16.1.1 Protocol and Amendments

Protocol Amendment 3, dated 27 February 2018 was generated and approved. Shortly thereafter, a decision was made to terminate the study program, and the amendment was not implemented. The last version of the protocol, under which the study was active, was Amendment 2, dated 15 October 2014.

CLINICAL STUDY PROTOCOL

Protocol Title:	Phase 1b/2, Multicenter, Open-label Study of Oprozomib and Dexamethasone in Combination with Lenalidomide or Oral Cyclophosphamide in Patients with Newly Diagnosed Multiple Myeloma
Protocol Number:	OPZ003
Name of Investigational Product:	Oprozomib
IND Number:	117,851
Sponsor:	Onyx Therapeutics 249 E. Grand Avenue South San Francisco, CA 94080 US
Study Medical Monitor:	[redacted], MD Senior Medical Director, Clinical Science 249 E. Grand Avenue South San Francisco, CA 94080 US [redacted] Email: [redacted]
Date of Original Protocol:	17 May 2013
Amendment 1/Date:	19 September 2013
Amendment 2/Date:	15 October 2014
Confidentiality Statement:	This material is the property of Onyx Therapeutics, a wholly owned subsidiary of Onyx Pharmaceuticals, an Amgen subsidiary. The material is highly confidential and is to be used only in connection with matters authorized by a senior representative of Onyx Therapeutics, and no part of it is to be disclosed to a third party without the express prior written permission of Onyx Therapeutics.
Compliance Statement:	This study will be conducted in accordance with Protocol OPZ003, the International Conference on Harmonisation (ICH), Good Clinical Practice (GCP) guidelines, and the applicable country and regional regulatory requirements.

NCT Number: NCT01881789
This NCT number has been applied to the document
for purposes of posting on clinicaltrials.gov

PROTOCOL APPROVAL SIGNATURE PAGE

Protocol Title:	Phase 1b/2, Multicenter, Open-label Study of Oprozomib and Dexamethasone in Combination with Lenalidomide or Oral Cyclophosphamide in Patients with Newly Diagnosed Multiple Myeloma
Protocol Number:	OPZ003
Sponsor:	Onyx Therapeutics 249 E. Grand Avenue South San Francisco, CA 94080 US
Date of Original Protocol:	17 May 2013
Amendment 1:	19 September 2013
Amendment 2:	15 October 2014

Approved by:

<See Electronic Signature>
[redacted] MD
Vice President, Clinical Development

Date

APPROVALS STATEMENT
This document is signed with electronic signatures at Onyx Therapeutics, a wholly owned subsidiary of Onyx Pharmaceuticals, an Amgen subsidiary. Electronic signatures made by our employees, agents, or representatives, located anywhere in the world, are the legally binding equivalent of traditional handwritten signatures.

PROTOCOL ACCEPTANCE PAGE

Issue/Date: OPZ003/Amendment 2/15 October 2014

I have read this protocol for Study OPZ003 entitled:

Phase 1b/2, Multicenter, Open-label Study of Oprozomib and Dexamethasone in Combination with Lenalidomide or Oral Cyclophosphamide in Patients with Newly Diagnosed Multiple Myeloma

As investigator, I understand and agree to conduct this study as outlined herein.

Investigator Name (print)

Investigator Signature Date

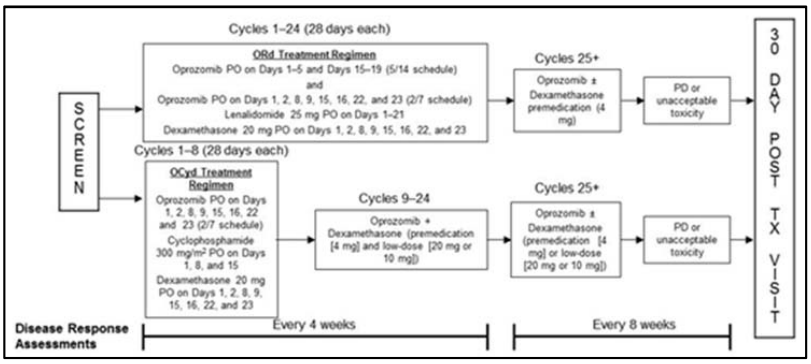
Signature on this page assures the sponsor that, to the best of the investigator's knowledge, the affiliated Institutional Review Board (IRB)/Independent Ethics Committee (IEC) operates in accordance with the governing regulations, and that the investigator understands, and agrees to abide by, all governing regulatory obligations and the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) while conducting this clinical investigation. Once signed, the original of this form should be detached from the protocol and returned to Onyx Therapeutics or its designee (please retain a copy for your files).

SYNOPSIS

Name of sponsor/company:	Onyx Therapeutics
Name of product:	Oprozomib
Title of study and protocol number:	Phase 1b/2, Multicenter, Open-label Study of Oprozomib and Dexamethasone, in Combination with Lenalidomide or Oral Cyclophosphamide in Patients with Newly Diagnosed Multiple Myeloma Protocol Number OPZ003
Study objective(s):	**Primary Objectives** Phase 1b • To establish the maximum tolerated dose (MTD) of oprozomib given in combination with lenalidomide and dexamethasone (ORd) or with cyclophosphamide and dexamethasone (OCyd). • To evaluate the safety and tolerability of the ORd and OCyd combination regimens, as assessed by the type, incidence, severity and seriousness of adverse events (AEs), and abnormalities in selected laboratory analytes. Phase 2 • To estimate the antitumor activity of the ORd and OCyd combination regimens, as measured by overall response rate (ORR) and complete response rate (CRR). • To evaluate the safety and tolerability of the ORd and OCyd combination regimens, as assessed by the type, incidence, severity and seriousness of AEs and abnormalities in selected laboratory analytes. **Secondary Objectives** • To evaluate population pharmacokinetic (PK) parameter estimates of oprozomib, and may include its metabolite(s), and the variability in these estimates. • To estimate the duration of response (DOR). • To estimate progression-free survival (PFS). **Exploratory Objectives** • To evaluate pharmacodynamics (PDn) biomarkers that may correlate with antitumor activity. • To evaluate genomic biomarkers that may predict response and resistance following treatment with proteasome inhibitors.
Study design:	This is an open-label, Phase 1b/2, two-combination regimen, non-randomized, multicenter study (see study schema below).

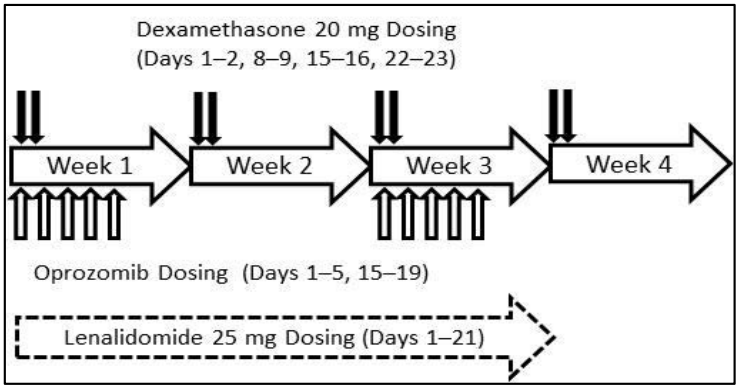
Study design (cont'd):

Study Schema for OPZ003



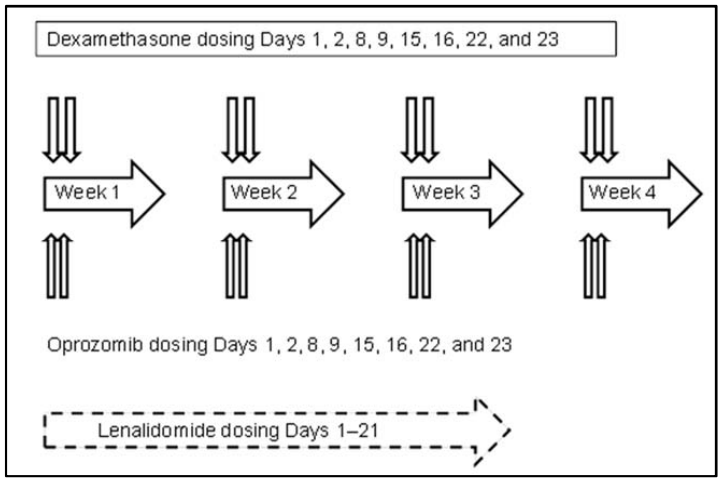
The ORd combination regimen treatment cycles are 28 days in duration. Subjects enrolled under the original protocol and Amendment 1 will receive oprozomib once daily on Days 1 through 5 and Days 15 through 19 (referred to as the 5/14 schedule). Subjects enrolled under Amendment 2 will receive oprozomib once daily on 2 consecutive days every 7 days; specifically on Days 1, 2, 8, 9, 15, 16, 22, and 23 (referred to as the 2/7 schedule). All subjects on the ORd arm will receive lenalidomide at a dose of 25 mg will be given on Days 1 through 21 and dexamethasone at a dose of 20 mg will be given on Days 1, 2, 8, 9, 15, 16, 22, and 23 of every 28-day cycle (see dose administration schemas below).

Dose Administration Schema for Oprozomib, Lenalidomide, and Dexamethasone (ORd) 5/14 Schedule (Original Protocol and Amendment 1)



Study design (cont'd):

Dose Administration Schema for Oprozomib, Lenalidomide, and Dexamethasone (ORd) 2/7 Schedule (Amendment 2)

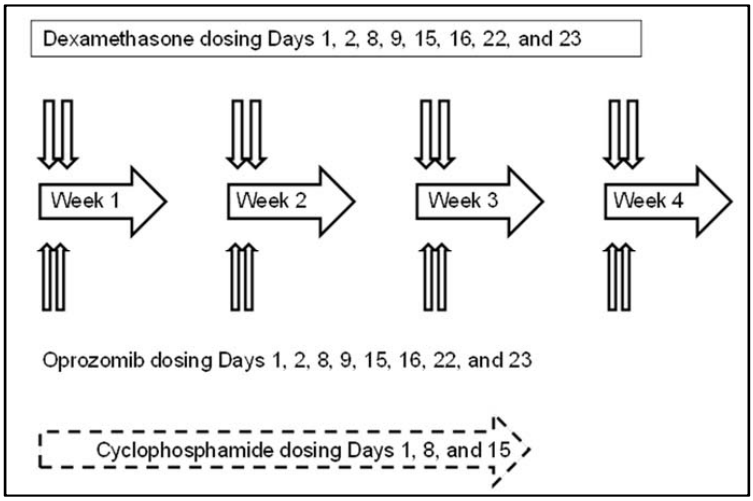


The ORd combination will be administered until progression of disease, unacceptable toxicity, or for 24 cycles (approximately 24 months), whichever occurs first. Subjects who complete 24 cycles of treatment, and have stable disease or better, will continue on oprozomib, with or without dexamethasone premedication (4 mg/day) until progression of disease or unacceptable toxicity. Lenalidomide will be administered for a maximum of 24 cycles. Dexamethasone will be administered at a dose of 20 mg/day, as described above, through the first cycle, after which the dose may be decreased to 10 mg/day in subjects > 75 years of age, at the discretion of the investigator.

The OCyd regimen treatment cycles are 28 days in duration. One (1) oprozomib dosing schedule (2/7) will be assessed during dose escalation. All study subjects will receive oprozomib administered orally, once daily on 2 consecutive days every 7 days; specifically on Days 1, 2, 8, 9, 15, 16, 22, and 23 (referred to as the 2/7 schedule) in combination with oral cyclophosphamide at a dose of 300 mg/m^2 on Days 1, 8, and 15, and dexamethasone at a dose of 20 mg on Days 1, 2, 8, 9, 15, 16, 22, and 23 of 28-day cycles (see dose administration schema below). Dexamethasone will be administered at a dose of 20 mg/day, as described above, through the first cycle, after which the dose may be decreased to 10 mg/day in subjects > 75 years of age, at the discretion of the investigator.

