2 Secondary Endpoints

Part 1:

- Overall response, defined as the best response of sCR, CR, VGPR, or PR, as determined by investigator according to the IMWG-URC
- Clinical benefit, defined as defined as the best response of MR or better, as determined by investigator according to the IMWG-URC and modified EBMT criteria
- Pharmacokinetic parameters, including maximum plasma concentration (C_{max}), time to maximum concentration (T_{max}), area under the plasma concentration time curve from time 0 to last time point ($AUC_{0-\tau}$), and area under the plasma concentration time curve from time 0 to time infinity ($AUC_{0-\infty}$) using noncompartmental methods

4 ANALYSIS POPULATIONS

All subjects who receive at least 1 dose of study treatment in Part 1 of the study 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.

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:

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

Study Day *n* = (Date of assessment – 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, POM or 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 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%, ≥ 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)

7.3.3 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 OPZ, POM and DEX.

- Duration of treatment (weeks), defined as (date of last dose – date of first dose + 1) divided by 7 for OPZ, POM and DEX
- Total number of treatment cycles during which one full daily dose of OPZ, POM 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, POM and DEX.
- Total doses received across all cycles of OPZ, POM 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 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), very good partial response (vGPR), or partial response (PR) as defined by International Myeloma Working Group Uniform Response Criteria (IMWG-URC). 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 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 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.

7.6 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
- TEAEs grade 3 or higher (PT)
- treatment-related adverse events (OPZ, POM, DEX, and study drug)

- serious TEAEs
- TEAEs that led to permanent discontinuation of study drug (OPZ, POM, DEX and study treatment)

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. Statistical/Analytical Issues

7.7 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.

7.8 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.