Study design (cont'd):

Dose Administration Schema for Oprozomib, Cyclophosphamide, and Dexamethasone (OCyd) 2/7 Schedule (Amendment 2)



The OCyd combination will be administered until progression of disease, unacceptable toxicity, or for 8 cycles (approximately 8 months), whichever occurs first. Subjects who complete 8 cycles of treatment and who have stable disease or better will continue on oprozomib, with dexamethasone premedication. Dexamethasone dosing, premedication and low-dose (e.g., 20 mg or 10 mg), should continue for a total of 24 cycles or until progression of disease or unacceptable toxicity. Subjects who complete 24 cycles of oprozomib therapy (total) without evidence of progression may continue therapy with or without dexamethasone, premedication or low-dose. A taper of dexamethasone after 24 cycles may be utilized per institutional guidelines. Cyclophosphamide will be administered for a maximum of 8 cycles.

Note: Subjects receiving either treatment regimen, who complete at least 4 cycles of study treatment and achieve a confirmed response (i.e., partial response [PR], very good partial response [VGPR], complete response [CR], or stringent complete response [sCR]) may, after discussion with the Onyx study medical monitor, suspend study treatment for up to 6 weeks to undergo a hematopoietic stem cell harvest. Stem cell mobilization will be conducted using a noncytotoxic regimen such as granulocyte colony-stimulating factor (G-CSF). These subjects may then resume study treatment until progression of disease, unacceptable toxicity, or for a total of 24 cycles of treatment with lenalidomide or a total of 8 cycles of treatment with cyclophosphamide, followed by oprozomib treatment with low-dose dexamethasone (20 mg or 10 mg) for subjects free from progression, as described above.

Phase 1b: The Phase 1b portion of the study will identify any dose-limiting toxicities (DLTs) and determine the MTD, evaluate the safety and tolerability, and assess PK/PDn of oprozomib when administered as described above in subjects with newly diagnosed symptomatic multiple myeloma (see the Study Population section below for details).

A standard 3 + 3 dose-escalation scheme will be used. For each combination regimen, oprozomib doses will be escalated in sequential cohorts of 3 subjects with expansion to up to 6 subjects if a DLT is observed in 1 of the first 3 subjects. The doses of lenalidomide, cyclophosphamide, and dexamethasone will remain fixed in all dose cohorts.

Study design (cont'd):

The initial cohort dose levels for each combination regimen is as follows:

- Original Protocol and Amendment 1 - ORd (5/14 schedule): 210 mg/day of oprozomib (current 5/14 cohort dose level is 150 mg/day of oprozomib)

  There have been 2 dose de-escalations in the ORd 5/14 arm in response to dose limiting toxicities (DLTs) occurring at the 210 mg and the 180 mg cohort level.
- Amendment 2 - ORd (2/7 schedule): 210 mg/day of oprozomib
- Amendment 2 - OCyd (2/7 schedule): 210 mg/day of oprozomib

The dose of oprozomib for cohorts will be escalated or de-escalated in 30 mg increments until the MTD is established. Subjects on the 5/14 schedule will not have their oprozomib dose escalated above 150 mg/day.

There will not be a predefined maximum dose to be studied. Subjects will be evaluated for DLTs according to the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03.

In the event that the ORd cohort at the 210 mg dose (2/7 schedule) is found to exceed the MTD, dosing will proceed at 180 mg or a lower dose as agreed to by the Cohort Safety Review Committee (CSRC), comprised of the Onyx study medical monitor, Onyx safety representative, and the active investigators.

In the event that the initial OCyd cohorts at the 210 mg dose (2/7 schedule) are found to exceed the MTD, dosing will proceed at 180 mg or a lower dose as agreed to by the CSRC. Intrasubject dose escalation to the MTD or recommended Phase 2 dose (RP2D) may be permitted once that dose has been determined and after a discussion has occurred between the treating physician and Onyx study medical monitor.

Maximum Tolerated Dose

For each dosing schedule, the MTD will be defined as the highest dose at which a DLT is observed in fewer than 2 of 6 patients. At least 6 patients must be treated at the MTD for a minimum of 1 cycle to establish this dose as tolerated.

Dose-Limiting Toxicities: During the Phase 1b portion, assessment of DLTs will occur during the first cycle of combination therapy (first 4 weeks).

For the purposes of this study, a DLT is defined as any of the following treatment-related events occurring in the first 28 days of treatment:

Nonhematologic DLT:

- Any ≥ Grade 3 nonhematologic toxicity with the following exceptions or qualifications:
  - ≥ Grade 3 nausea, vomiting, diarrhea, or constipation will be considered a DLT only if lasting for > 7 days, despite optimal supportive care, including (at a minimum) a 5-hydroxytryptamine type-3 (5-HT3) antagonist and aprepitant for nausea/vomiting and (e.g. Imodium) and diphenoxylate/atropine (e.g., Lomotil) for diarrhea
  - Asymptomatic Grade 3 hypophosphatemia is not considered a DLT
  - ≥ Grade 3 hyperglycemia or toxicity solely due to dexamethasone is not considered a DLT (see dose reduction guidelines for dexamethasone in Section 9.3.2)
  - Grade 3 fatigue lasting < 14 days is not considered a DLT
  - ≥ Grade 3 rash attributed specifically to lenalidomide is not a DLT

Study design (cont'd):

Hematologic DLT:

- Grade 4 neutropenia: Absolute neutrophil count (ANC) < 0.5 × 109/L lasting ≥ 7 days, despite myeloid growth factor support
- Febrile neutropenia: Any single temperature ≥ 38.3°C or a sustained temperature of ≥ 38.0°C for over 1 hour with ≥ Grade 3 neutropenia (ANC < 1.0 × 10^9/L)
- Grade 4 thrombocytopenia lasting ≥ 7 days or
- Grade 4 thrombocytopenia lasting < 7 days with ≥ Grade 2 clinically significant bleeding or < 10,000 platelets requiring platelet transfusion, or
- Grade ≥ 3 thrombocytopenia with clinically significant bleeding or requiring platelet transfusion.

Note: Grade 4 anemia will ***not*** be considered a DLT, but should be treated with supportive measures in accordance with institutional guidelines.

Subject Replacement

Phase 1b: In the Phase 1b portion of the study, subjects must meet the following criteria to be considered evaluable for MTD determination during the 4-week DLT evaluation period:

- A minimum of 8 of 10 planned doses of oprozomib must be received for the 5/14 dosing schedule
- A minimum of 7 of 8 planned doses of oprozomib must be received for the 2/7 dosing schedule
- A minimum of 6 of 8 planned doses of dexamethasone must be received
- All 3 planned doses of cyclophosphamide must be received (OCyd combination regimen only)
- A minimum of 17 of 21 planned doses of lenalidomide must be received (ORd combination regimen only)
- Subjects not meeting all of the above criteria or assessed as unevaluable will be replaced. Subjects who do not meet the criteria above because of a DLT will be considered DLT-evaluable.

Subjects who discontinue study treatment for any reason after Cycle 1 will not be replaced.

Phase 2: The Phase 2 portion of the study will include up to 35 additional subjects in each of the 2 combination regimens, with the same eligibility criteria as those in Phase 1b. Phase 2 subjects will be treated at the RP2D of oprozomib identified during the Phase 1b portion of the study in order to better characterize the safety and tolerability, antimyeloma activity, and PK. The RP2D determined by the CSRC may or may not be the same as the MTD, and will be assessed on the basis of the totality of safety and PK/PDn data. Subjects enrolled under Amendment 2 will receive Oprozomib Extended Release (ER) Tablets.

Pharmacokinetics: A sparse sampling strategy will be employed for PK sample collection from all subjects for both phases of the study. Blood samples for determination of plasma concentrations of oprozomib and metabolite(s) will be collected for subjects in both phases of the study at time points and blood volumes detailed in the Laboratory Manual. Population-based PK analyses will be performed for oprozomib and, may include its metabolite(s).

Pharmacodynamics: Blood samples for the determination of proteasome inhibition by oprozomib will be drawn from all subjects in Phase 1b at the time points specified in the Laboratory Manual.

Study design (cont'd):	**Genomics:** Analysis of genetic, gene expression, and cell surface biomarkers that may predict response and resistance following treatment with proteasome inhibitors will be conducted on all subjects from both phases of the study who consent to optional genomic biomarker analysis. These analyses will be performed on a bone marrow aspirate collected at Baseline, prior to dosing on Cycle 1 Day 1 (C1D1), and a sample of blood and/or saliva will be collected at Baseline, prior to dosing on C1D1. The bone marrow aspirate used for Genomics is the remaining portion of bone marrow sample left after the amount required for fluorescent in situ hybridization (FISH) is performed. No additional bone marrow sample is required at Baseline. Additional bone marrow samples for biomarkers may be collected at the End of Study Treatment visit from all subjects who consent. End of Study Treatment is defined as at disease progression or at the end of protocol-defined therapy if end of treatment is due to progressive disease (PD). **Activity:** The International Myeloma Working Group-Uniform Response Criteria (IMWG-URC) will be used to evaluate response. Disease response assessments will be performed at the end of every 4-week cycle for 24 cycles of ORd or OCyd treatment, and will continue every 8 weeks thereafter, until confirmed PD (see study schema and dose administration schemas for details on the duration of cyclophosphamide dosing). Overall response rate and CRR will be determined based on subjects' best overall response. **Safety:** Safety assessments will include monitoring and assessment of all AEs, selected laboratory analytes, electrocardiograms (ECGs), and vital signs. Safety assessments will begin after the subject has signed the informed consent form and will continue until 30 days after the last administration of all study drugs. All subjects will be closely monitored for both expected and unexpected AEs. The safety and tolerability of oprozomib will be assessed through documentation of AEs graded according to NCI-CTCAE (Version 4.03).
Study population:	The study population will consist of patients with newly diagnosed, symptomatic multiple myeloma for whom a hematopoietic stem cell transplant is not planned or scheduled during the study or are considered ineligible for hematopoietic stem cell transplant at the discretion of the investigator, and who are considered to be appropriate for this clinical study by their treating physicians.
Number of investigational sites:	Approximately 20 sites in the United States (US) will participate in this study.
Planned number of subjects:	Total enrollment of up to approximately 134 evaluable subjects is planned for this study, including up to approximately 64 evaluable subjects for the Phase 1b portion of the study (40 and 24 for ORd and OCyd, respectively) and approximately 70 subjects for the Phase 2 portion of the study (35 subjects for each combination regimen).
Sample size justification:	The estimated sample size for the dose-escalation portion of the study of up to 40 subjects for the ORd combination regimen and up to 24 subjects for the OCyd combination regimen is based upon standard 3 + 3 dose-escalation rules and the expectation that 2–6 dosing cohorts of 3–6 subjects per cohort will be required to establish the MTD for each treatment regimen. Enrollment of 35 additional subjects in each combination regimen during the Phase 2 portion of the study is based upon the goal of ruling out an ORR < 85% and a CRR < 50% based upon the approximate lower 1-sided 90% confidence interval for each parameter. This sample size is based upon a simulation of a multinomial outcome of CR, PR, or PD for various cohort sizes. With 35 subjects per combination regimen, and an assumed true ORR and true CRR of 95% and 75%, respectively, the probability of ruling out an ORR < 85% and a CRR < 50% with 90% confidence is approximately 88%, from the simulation described above. The same assumptions for ORR and CRR are used in determining the sample size for each combination regimen.

Duration of study/ treatment periods:	The total study duration is expected to be approximately 59 months based upon the assumption that approximately 35 months may be required to enroll all subjects (approximately 23 months to enroll Phase 1b subjects and up to approximately 12 months to enroll Phase 2 subjects) and that the average time on study will be approximately 24 months. Following completion of 24 cycles of ORd or OCyd treatment, disease response assessments will continue every 8 weeks until confirmed PD. For subjects who discontinue treatment before PD occurs (such as for an AE, noncompliance, etc.), disease response assessments will be performed every 4 weeks during the first 24 months of the study and every 8 weeks thereafter, until confirmed PD, or the start of alternative, nonprotocol antimyeloma therapy. Subjects must complete an End of Study Treatment visit approximately 4 weeks after the last study treatment for safety follow-up.
Test product, dose, and mode of administration:	Oprozomib Tablets containing 60, 90, or 120 mg of oprozomib or Oprozomib ER Tablets with strengths of 120, 150, 180, 210, 240, and 270 mg to be given orally (PO) Lenalidomide 25 mg to be given PO Cyclophosphamide 300 mg/m^2 (up to 600 mg) to be given PO Dexamethasone 20 mg to be given PO **New Oprozomib Formulation**: A new oprozomib tablet, the Oprozomib ER Tablet, will be introduced in the trial with Amendment 2. There are minimal changes in the tablet coating and ratio of current excipients, and no change in the ratio of active pharmaceutical ingredient to excipients. Given these minimal changes, the new Oprozomib ER Tablet is not expected to result in altered exposure or additional adverse events related to formulation. Subjects enrolled in the original protocol or Amendment 1 will receive Oprozomib Tablets and may receive Oprozomib ER Tablets when available. Subjects enrolled under Amendment 2 will receive Oprozomib ER Tablets only.
Reference therapy	Not applicable.
Treatment regimen(s):	Oprozomib will be administered in a 28-day cycle at the assigned dose in combination with dexamethasone and either lenalidomide (ORd) or cyclophosphamide (OCyd): • Oprozomib administered on Days 1 through 5 and Days 15 through 19 (5/14 schedule) or on Days 1, 2, 8, 9, 15, 16, 22, and 23 (2/7 schedule) • Lenalidomide administered on Days 1 through 21, for those subjects receiving the ORd combination regimen (5/14 and 2/7 schedules) • Cyclophosphamide administered on Days 1, 8, and 15, for those subjects receiving the OCyd combination regimen (2/7 schedule only) • Dexamethasone administered on Days 1, 2, 8, 9, 15, 16, 22, and 23, for all subjects in the study (5/14 and 2/7 schedules) Oprozomib doses may be reduced in 30-mg decrements for up to 2 dose reductions for toxicities per the discretion of the investigator. Interruption of oprozomib dosing for > 4 weeks for any reason will result in permanent discontinuation of oprozomib. No dose reductions of oprozomib are allowed in Cycle 1. Subjects who permanently discontinue lenalidomide or cyclophosphamide for reasons other than disease progression may continue treatment with oprozomib and dexamethasone, until disease progression as described above. After 24 months, the dose of dexamethasone may be decreased to premedication doses (4 mg) with allowances for a taper as clinically indicated.

Treatment regimen(s) (cont'd):	Subjects receiving the ORd treatment regimen who permanently discontinue oprozomib for reasons other than disease progression following the completion of Cycle 1, may continue treatment with lenalidomide and dexamethasone until disease progression or for a maximum of 24 cycles, whichever occurs first. Subjects who discontinue both lenalidomide and oprozomib may not continue treatment with dexamethasone alone. Subjects receiving the OCyd treatment regimen who permanently discontinue oprozomib for reasons other than disease progression following the completion of Cycle 1, may continue treatment with cyclophosphamide and dexamethasone until disease progression or for a maximum of 8 cycles, whichever occurs first. Subjects who discontinue both cyclophosphamide and oprozomib may not continue treatment with dexamethasone alone.
Inclusion criteria:	**Main inclusion criteria** 1. Newly diagnosed multiple myeloma patients for whom treatment is indicated per the National Comprehensive Cancer Network (NCCN) guidelines, and for whom a hematopoietic stem cell transplant is not planned or scheduled during the study or are considered ineligible for hematopoietic stem cell transplant, with measurable disease as indicated by 1 or more of the following: a. Serum M-protein ≥ 500 mg/dL b. Urine M-protein ≥ 200 mg/24 hour c. Serum free light chain (SFLC): Involved SFLC level ≥ 10 mg/dL provided SFLC ratio is abnormal 2. Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0–2 3. Males and females ≥ 18 years of age 4. Adequate hepatic function, with bilirubin ≤ 1.5 times the upper limit of normal (ULN), aspartate aminotransferase (AST) ≤ 3 times ULN, and alanine aminotransferase (ALT) ≤ 3 times ULN (Note: Patients with documented Gilbert Syndrome may be enrolled with an elevated unconjugated bilirubin after discussion with the Onyx study medical monitor) 5. Absolute neutrophil count ≥ 1.0×10^9/L, hemoglobin ≥ 7.0 g/dL, and platelet count ≥ 75×10^9/L a. Patients must not have received platelet transfusions for at least 1 week prior to Screening b. Screening ANC must be independent of G-CSF or granulocyte/ macrophage-colony stimulating factor (GM-CSF) support for *at least* 1 week and pegylated G-CSF support for ≥ 2 weeks c. Patients may receive red blood cell transfusions or supportive care with erythropoietin or darbepoetin in accordance with institutional guidelines 6. Creatinine clearance rate of ≥ 50 mL/min, either measured or calculated using the formula of Cockcroft and Gault [(140 – age) × mass (kg) / (72 × serum creatinine mg/dL)]. Multiply result by 0.85 if female. 7. Patients must sign a written informed consent form in accordance with federal, local, and institutional guidelines 8. For both treatment regimens (ORd and OCyd): Females of childbearing potential (FCBP) must agree to ongoing pregnancy testing and to practice contraception as outlined in the Revlimid Risk Evaluation and Mitigation Strategy (REMS) Guide. Two effective contraceptive methods must be used by FCBP for at least 4 weeks prior to start of lenalidomide or cyclophosphamide therapy, during therapy, and during dose interruptions, and for 3 months following the discontinuation of oprozomib. Postmenopausal females (> 45 years old and without menses for > 24 consecutive months) and surgically sterilized females are exempt from these requirements.

Inclusion criteria (cont'd):	9. For both treatment regimens (ORd and OCyd): Male subjects must agree to practice contraception as outlined in the Revlimid REMS Guide. Male subjects receiving lenalidomide or cyclophosphamide must use an effective method of contraception during any sexual contact with FCBP during the study, even if the subject has undergone a successful vasectomy, and for 3 months following the discontinuation of oprozomib.
Exclusion criteria:	**Main exclusion criteria** 1. Radiation therapy within 2 weeks prior to first dose 2. Any prior systemic antimyeloma therapy except oral steroids (dexamethasone up to a total dose of 160 mg or equivalent within 14 days prior to the first dose of study treatment). Use of topical or inhaled steroids is acceptable. 3. Participation in an investigational therapeutic study within 3 weeks prior to first dose 4. Plasmapheresis is not permitted at any time during the Screening period or while the subject is receiving study treatment. If a subject that has started Screening procedures requires plasmapheresis, or is anticipated to require plasmapheresis during or after the Screening period, this patient will be considered ineligible and should not be enrolled. 5. Major surgery within 3 weeks prior to first dose 6. Clinically significant gastrointestinal (GI) bleed in the 6 months prior to C1D1 first dose 7. 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 8. A history of deep vein thrombosis or pulmonary embolism, with contraindication to anticoagulation and antiplatelet options 9. Active infection requiring systemic antibiotics, antivirals, or antifungals within 2 weeks prior to first dose 10. Known or suspected human immunodeficiency virus (HIV) infection or subjects who are HIV seropositive 11. Active hepatitis A, B, or C infection 12. Significant neuropathy (Grade 3, Grade 4, or Grade 2 with pain) at the time of first dose 13. Other malignancy within the past 3 years except those considered cured by surgical resection including some cases of: • Adequately treated basal or squamous cell carcinoma of the skin • Thyroid cancer • Carcinoma in situ of the cervix or breast • Prostate cancer with Gleason Score of 6 or less with stable prostate-specific antigen levels 14. Plasma cell leukemia 15. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) 16. Known amyloidosis 17. Uncontrolled diabetes or hypertension 18. Female subjects who are pregnant or nursing 19. Any clinically significant psychiatric or medical condition that, in the opinion of the investigator, could increase patient risk, interfere with protocol adherence, or a subject's ability to give informed consent

Overview of treatment and assessments:	Treatments will be given in 28-day cycles. Details are provided in the Schedule of Assessments.
Criteria for evaluation:	
Efficacy variables:	Disease response assessments will be performed at the end of every 4-week cycle for 24 cycles of ORd or OCyd treatment, and will continue every 8 weeks thereafter, until confirmed PD (see study schema and dose administration schemas for details on the duration of cyclophosphamide dosing).
Safety variables:	The safety and tolerability of oprozomib will be assessed using the following measures: AEs graded according to the NCI-CTCAE (Version 4.03), blood counts, serum chemistries, vital signs, and ECGs.
Other:	**Pharmacokinetics:** Blood samples will be drawn for plasma concentration of oprozomib and its metabolite(s) at various time points during the study. Population PK parameter estimates and variability in these estimates for oprozomib (and possibly its metabolite [s]) will be determined using a sparse sampling strategy and population-based analysis methodology. **Pharmacodynamics:** Blood samples will be drawn for assessments of proteasome inhibition in whole blood and peripheral blood mononuclear cells (PBMCs) via a fluorogenic substrate assay or enzyme–linked immunosorbent assay. **Genomics:** Whole genome sequencing (WGS), whole exome sequencing (WES), whole transcriptome sequencing (RNA-Seq), and/or other forms of nucleic acid and protein quantification will be conducted on isolated tumor ($CD138^{+}$) cells from bone marrow samples taken at Baseline, prior to dosing on C1D1, and at disease progression. In addition, WGS or WES will be performed on a normal tissue sample (e.g., saliva or $CD3^{+}$ T-cells isolated from PBMCs) to distinguish germline mutations from somatic mutations in tumor cell samples. Data will be analyzed to characterize whether drug response is related to alterations in genes regulated by or involved in immunoglobulin production and protein homeostasis, i.e., IGH, as well as in genes regulated by or involved in the activation of nuclear factor kappa light chain enhancer of activated B cell (NF-Kappa B) transcription factors. Immunoglobulin levels in tumor cells will be quantified by qPCR, or immunocytochemistry and/or other protein or gene expression quantification methods. These data will also be used to derive hypotheses about mechanisms of drug response, resistance, and safety.

Statistical methods and analyses:	Phase 1b: The Safety population includes all subjects receiving treatment with any amount of the treatment regimen (oprozomib and dexamethasone with either lenalidomide or cyclophosphamide) under study. Phase 2: Safety and efficacy analyses will be performed using the Safety population. Additional efficacy analyses will be performed using the Response Evaluable population, defined as subjects who are included in the Safety population, and have a baseline disease assessment and at least 1 postbaseline disease assessment, or dropped out due to AE or other reasons prior to first post-baseline disease assessment. The safety endpoints for both combination regimens (ORd and OCyd) in the Phase 1b and Phase 2 portions of the study are the incidence, nature, and severity of AEs, serious adverse events (SAEs), and DLTs (Phase 1b only) of oprozomib, given in combination with dexamethasone, and either lenalidomide or cyclophosphamide, as well as changes from baseline in selected laboratory analytes, vital signs, and ECG findings. For both combination regimens (ORd and OCyd), the primary efficacy endpoints for the Phase 2 portion of the study are overall response and CR for subjects treated at the recommended Phase 2 dose. Response evaluation will be carried out according to the International Myeloma Working Group - Uniform Response Criteria (IMWG-URC). • Overall response: defined as a best overall response of sCR, CR, VGPR, or PR • Complete response: defined as a best overall response of sCR or CR Point estimates for the ORR and CRR along with the approximate lower 1-sided 90% confidence intervals will be calculated. The distributions of time-to-event endpoints (DOR and PFS) will be summarized descriptively using the Kaplan-Meier method. Safety and tolerability will be assessed through summaries of study drug administration, DLTs (Phase 1b only), AEs, changes in laboratory analytes, ECGs, and vital signs by dose cohort, the combined MTD dose levels, and for all subjects. All AE data will be listed by study site, treatment regimen, dose cohort, subject number, and study day. All AEs occurring on or after treatment on C1D1 will be summarized by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), and NCI-CTCAE (Version 4.03) toxicity grade. In addition, all SAEs, including deaths, will be listed separately and summarized. Extent of exposure to the study treatment will be summarized using descriptive statistics.

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1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-HT_3	5-hydroxytryptamine type-3
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
AUC	area under the curve
BP	blood pressure
C1D1	Cycle 1 Day 1
C1D2	Cycle 1 Day 2
C1D5	Cycle 1 Day 5
C1D8	Cycle 1 Day 8
C4D1	Cycle 4 Day 1
CBC	complete blood count
CBR	clinical benefit rate
CR	complete response
CrCl	creatinine clearance
CRd	carfilzomib, Revlimid (lenalidomide), and dexamethasone
CRR	complete response rate
CSRC	Cohort Safety Review Committee
Cyd	cyclophosphamide and dexamethasone
CYP3A	cytochrome P450 3A
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme linked immunosorbent assay
ER	Extended Release
FCBP	female(s) of childbearing potential
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization

Abbreviation	Definition
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GLP	Good Laboratory Practice
GM-CSF	granulocyte macrophage-colony stimulating factor
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
IB	investigator's brochure
IC_{50}	50% inhibition concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGH	immunoglobulin heavy locus
IMWG	International Myeloma Working Group
IMWG-URC	International Myeloma Working Group - Uniform Response Criteria
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous(ly)
ISS	International Staging System
LDH	lactate dehydrogenase
LFT	liver function test
MAD	maximum administered dose
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MR	minimal response
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
nCR	near complete response
NF-Kappa B	nuclear factor kappa light chain enhancer of activated B cells
NHL	non-Hodgkin lymphoma
NSCLC	non-small-cell lung cancer
OCyd	oprozomib, cyclophosphamide, dexamethasone
OPZ	oprozomib
ORd	oprozomib, lenalidomide, dexamethasone
ORR	overall response rate

Abbreviation	Definition
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PDn	pharmacodynamics
PFA-100	platelet function analyzer
PFS	progression-free survival
PIC	Powder in capsule
PK	pharmacokinetic(s)
PO	oral(ly)
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes
PR	partial response
qPCR	quantitative polymerase chain reaction
QTc	corrected QT interval
RBC	red blood cell
Rd	lenalidomide and dexamethasone
REMS	Risk Evaluation and Mitigation Strategy
RNA-Seq	whole transcriptome sequencing
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAH	subachnoid hemorrhage
sCR	stringent complete response
SD	stable disease
SFLC	serum free light chain
SPEP	serum protein electrophoresis
STD_{10}	severely toxic dose to 10% of test animals
TLS	tumor lysis syndrome
ULN	upper limit of normal
UPEP	urine protein electrophoresis.
US	United States
VGPR	very good partial response
WBC	white blood cell
WES	whole exome sequencing
WGS	whole genome sequencing
WM	Waldenström macroglobulinemia

2 BACKGROUND INFORMATION

2.1 INTRODUCTION

This is a Phase 1b/2 clinical trial of the oral proteasome inhibitor, oprozomib in combination with dexamethasone and lenalidomide or oral cyclophosphamide, in subjects with newly diagnosed multiple myeloma. See Section 4 for a complete description of the study design.

The protocol has been amended twice with changes to the study design based on emerging safety data from other oprozomib studies. A summary of changes for each amendment is included in the appendix of each version of the protocol. The primary purposes for each amendment are summarized below.

Amendment 1

Study Design

1. The OCyd treatment regimen was added to the protocol to assess the safety and activity of the combination. No formal comparisons between the OCyd and ORd arms are planned. Resultant data will inform future trial designs.

Dose-Modification Guidelines/Safety Guidance for the Investigator

2. Updated tables of dose-modification guidelines for hematologic and nonhematologic toxicities to include guidance for cyclophosphamide related toxicities.
3. Added text to provide specific guidance for the treatment of tumor lysis syndrome.
4. Added text to provide specific guidance for antinausea and antiemetics, and antidiarrheals.

Amendment 2

Study Design

1. The current dose of oprozomib on the 5/14 schedule is 150 mg. The study was initiated at 210 mg and the dose was reduced to 150 mg after DLTs were reported in the 210 and 180 mg cohorts. The protocol has been updated throughout to reflect these events. The 150 mg dose is 3 full dose levels below the single-agent maximum tolerated dose (MTD).
2. The dosing schedule was changed from 5/14 to 2/7 for subsequent cohorts in the ORd arm and for all subjects in the OCyd arm to provide an increased margin of safety for subjects participating in this study. The initial dose of oprozomib for the OCyd and ORd arms on the 2/7 schedule is 210 mg. It is 3 full dose levels below the single agent MTD on the 2/7 schedule.

3. Introduced the new Oprozomib Extended Release (ER) Tablet and the strengths to be used in this study.

Exclusion Criteria

4. Added language excluding patients undergoing or expected to require plasmapheresis during the screening process or any time during the study.
5. Added exclusion criterion for patients with prior clinically significant bleed in the 6 months prior to first dose of study treatment.

Dose Modification Guidelines/Safety Guidance for the Investigator

6. Additional safety guidance regarding Grade 3 or 4 GI hemorrhage.
7. Added guidance for subjects receiving antihypertensive therapy about the risk for hypotension.

Laboratory Evaluations for Safety

8. Platelet function assessment to understand impact of oprozomib, if any, on platelet adherence, activation, aggregation and interaction with clotting factors.

2.2 MULTIPLE MYELOMA

Multiple myeloma, a clonal neoplastic proliferation of plasma cells, is the second most common hematologic malignancy and is responsible for approximately 72,000 annual deaths worldwide (Ferlay 2010). There are an estimated 11,000 deaths per year in the United States (US) and more than 19,000 deaths per year in Europe (American Cancer Society 2005; Boyle 2005). Multiple myeloma is characterized by anemia, bone destruction, monoclonal gammopathy, renal failure, hypercalcemia, and increased susceptibility to infections.
The disease is systemic, and chemotherapy is indicated for management of symptomatic myeloma. Current treatment options for multiple myeloma commonly include combination regimens using alkylators such as melphalan (Alkeran) or cyclophosphamide (Cytoxan), bortezomib (Velcade), carfilzomib (Kyprolis), an immunomodulatory agent including thalidomide (Thalomid), lenalidomide (Revlimid), or pomalidomide (Pomalyst), with and without corticosteroids such as dexamethasone or prednisone, and other agents. Eligible subjects 65 to 70 years old or younger frequently undergo consolidation therapy with myeloablative chemotherapy, or radiation followed by autologous stem cell transplantation. Although improvements in progression-free survival (PFS) and overall survival (OS) have occurred in the past 5 years, even with the best available approved agents, essentially all patients eventually relapse. Median OS from diagnosis was reported at 3 years for high-risk

subjects, 4 to 5 years for intermediate-risk subjects, and 8 to 20 years for standard-risk subjects (Mikhael 2013).

2.3 PROTEASOME BACKGROUND

The proteasome is a multicatalytic proteinase complex that is responsible for degradation of a wide variety of protein substrates within normal and transformed cells. Intracellular proteins targeted for degradation by the proteasome are first ubiquitinated via the ubiquitin conjugation system. Ubiquitinated proteins are cleaved within the proteasome by 1 or more of 3 separate N-terminal threonine protease activities: a chymotrypsin-like activity, a trypsin-like activity, and a caspase-like activity.

2.4 OPROZOMIB

2.4.1 PRECLINICAL BACKGROUND

Oprozomib is a tripeptide epoxyketone-based inhibitor of the 20S proteasome that primarily targets the chymotrypsin-like activity. Oprozomib (formerly ONX 0912) is a structural analogue of carfilzomib (Kyprolis), an intravenously administered tetrapeptide epoxyketone that received accelerated approval in the US for the treatment of patients with multiple myeloma who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy (Kyprolis Prescribing Information [Onyx Pharmaceuticals 2012]). Like carfilzomib, oprozomib is an irreversible and highly selective proteasome inhibitor that binds most potently to the chymotrypsin-like subunit of the proteasome (50% inhibition concentration [IC_{50}] 50–80 nM) (Zhou 2009). In addition, when measured against a broad panel of proteins containing metallo-, aspartyl-, and serine-proteases, oprozomib demonstrated minimal reactivity against these nonproteasomal proteases.

Exposure to oprozomib is associated with potent pro-apoptotic activity across a broad panel of tumor-derived cell lines in culture. The antitumor efficacy of oprozomib has been tested in a variety of mouse xenograft models, including those for both solid (colorectal adenocarcinoma, non-small cell lung cancer [NSCLC]) and hematologic (multiple myeloma, non-Hodgkin lymphoma [NHL]) tumors. Oprozomib has shown an equivalent antitumor

activity to carfilzomib in preclinical models where both compounds have been tested (Zhou 2009).

In Good Laboratory Practice (GLP)-compliant toxicity studies, oprozomib was administered orally for 2 complete cycles of daily dosing for 5 days with 9 days rest to rats at doses of 120, 180, and 240 mg/m^2 (20, 30, and 40 mg/kg, respectively). Administration at 180 mg/m^2 (30 mg/kg) resulted in mortality in 1 of 26 animals during the first cycle of dosing. Surviving animals received a second cycle of oprozomib administration without additional severe toxicities, and this dose was determined to be the severely toxic dose to 10% of test animals (STD_{10}). Proteasome inhibition was > 90%, as measured in whole blood 1 hour after the first dose. Mortality of > 10% was noted at the next highest dose level (240 mg/m^2) also in the first cycle of dosing. In this study, mortality was restricted to females, where exposure (as determined by pharmacokinetics [PK]) was 3-fold to 5-fold higher than in males on the first day of dosing. The apparent cause of death could not be determined, but histologic analysis of the surviving animals showed mucosal hyperplasia in the small intestines.

Oprozomib was administered orally to dogs at 60, 120, and 200 mg/m^2 (3, 6, and 10 mg/kg, respectively) using the same schedule of administration. A dose of 120 mg/m^2 (6 mg/kg) was determined to be the highest non-severely toxic dose (HNSTD). Mortality or early sacrifice was noted in 3 of 14 animals at the highest dose (200 mg/m^2). Clinical observations in these animals preceding death included emesis, decreased activity, lethargy, high body temperatures, cold to touch, weight loss, decreased food consumption, and brown/pink nasal discharge and, in 1 of the animals, irregular gait. The apparent cause of death for these animals was attributed to mucosal hemorrhage and atrophy of the small and large intestines, which was associated with frequent watery diarrhea and occasionally the presence of blood in the stool.

In both rats and dogs, all doses of oprozomib resulted in > 80% inhibition of proteasome activity in whole blood as measured 1 hour after the first dose. In both rats and dogs, exposure as measured by area under the curve (AUC), showed a greater than dose proportional increase when the dose was increased above the STD_{10}/HNSTD.

In a cardiovascular safety pharmacology study conducted in male and female dogs, a single dose of oprozomib at 120 mg/m^2 was not associated with cardiovascular toxicity. Hypotension, beginning approximately 4 hours after dose administration was noted in all animals at 200 and 400 mg/m^2, and was dose-dependent in severity. In all but 1 animal, this was accompanied by an increase in heart rate. There were no observed corrected QT intervals (QTc) prolongations in any animals.

Further information about the preclinical pharmacology and toxicology of oprozomib is presented in the Oprozomib Investigator's Brochure (IB).

2.4.2 OPROZOMIB - CLINICAL BACKGROUND

2.4.2.1 Study 2009-003: A Phase 1, Open-label, Dose Escalation Study of ONX 0912 Administered Orally in Patients with Advanced Refractory or Recurrent Solid Tumors

Efficacy

In Study 2009-003, oprozomib, dosed as powder in capsule, was studied in solid tumor subjects. The Phase 1 study in refractory solid tumors (n = 44), no subject achieved an objective response. Stable disease (SD) was observed in 6 subjects (30%) in the once daily dosing group and 4 subjects (23.5%) in the split daily dosing group.

Safety

The majority of AEs were Grade 1 and 2, manageable, and there were no apparent cumulative toxicities. The most common AEs were in the gastrointestinal (GI) system organ class. This was consistent with preclinical animal studies with oprozomib. Dose-limiting toxicities (DLTs) for the once daily dose group in Study 2009-003 included Grade 3 dehydration/vomiting and Grade 3 hypophosphatemia in the 180 mg cohort. The MTD for the once daily x 5 days dose group is 150 mg. Dose-limiting toxicities for the split daily x 5 days dosing group in Study 2009-003 included Grade 3 hypophosphatemia at 180 mg and Grade 5 GI bleed and Grade 3 hallucinations at 210 mg. The MTD for the split daily dosing group is 180 mg.

2.4.2.2 Study 2011-001: Phase 1b/2, Multicenter, Open-label Study of the Safety and Activity of ONX 0912 in Patients with Hematological Malignancies

Efficacy

As of 21 January 2014, the Phase 1b portion of Study 2011-001 has completed enrollment; 61 response-evaluable subjects with hematologic malignancies have received Oprozomib in Capsules in split dosing, or Oprozomib Tablets with daily dosing, on a 5 consecutive day bimonthly (5/14) schedule or a 2 consecutive day weekly (2/7) schedule in Phase 1. Response rates for subjects with multiple myeloma (n = 43) and subjects with Waldenström macroglobulinemia ([WM]; n =18) by schedule and formulation are summarized in Table 1 and Table 2, respectively.

Table 1 Phase 1 Response Rates for Subjects with Multiple Myeloma, by Schedule and Formulation

Formulation/Schedule (n)	Dose Range (mg)	ORR	Clinical Benefit Rate
PIC 5/14 (10)	120–210	40%	50%
Tablets 5/14 (18)	150–270	27.8%	38.9%
Tablets 2/7 (15)	150–330	20.0%	46.7%

ORR = overall response rate; PIC = powder in capsule.

Table 2 Phase 1 Response Rates for Subjects with Waldenström macroglobulinemia, by Schedule and Formulation

Formulation/Schedule (n)	Dose Range (mg)	ORR[a]	Major Response[b]
Tablets 5/14 (11)	150–270	63.6%	54.5%
Tablets 2/7 (7)	150–330	42.9%	14.3%

MR = minimal response; ORR = overall response rate; PR = partial response.
[a] ORR is defined as ≥ MR.
[b] Major response is defined as ≥ PR.

The Phase 2 portion of Study 2011-001 is ongoing. Eight (8) response-evaluable subjects have received Oprozomib Tablets on the 5/14 schedule with once daily dosing in Phase 2; 7 subjects had SD, and 1 subject was off study prior to any disease response assessment.

Safety

In the Phase 1 portion of the study (as of 21 January 2014):

- Thirty-two (32) subjects have been enrolled on the 5/14 schedule. Dose-limiting toxicities for the 5/14 schedule observed at the maximum administered dose (MAD) of 270 mg were tumor lysis syndrome (TLS) and Grade 3 vomiting. The MTD was defined as 240 mg, and this was initially selected for the Phase 2 portion for the 5/14 schedule. Due to toxicities, including fatal GI bleeding in 2 subjects, and a high rate of discontinuations observed at this dose level, the dose under evaluation in Phase 2 has been reduced. The Phase 2 portion of the study will reopen using a step-up dose approach starting with 150 mg as the initial dose level, with an increase to 180 mg in Cycle 2.
- Twenty-nine (29) subjects have been enrolled on the 2/7 schedule. Dose-limiting toxicities for the 2/7 schedule observed at the MAD of 330 mg were Grade 3 diarrhea and Grade 4 thrombocytopenia. The MTD was defined as 300 mg. With the opening of Amendment 6, a step-up dosing regimen using 240 mg as the initial dose level, with an increase to 300 mg in Cycle 2, was selected for Phase 2 portion for the 2/7 schedule.

In the Phase 2 portion of the study (as of 21 January 2014):

- A total of 13 subjects have been enrolled in the 5/14 schedule
- No subjects have been enrolled in the 2/7 schedule

Nineteen subjects (19) experienced serious adverse events (SAEs) across both schedules. The 11 treatment-related SAEs comprised 4 GI events (diarrhea, nausea/vomiting, fatigue/dehydration/nausea, and dehydration), 2 hematological events (anemia and neutropenia), 2 cases of TLS, 1 infection (pneumonia), and 1 general event (fatigue/dehydration/nausea; events could be counted in more than 1 category). All of these are expected events based on the Oprozomib IB (Version 6). There were 2 cases of renal failure. There were also 2 Grade 5 GI hemorrhages at the 240 mg dose level on the 5/14 schedule.

2.4.2.3 Study 2012-001: Phase 1b/2, Multicenter, Open-label Study of Oprozomib and Dexamethasone in Patients with Relapsed and/or Refractory Multiple Myeloma

Efficacy

For the 2012-001 Phase 1b/2 study, as of 31 March 2014, 5 response-evaluable relapsed and/or refractory multiple myeloma subjects received Oprozomib Tablets on a 5 consecutive

day in combination with dexamethasone on a bimonthly schedule with daily dosing and 1 subject had MR and 4 subjects had SD as their best response. As of 31 March 2014, 8 response-evaluable subjects have received Oprozomib Tablets administered orally, once daily, on Days 1, 2, 8, and 9 of a 14-day cycle in combination with 20 mg of dexamethasone and 1 subject had a very good partial response (VGPR) (unconfirmed), 2 subjects had a partial response (PR) (confirmed or unconfirmed), 1 subject had a MR, and 4 subjects had SD as the best response.

Safety

The 2012-001 Phase 1b/2 study assessing safety and activity of Oprozomib Tablets in combination with dexamethasone is currently enrolling in the Phase 1b portion of the study.

- As of May 2014, 12 subjects have been enrolled and treated at doses of 180 mg (n = 5) to 210 mg (n = 7) on the 5/14 schedule, and 4 subjects remain on study. Three subjects have experienced DLTs at the 210 mg dose, including 1 subject with a subarachnoid hemorrhage, 1 subject with Grade 3 transaminitis, and 1 subject with Grade 4 thrombocytopenia. In addition, 1 subject had 3 SAEs (esophagitis, urinary tract infection, and pneumonia). Data suggest that the 180-mg dose level will be the tolerable dose in combination with dexamethasone. This dose level exceeds the starting dose for the combination of oprozomib, pomalidomide, and dexamethasone (OPomd) of 150 mg.
- As of May 2014, 13 subjects have been enrolled and treated at doses of 180 mg (n = 3), 210 mg (n = 3), 240 mg (n = 3), to 270 mg (n = 4) on the 2/7 schedule, and 7 subjects remain on study. One DLT of Grade 4 thrombocytopenia has been observed. Dose escalation is ongoing at the 300-mg dose level, suggesting that doses of 270 mg in combination with dexamethasone are tolerable. Current doses explored in this schedule exceed the starting dose for the combination of OPomd of 210 mg.

As of 31 March 2014, ten (10) subjects experienced SAEs across both schedules. The 3 treatment-related SAEs were 1 subject with a subachnoid hemorrhage (SAH) hypertension and headache, 1 subject with thrombocytopenia, pneumonia, and sepsis, and 1 subject with delirium. Thrombocytopenia and infection were expected events based on the Oprozomib IB (Version 6), but the SAH, hypertension, headache, and delirium were not.

2.4.2.4 Study OPZ003: Phase 1b/2, Multicenter, Open-label Study of Oprozomib and Dexamethasone in Combination With Lenalidomide or Oral Cyclophosphamide in Patients with Newly Diagnosed Multiple Myeloma

Efficacy

No efficacy data are available at this time.

Safety

The OPZ003 Phase 1b/2 study is currently enrolling in the Phase 1b portion of the study. Subject enrollment has been in the ORd arm only. No subjects have been enrolled in the OCyd arm.

As of 18 July 2014, ten subjects have been enrolled and 1 subject remained on study. Of the 3 subjects enrolled at the 210 mg dose level (ORd regimen), 2 of those subjects experienced Grade 3 syncope. Nausea and vomiting with dehydration and concomitant medications were contributing factors in 1 case. In the other, no cause was identified. Cardiac and neurologic evaluations were unremarkable. Both syncopal events were described as related to oprozomib. As such, they represented DLTs and the cohort dose was de-escalated to 180 mg. One subject who experienced syncope discontinued treatment, and the other continued after a dose reduction to 180 mg.

No further syncopal events have been reported. Syncope has been identified as an event of interest for oprozomib.

Seven subjects were enrolled in the 180 mg cohort. Six of the 7 were DLT evaluable. Two subjects experienced dose limiting toxicities. The first had Grade 3 abdominal pain with distension in the setting of diarrhea. The second subject developed Grade 3 hypotension in the setting of diarrhea and continued anti-hypertensive and cardiac rate controlling medication use.

The cohort dose was subsequently de-escalated to 150 mg. No DLTs have been reported in this cohort as of the writing of this amendment.

2.4.3 LENALIDOMIDE BACKGROUND

Lenalidomide is a derivative of thalidomide and has both immunomodulatory and anti-angiogenic properties which confer antitumor effects.

Combining lenalidomide with high-dose dexamethasone has led to significantly improved efficacy outcomes compared with high-dose dexamethasone alone as measured by time to progression, ORR, and OS; indeed, lenalidomide and dexamethasone have become a standard treatment for relapsed multiple myeloma (Dimopoulos 2007; Weber 2007). In a recent study of high-dose versus low-dose therapeutic dexamethasone, both with lenalidomide in newly diagnosed multiple myeloma (Rajkumar 2010), lenalidomide combined with low-dose dexamethasone (once weekly) was associated with reduced rates of deep vein thrombosis, infection, and other nonhematologic reactions. There was no difference seen in PFS between treatment arms, however, in subjects over 65 years of age, low-dose therapeutic dexamethasone combined with lenalidomide was associated with greater OS (p-value = 0.0002). Thus, the use of low-dose therapeutic dexamethasone is currently recommended in combination with lenalidomide and will be used in this study.

2.4.4 CYCLOPHOSPHAMIDE BACKGROUND

Alkylating agents such as melphalan and cyclophosphamide have been the backbone of multiple myeloma therapy for over 40 years. In current practice they are widely used during induction therapy in subjects with newly diagnosed multiple myeloma in combination with steroids and 1 of the novel agents, particularly a proteasome inhibitor (Dispenzieri 2007). Cyclophosphamide is less stem-cell toxic than other alkylating agents, and has predictable, short duration myelosuppression when administered at doses currently in use in multiple myeloma (300–500 mg/m^2) (Volpe 2003; Morgan 2011). These properties have encouraged the use of oral cyclophosphamide in combination with a steroid and proteasome inhibitor in both front-line and relapsed and/or refractory multiple myeloma (Kropff 2007; Kropff 2009; Reece 2008; Reeder 2009; Reeder 2010). The largest published experience with cyclophosphamide-based induction regimens was reported by Reeder (2010) who combined cyclophosphamide 300 mg/m^2 orally (PO) on Days 1, 8, 15, and 22, with dexamethasone 40 mg PO on Days 1 through 4, 9 through 12, and 17 through 20 or Days 1, 8, 15, and 22 and

bortezomib 1.3 mg/m^2 intravenous (IV) on Days 1, 4, 8, and 11 or 1.5 mg/m^2 IV on Days 1, 8, 15, and 22 every 28 days for 4 cycles in transplant-eligible subjects (Reeder 2010). The overall response rate (PR or better) for 63 subjects enrolled in this trial was 90%, with 41% complete response/near complete response (CR/nCR) and 60% VGPR or better. Weekly (Days 1, 8, 15, 22) bortezomib administration led to reduction in Grades 3 and 4 toxicity (37% versus 48%), without apparent reduction in efficacy.

2.4.4.1 Cyclophosphamide and Dexamethasone with Epoxyketone Proteasome Inhibitors

The safety, tolerability, and efficacy of carfilzomib in combination with cyclophosphamide and dexamethasone are being evaluated in a Phase 2 study (Palumbo 2012). Transplant-ineligible subjects with newly diagnosed multiple myeloma received oral cyclophosphamide 300 mg/m^2 on Days 1, 8, and 15; oral dexamethasone 40 mg on Days 1, 8, 15, and 22; and IV carfilzomib 20 mg/m^2 on Days 1 and 2 and 36 mg/m^2 on Days 8, 9, 15, and 16 in Cycle 1, Cycle 2, and beyond, every 28 days for 9 cycles. Median age of the 34 enrolled subjects was 70 years; 46% had International Staging System (ISS) Stage III. Nineteen subjects were evaluable for response and safety after at least 4 cycles. All subjects had achieved at least a PR, 74% at least a VGPR, and 42% CR/nCR including 10% stringent complete response (sCR). Responses were rapid with a median time to PR of 1 month. At least 1 Grade 3 or 4, nonhematologic adverse event (AE) was reported in 4 subjects (21%). No subjects discontinued treatment and 4 subjects (21%) required carfilzomib dose reduction due to AEs (Grade 4 neutropenia, Grade 3 pneumonia, Grade 3 atrial fibrillation, and Grade 3 renal failure). These results are consistent with the report of the "CYCLONE" Phase 1/2 study in patients with newly diagnosed multiple myeloma investigating a combination of carfilzomib with oral cyclophosphamide 300 mg/m^2 on Days 1, 8, and 15; thalidomide 100 mg. Days 1 through 28, and dexamethasone 40 mg on Days 1, 8, 15, and 22 in transplant-eligible subjects. In this report, doses of carfilzomib up to 45 mg/m^2 were safely delivered without DLTs and with a high ORR of 96% (Mikhael 2013).

These data, along with the emerging data that oprozomib has similar activity as carfilzomib, suggest that oprozomib, cyclophosphamide, and dexamethasone may be an active regimen for initial treatment of multiple myeloma regardless of transplant eligibility. However, the

safety, tolerability and MTD of oprozomib in this combination have not been evaluated. This study will investigate the MTD for oprozomib when given in combination with cyclophosphamide and dexamethasone.

2.5 DOSE RATIONALE

2.5.1 AMENDMENT 1

The OPZ003 study was initiated in 2013 utilizing a 3 x 3 dose escalation schema. The starting dose for the oprozomib, lenalidomide, dexamethasone (ORd) and oprozomib, cyclophosphamide, dexamethasone (OCyd) arms was 210 mg for 5 consecutive days (5/14 schedule) in the Phase 1b component of the study. This initial dose and schedule were selected based upon preclinical data that suggested improved antimyeloma activity with consecutive day dosing of epoxyketone proteasome inhibitors (Demo 2007) and clinical data collected for subjects exposed to oprozomib in ongoing and completed clinical studies.

Safety results from Study 2009-003 in subjects with solid tumors, and 2011-001 in subjects with hematologic malignancy demonstrated acceptable tolerability profiles for once daily × 5 bimonthly dosing schedule (5/14 schedule). The MTD for single agent oprozomib in the 2011-001 trial was 240 mg.

In the 2011-001 trial the tolerability of the once daily × 2 weekly (2/7 schedule) and the 5/14 schedule was similar. In addition, antimyeloma activity (confirmed minimal response [MR] or better) was reported with the 2/7 schedule and the 5/14 schedule, both beginning at a daily dose of 150 mg (Kaufman 2013). See Section 2.4.2.

Given the activity against multiple myeloma, the acceptable safety profile demonstrated, and the increased experience with the 5/14 schedule compared to the 2/7 schedule, the 5/14 schedule was chosen for the OPZ003 study.

2.5.2 AMENDMENT 2

Two of the 3 subjects enrolled in the 210 mg cohort of the OPZ003 ORd arm experienced syncope, a DLT (see Section 2.4.2.4). These DLTs prompted a dose de-escalation to the 180 mg cohort. Seven subjects were enrolled at the 180 mg dose level. Two DLTs,

abdominal pain with distension and hypotension were observed prompting dose de-escalation to 150 mg on the 5/14 schedule.

The dose of oprozomib for subjects enrolled in the ORd arm will continue at 150 mg on the 5/14 schedule unless 2 or more DLTs are reported.

Given the increased clinical experience with the 2/7 schedule in 2011-001, and the experience in Amendment 1 of this trial, the starting dose for subjects enrolling in the ORd arm under Amendment 2 will be 210 mg on the 2/7 schedule.

The starting dose for subjects enrolled in the OCyd arm under Amendment 2 will also be 210 mg on the 2/7 schedule. No subjects were enrolled in the OCyd arm prior to Amendment 2.

Starting with Amendment 2, an ER tablet will be administered. There are minimal changes between the ER formulation and the modified release formulation used in Amendment 1. As such, dosing with the ER formulation will occur at the same level as the modified formulation.

Subjects enrolled in the original protocol or Amendment 1 will receive Oprozomib Tablets and may receive Oprozomib Extended Release (ER) Tablets when available. Subjects enrolled under Amendment 2 will receive Oprozomib ER Tablets only.

2.6 STUDY RATIONALE

Preclinical studies show that lenalidomide sensitizes multiple myeloma to the proteasome inhibitor bortezomib, suggesting combination therapy may enhance clinical activity. The combination of a proteasome inhibitor and an immunomodulatory agent is attractive as the expected overlapping toxicities would be manageable. This concept was confirmed in Phase 1 and 2 studies of lenalidomide, high-dose dexamethasone, and bortezomib, which demonstrated synergistic effects in relapsed and refractory multiple myeloma (Richardson 2006a; Anderson 2009), although treatment-emergent peripheral neuropathy (observed in 35% of subjects) may limit the utility of that combination (Richardson 2006b). An ongoing, Phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose

dexamethasone in subjects with newly diagnosed multiple myeloma has demonstrated excellent activity and tolerability with 62% of 53 subjects achieving nCR or better and with only Grade 1/2 peripheral neuropathy reported in 23% of subjects (Jakubowiak 2012). Preliminary results from an ongoing Phase 2 study of CRd in untreated newly diagnosed nontransplant and transplant candidates with multiple myeloma have also been reported. After a median of 4 cycles of CRd completed (range 1–8) in 15 evaluable subjects, 40% of subjects achieved nCR or better (4 sCR and 2 nCR), 33% of subjects had VGPR (n = 5), 20% of subjects had PR (n = 3), and 1 subject had SD (6%). No subjects reported ≥ Grade 3 neuropathy (Korde 2012).

Likewise, and as described above in Section 2.4.4, the combination of carfilzomib and cyclophosphamide also appears to have good antimyeloma activity and an acceptable safety profile.

Oprozomib appears to have single-agent activity in an ongoing study (2011-001, see Section 2.4.2.2) of patients with hematologic malignancies, including multiple myeloma. Combining oprozomib with low-dose therapeutic dexamethasone, plus either cyclophosphamide or lenalidomide, to provide an all oral treatment regimen for the frontline treatment of multiple myeloma has appeal due to increased convenience. The current study is designed to establish the MTD of oprozomib when combined with low-dose therapeutic dexamethasone and standard doses of either cyclophosphamide or lenalidomide, and to provide a preliminary assessment of the antimyeloma activity of these combinations.

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

The primary objectives are:

Phase 1b

- To establish the MTD of oprozomib given in combination with lenalidomide and dexamethasone (ORd) or with cyclophosphamide and dexamethasone (OCyd)
- To evaluate the safety and tolerability of the ORd and OCyd combination regimens, as assessed by the type, incidence, severity and seriousness of AEs, and abnormalities in selected laboratory analytes

Phase 2

- To estimate the antitumor activity of the ORd and OCyd combination regimens, as measured by overall response rate (ORR) and complete response rate (CRR)
- To evaluate the safety and tolerability of the ORd and OCyd combination regimens, as assessed by the type, incidence, severity and seriousness of AEs, and abnormalities in selected laboratory analytes

3.2 SECONDARY OBJECTIVES

The secondary objectives are:

- To evaluate population PK parameter estimates of oprozomib, and may include its metabolite(s), and the variability in these estimates
- To estimate the duration of response (DOR)
- To estimate PFS

3.3 EXPLORATORY OBJECTIVES

The exploratory objectives are:

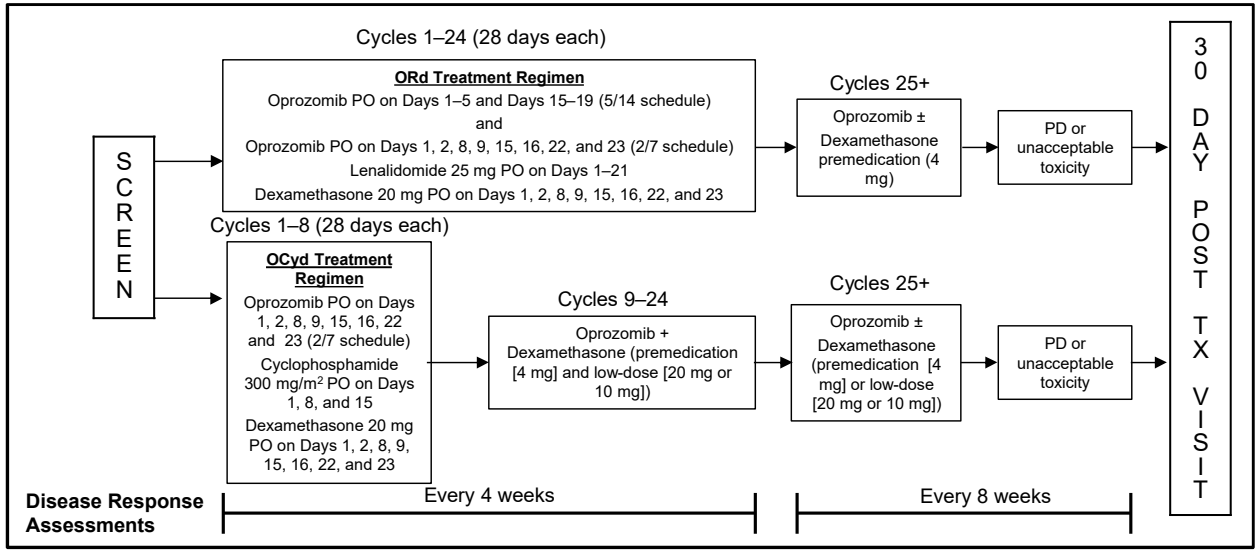
- To evaluate PDn biomarkers that may correlate with antitumor activity
- To evaluate genomic biomarkers that may predict response and resistance following treatment with proteasome inhibitors

4 STUDY DESIGN

4.1 TYPE/DESIGN OF STUDY

This study is an open-label, Phase 1b/2, two-combination regimen, non-randomized, multicenter study (Figure 1).

Figure 1 Study Schema for OPZ003



The ORd combination regimen treatment cycles are 28 days in duration. Two (2) oprozomib dosing schedules will be assessed during dose escalation. Subjects enrolled under the original protocol and Amendment 1 will receive oprozomib once daily on Days 1 through 5 and Days 15 through 19 (referred to as the 5/14 schedule). Subjects enrolled under Amendment 2 will receive oprozomib once daily on 2 consecutive days every 7 days; specifically on Days 1, 2, 8, 9, 15, 16, 22, and 23 (referred to as the 2/7 schedule). All subjects on the ORd arm will receive lenalidomide at a dose of 25 mg will be given on Days 1–21 and dexamethasone at a dose of 20 mg will be given on Days 1, 2, 8, 9, 15, 16, 22, and 23 of every 28-day cycle (Figure 2 and Figure 3).

Figure 2 Dose Administration Schema for Oprozomib, Lenalidomide, Dexamethasone (ORd) 5/14 Schedule (Original Protocol and Amendment 1)

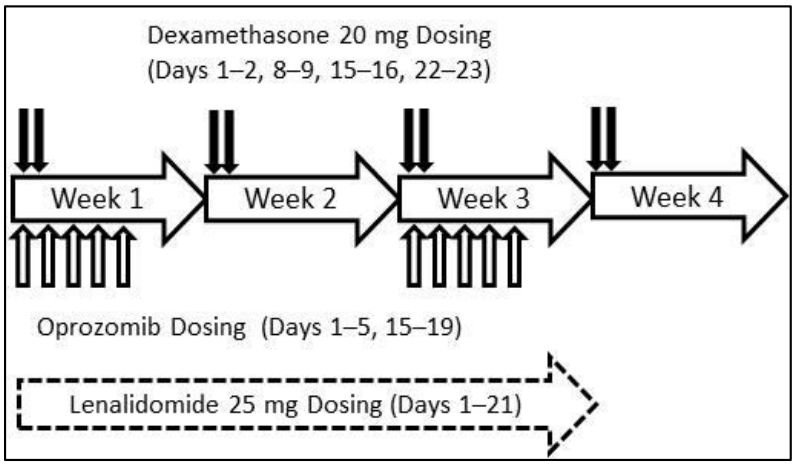
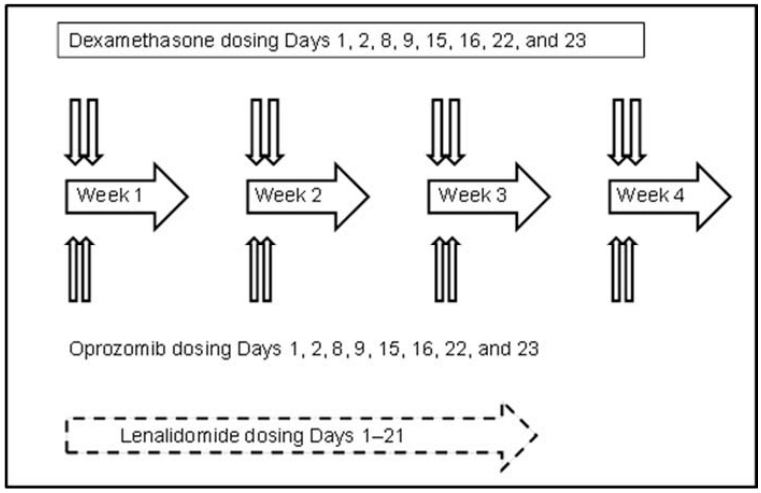


Figure 3 Dose Administration Schema for Oprozomib, Lenalidomide, Dexamethasone (ORd) 2/7 Schedule (Amendment 2)

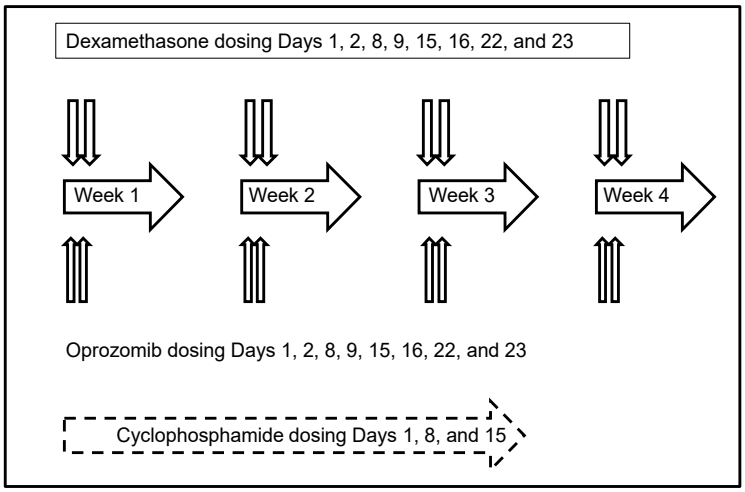


The ORd combination will be administered until progression of disease, unacceptable toxicity, or for 24 cycles (approximately 24 months), whichever occurs first. Dexamethasone will be administered at a dose of 20 mg/day, as described above, through the first cycle, after which the dose may be decreased to 10 mg/day in subjects > 75 years of age, at the discretion of the investigator. Subjects who complete 24 cycles of treatment and who demonstrate a response of stable disease or better will continue oprozomib, with or without dexamethasone premedication (4 mg/day) until progression of disease or unacceptable toxicity. Lenalidomide will be administered for a maximum of 24 cycles.

The OCyd regimen treatment cycles are 28 days in duration. One oprozomib dosing schedule will be assessed during dose escalation. All study subjects will receive oprozomib on 2 consecutive days every 7 days; specifically on Days 1, 2, 8, 9, 15, 16, 22, and 23 (referred to as the 2/7 schedule). Cyclophosphamide at a dose of 300 mg/m^2 will be given on Days 1, 8, and 15 and dexamethasone at a dose of 20 mg will be given on Days 1, 2, 8, 9, 15, 16, 22, and 23 of every 28-day cycle (Figure 4).

Dexamethasone will be taken at a dose of 20 mg/day, as described above, through the first cycle, after which the dose may be decreased to 10 mg/day in subjects > 75 years of age, at the discretion of the investigator.

Figure 4 Dose Administration Schema for Oprozomib, Cyclophosphamide, Dexamethasone (OCyd) 2/7 Schedule (Amendment 2)



The OCyd combination will be administered until progression of disease, unacceptable toxicity, or for 8 cycles (approximately 8 months), whichever occurs first. Subjects who complete 8 cycles of treatment and have stable disease or better will continue on oprozomib, with dexamethasone premedication. Dexamethasone dosing, premedication and low-dose (e.g., 20 mg or 10 mg), should continue for a total of 24 cycles or until progression of disease or unacceptable toxicity. Subjects who complete 24 cycles of oprozomib therapy (total) without evidence of progression may continue therapy with or without dexamethasone, premedication or low-dose. A taper of dexamethasone after 24 cycles may be utilized as per institutional guidelines. Cyclophosphamide will be administered for a maximum of 8 cycles.

Both the Phase 1b and Phase 2 portions of this trial will enroll patients with newly diagnosed, symptomatic multiple myeloma for whom a hematopoietic stem cell transplant is not planned or scheduled during the study, or are considered ineligible for hematopoietic stem cell transplant at the discretion of the investigator.

Subjects in either treatment cohort who complete at least 4 cycles of study treatment and achieve a confirmed response (i.e., PR, VGPR, CR, or sCR) may, after discussion with the Onyx study medical monitor, suspend study treatment for up to 6 weeks to undergo a hematopoietic stem cell harvest. Stem cell mobilization will be conducted using a noncytotoxic regimen such as granulocyte colony-stimulating factor (G-CSF). These subjects may then resume study treatment until progression of disease, unacceptable toxicity, or for a total of 24 cycles of treatment with lenalidomide or a total of 8 cycles of treatment with cyclophosphamide, followed by oprozomib treatment with low-dose dexamethasone (20 mg or 10 mg) for subjects free from progression, as described above.

In the Phase 1b portion, subjects will be enrolled in escalating or dose-de-escalating dose cohorts in each combination regimen (see Section 4.2 and Table 3, Table 4, and Table 5 for doses/cohorts, and see Section 9.1.2 for methods of dose escalation to the MTD). Dose escalation will proceed only after the safety and tolerability of the previous dose level has been assessed as acceptable by the Cohort Safety Review Committee (CSRC) comprised of Onyx's study medical monitor, Onyx's drug safety representative, and the investigators, or until a MTD has been determined.

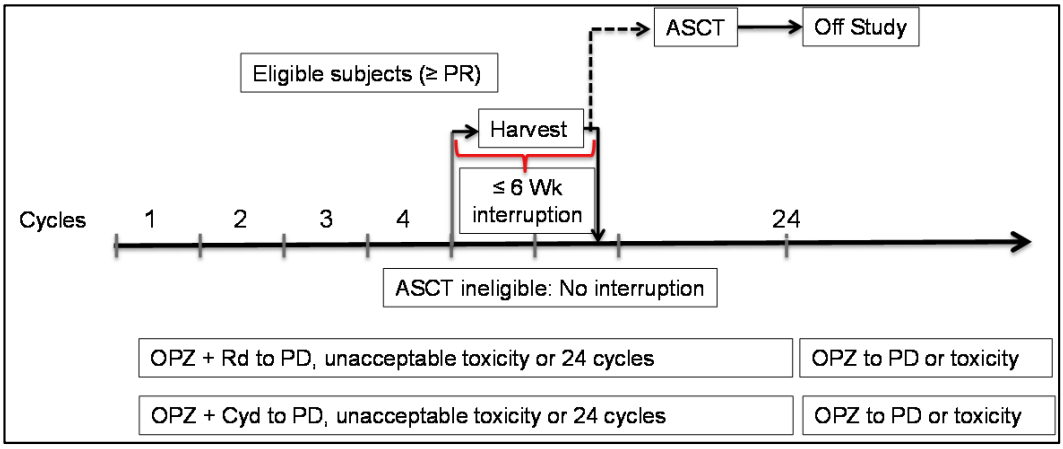
In the Phase 2 portion, oprozomib will be given in combination with dexamethasone and either lenalidomide or cyclophosphamide at the recommended Phase 2 dose (RP2D), as defined in the Phase 1b portion of the study. The RP2D may or may not be the same as the MTD, and will be assessed on the basis of the totality of safety and PK/PDn data.

4.1.1 PATIENTS ELECTING TO HAVE STEM CELLS COLLECTED

Subjects enrolling in the OPZ003 study must be newly diagnosed and require treatment as per the 2013 National Comprehensive Cancer Network (NCCN) guidelines. Subjects scheduled for or planning to proceed with transplant in the front-line setting should not be enrolled. However, subjects may have their stem cells collected for future salvage transplant. The schema below (Figure 5) depicts the schedule for subjects electing to bank their stem cells.

In the event that a subject who had not previously intended to proceed to front-line transplant elects to proceed, that subject will be discontinued from the study (see Section 11).

Figure 5 Schedule for Stem Cell Collection



ASCT = autologous stem cell transplantation; Cyd = cyclophosphamide and dexamethasone. OPZ = oprozomib; PD = progressive disease; PR = partial response; Rd = lenalidomide and dexamethasone.

4.2 DOSE-ESCALATION PLAN

In the Phase 1b portion of the study, oprozomib doses will be escalated in sequential groups of 3 subjects for each combination regimen, with expansion to up to 6 subjects if a DLT is observed in 1 of the first 3 subjects. The doses of lenalidomide, cyclophosphamide, and dexamethasone will remain fixed in all dose cohorts.

Enrollment in the initial cohort (Table 3) for the ORd arm was entered at a daily dose level of 210 mg on the 5/14 schedule. Two DLTs (syncope) were observed in the first 3 subjects and the cohort dose was decreased by 1 dose level to 180 mg of oprozomib. The dosing cohort was de-escalated to 150 mg after 2 DLTs (abdominal pain and hypotension) in 6 DLT evaluable subjects were reported at the 180 mg dosing level. With the introduction of the ER Tablet with Amendment 2, there will be no further attempt at dose escalation in the 5/14 schedule with the tablet formulation.

The starting dose for subjects enrolled in the ORd and OCyd arms under Amendment 2 will be 210 mg on the 2/7 schedule (Table 4 and Table 5). The dose of oprozomib for subsequent cohorts will be escalated or de-escalated by 30-mg increments until the MTD is established. The maximum dose to be tested has not been defined. It is anticipated that dosing will not

exceed the oprozomib single agent MTD. Biweekly investigator calls and CSRC meetings, during which safety data will be reviewed from this and other oprozomib studies will occur before all cohort dose escalation decisions and implementation. Additional details regarding dose escalation can be found in the Cohort Management Plan. Details on subject replacement are provided in Section 9.1.4. The MTD will be defined as the highest dose in which a DLT is observed in fewer than 2 of 6 patients (Kummar 2006). At least 6 patients must be treated at the MTD for a minimum of 1 cycle to establish this dose as tolerated.

Table 3 Dose-Escalation Scheme: Oprozomib Tablets in Combination with Lenalidomide and Dexamethasone (ORd) for 5/14 Dosing Schedule (Original Protocol and Amendment 1)

Cohorts	Oprozomib Daily Dose (mg)[a, b]	Lenalidomide Doses (mg)	Dexamethasone Doses (mg)
-102	150	25	20
-101[c]	180	25	20
101	210	25	20
102	240	25	20
103	270	25	20
104	300	25	20

[a] Subjects enrolled in the Phase 1b prior to the availability of Oprozomib ER Tablets, will initiate treatment with oprozomib tablets. These subjects may have their oprozomib tablets replaced with Oprozomib ER Tablets after they have completed the 1st cycle of ORd treatment and when the Oprozomib ER Tablets are available.

[b] Re-escalation of oprozomib dosing in the ORd arm may occur if significant differences in the pharmacokinetic profile of the extended and modified release formulations are observed. In this case, enrollment would start at 150 mg or the MTD established with the ER formulation and subsequent cohorts of 3-6 subjects enrolled with doses escalated by 30 mg until the MTD (the highest dose at which a DLT is observed in less than 2 of 6 evaluable subjects) with the new formulation is defined.

[c] DLTs were observed in 2 subjects in the 101 cohort at a dose level of 210 mg, and in the -101 cohort at a dose level of 180 mg. Dosing will proceed at 150 mg as agreed with the Cohort Safety Review Committee (CSRC). The number of subjects may be expanded to include up to 6 evaluable subjects.

Table 4 Dose-Escalation Scheme: Oprozomib Tablets in Combination with Lenalidomide and Dexamethasone (ORd) for 2/7 Dosing Schedule (Amendment 2)

Cohorts	Oprozomib Daily Dose (mg)[a,b]	Lenalidomide Doses (mg)	Dexamethasone Doses (mg)
-202	150	25	20
-201 [a]	180	25	20
201 [b]	210	25	20
202	240	25	20
203	270	25	20
204	300	25	20
205	330	25	20
206	360	25	20

[a] If DLTs are observed in 2 or more subjects at the first dose level of 210 mg, dosing of Cohort -201 will proceed at 180 mg, or a lower dose as agreed with the Cohort Safety Review Committee (CSRC) and may be expanded to include up to 6 evaluable subjects.

[b] Cohorts of 3–6 subjects will continue to be enrolled with doses escalated by 30 mg until the MTD (the highest dose at which a DLT is observed in less than 2 of 6 evaluable subjects) is defined.

Table 5 Dose-Escalation Scheme: Oprozomib ER Tablets in Combination with Cyclophosphamide and Dexamethasone (OCyd) for the 2/7 Dosing Schedule (Amendment 2)

Cohorts	Oprozomib ER Tablets Daily Dose (mg)	Cyclophosphamide Doses (mg/m^2)	Dexamethasone Doses (mg)
-302	150	300	20
-301[a]	180	300	20
301[b]	210	300	20
302	240	300	20
303	270	300	20
304	300	300	20
305	330	300	20

[a] If DLTs are observed in 2 or more subjects at the first dose level of 210 mg, dosing of Cohort -301 will proceed at 180 mg, or a lower dose as agreed with the Cohort Safety Review Committee (CSRC) and may be expanded to include up to 6 evaluable subjects.

[b] Cohorts of 3–6 subjects will continue to be enrolled with doses escalated by 30 mg until the MTD (the highest dose at which a DLT is observed in less than 2 of 6 evaluable subjects) is defined.

4.3 MINIMIZING BIAS

4.3.1 RANDOMIZATION

This is an open-label study. Subjects will be assigned to dose levels in a sequential manner (see Section 4.1).

4.3.2 BLINDING

Not applicable; this is an open-label study.

4.4 NUMBER OF CENTERS

Approximately 20 study centers in the US will be recruited for participation in this study.

4.5 NUMBER OF SUBJECTS

Total enrollment of up to approximately 134 evaluable subjects is planned for this study, including up to approximately 64 evaluable subjects for the Phase 1b portion of the study (40 and 24 for ORd and OCyd, respectively) and approximately 70 subjects for the Phase 2 portion of the study (35 subjects for each combination regimen).

4.5.1 PHASE 1b

The estimated sample size of up to 40 subjects for the ORd combination regimen and up to 24 subjects for the OCyd combination regimen is based upon standard 3 + 3 dose-escalation rules (see Section 9.1.2) and the expectation that 2–6 dosing cohorts of 3–6 subjects per cohort will be required to establish the MTD for each treatment regimen.

4.5.2 PHASE 2

Enrollment of 35 additional subjects in each combination regimen during the Phase 2 portion of the study is based upon the goal of ruling out an ORR < 85% and a CRR < 50% based upon the approximate lower 1-sided 90% confidence interval. The same assumptions are used in determining the sample size for each combination regimen.

4.6 ESTIMATED STUDY DURATION

The total study duration is expected to be approximately 59 months based upon the assumptions that approximately 35 months may be required to enroll all subjects

(approximately 23 months to enroll Phase 1b subjects and approximately 12 months to enroll Phase 2 subjects) and that the average time on study will be approximately 24 months.

5 SUBJECT SELECTION

Up to approximately 134 patients with newly diagnosed, symptomatic multiple myeloma for which a hematopoietic stem cell transplant is not planned or scheduled during the study or are considered ineligible for hematopoietic stem cell transplant at the discretion of the investigator, and are considered to be appropriate for this clinical study by their treating physicians may enroll.

5.1 INCLUSION CRITERIA

1. Newly diagnosed multiple myeloma patients for whom treatment is indicated per the NCCN guidelines, and for whom a hematopoietic stem cell transplant is not planned or scheduled during the study or are considered ineligible for hematopoietic stem cell transplant, with measurable disease as indicated by 1 or more of the following:
    a. Serum M-protein ≥ 500 mg/dL
    b. Urine M-protein ≥ 200 mg/24 hour
    c. Serum free light chain (SFLC): Involved SFLC level ≥ 10 mg/dL provided SFLC ratio is abnormal
2. Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0–2
3. Males and females ≥ 18 years of age
4. Adequate hepatic function, with bilirubin ≤ 1.5 times the upper limit of normal (ULN), aspartate aminotransferase (AST) ≤ 3 times ULN, and alanine aminotransferase (ALT) ≤ 3 times ULN (Note: Patients with documented Gilbert Syndrome may be enrolled with an elevated unconjugated bilirubin after discussion with the Onyx study medical monitor)
5. Absolute neutrophil count (ANC) ≥ 1.0×10^9/L, hemoglobin ≥ 7.0 g/dL, and platelet count ≥ 75×10^9/L
    a. Patients must not have received platelet transfusions for at least 1 week prior to Screening
    b. Screening ANC must be independent of granulocyte colony-stimulating factor (G-CSF) or granulocyte/macrophage-colony-stimulating factor (GM-CSF) support for ***at least*** 1 week and of pegylated G-CSF support for ≥ 2 weeks
    c. Patients may receive red blood cell (RBC) transfusions or receive supportive care with erythropoietin or darbepoetin in accordance with institutional guidelines

6. Creatinine clearance (CrCl) rate of ≥ 50 mL/min, either measured or calculated using the formula of Cockcroft and Gault [(140 – age) × mass (kg) / (72 × serum creatinine mg/dL)]. Multiply result by 0.85, if female.
7. Patients must sign written informed consent form (ICF) in accordance with federal, local, and institutional guidelines
8. For both treatment regimens (ORd and OCyd): Females of childbearing potential (FCBP) must agree to ongoing pregnancy testing and to practice contraception as outlined in the Revlimid REMS Guide (Appendix K). Two effective contraceptive methods must be used by FCBP for at least 4 weeks prior to start of lenalidomide or cyclophosphamide therapy, during therapy, and during dose interruptions, and for 3 months following the discontinuation of oprozomib. Postmenopausal females (> 45 years old and without menses for > 24 consecutive months) and surgically sterilized females are exempt from these requirements.
9. For both treatment regimens (ORd and OCyd): Male subjects must agree to practice contraception as outlined in the Revlimid Risk Evaluation and Mitigation Strategy (REMS) Guide (Appendix K). Male subjects receiving lenalidomide or cyclophosphamide must use an effective method of contraception during any sexual contact with FCBP during the study, and for 3 months following the discontinuation of oprozomib, even if the subject has undergone a successful vasectomy.

5.2 EXCLUSION CRITERIA

1. Radiation therapy within 2 weeks prior to first dose
2. Any prior systemic antimyeloma therapy except oral steroids (dexamethasone up to a total dose of 160 mg or equivalent within 14 days prior to the first dose of study treatment). Use of topical or inhaled steroids is acceptable.
3. Participation in an investigational therapeutic study within 3 weeks prior to first dose
4. Plasmapheresis is not permitted at any time during the Screening period or while the subject is receiving study treatment. If a subject has started Screening procedures requiring plasmapheresis, or is anticipated to require plasmapheresis during or after the Screening period, this patient will be considered ineligible and should not be enrolled.
5. Major surgery within 3 weeks prior to first dose
6. Clinically significant GI bleed in the 6 months prior to Cycle 1 Day 1 (C1D1) first dose
7. 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
8. A history of deep vein thrombosis or pulmonary embolism, with contraindication to anticoagulation and antiplatelet options

9. Active infection requiring systemic antibiotics, antivirals, or antifungals within 2 weeks prior to first dose
10. Known or suspected human immunodeficiency virus (HIV) infection or subjects who are HIV seropositive
11. Active hepatitis A, B, or C infection
12. Significant neuropathy (Grade 3, Grade 4, or Grade 2 with pain) at the time of first dose
13. Other malignancy within the past 3 years except those considered cured by surgical resection including some cases of:
    a. Adequately treated basal or squamous cell carcinoma of the skin
    b. Thyroid cancer
    c. Carcinoma in situ of the breast or cervix
    d. Prostate cancer with Gleason Score of 6 or less with stable prostate-specific antigen levels
14. Plasma cell leukemia
15. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
16. Known amyloidosis
17. Uncontrolled diabetes or hypertension
18. Female subjects who are pregnant or nursing
19. Any clinically significant psychiatric or medical condition that in the opinion of the investigator could increase patient risk, interfere with protocol adherence, or a subject's ability to give informed consent

6 SUBJECT SCREENING

A signed and dated ICF will be obtained before any screening procedures are performed. Evaluations obtained as part of routine medical care and performed prior to obtaining informed consent may be used in place of the study-specific evaluations, provided they meet the time windows described in the Schedule of Assessments (Appendix A and Appendix B). Subjects will acknowledge and agree to the possible use of this information for the study by giving informed consent. The screening period for a particular subject commences when the subject undergoes the first study-specific screening assessment, and must be completed within 21 days. The window of assessment for bone marrow aspirate and biopsy in the

Phase 1b is 8 weeks and is the only exception to the 21-day screening assessment window. In the Phase 2, the bone marrow assessments must be performed within 28 days prior to C1D1 and is the only exception to the 21-day screening assessment window.

7 SUBJECT ENROLLMENT

All subjects who sign consent will be assigned a unique study number. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The Onyx study medical monitor will review the subject's information before enrollment. Only subjects who are approved by the Onyx study medical monitor or designee will be allowed to enroll into the study. A minimum of 24 hours during weekdays (Monday through Friday) will be required for the Onyx study medical monitor to approve a subject for enrollment, and additional time may be required when approval is sought during a weekend or holiday. Subjects are only considered enrolled when the Onyx study medical monitor approves the patient for enrollment. The logistics of cohort assignment are detailed in the Cohort Management Plan.

8 STUDY DRUG

8.1 OPROZOMIB TABLETS AND OPROZOMIB EXTENDED RELEASE TABLETS

8.1.1 PHYSICAL DESCRIPTION

Oprozomib is a synthetic small molecule peptide epoxyketone. The molecular formula is $C_{25}H_{32}N_4O_7S$ and the molecular weight is 532.61 (Oprozomib IB). It specifically functions as an inhibitor of the chymotrypsin-like activity of the 20S proteasome, which leads to the accumulation of protein substrates within the cell and induction of apoptosis.

8.1.2 PACKAGING AND LABELING

Oprozomib will be provided as a tablet for oral administration. Subjects enrolled under the original protocol or Amendment 1 will receive Oprozomib Tablets containing 60, 90, or 120 mg of oprozomib drug substance. Subjects enrolled under Amendment 2 will receive Oprozomib ER Tablets containing 120, 150, 180, 210, 240, or 270 mg oprozomib drug substance. Oprozomib Tablets and Oprozomib ER Tablets are intended to have an average release greater than or equal to 75% (Quantity) of the total dose of oprozomib over 8 hours.

Oprozomib Tablets are white to off-white, film-coated, round biconvex tablets and are manufactured at 3 dosage strengths:

- Oprozomib 60 mg tablets are debossed with "1" on one side and contain 60 mg of oprozomib
- Oprozomib 90 mg tablets are debossed with "3" on one side and contain 90 mg of oprozomib
- Oprozomib 120 mg tablets debossed with "5" on one side and contain 120 mg of oprozomib

Oprozomib ER Tablets are white to off-white, film-coated, tablets manufactured at 6 dosage strengths:

- Oprozomib 120 mg tablets are debossed with "G" on one side and contain 120 mg of oprozomib.
- Oprozomib 150 mg tablets are debossed with "H" on one side and contain 150 mg of oprozomib.
- Oprozomib 180 mg tablets are debossed with "I" on one side and contain 180 mg of oprozomib.
- Oprozomib 210 mg tablets are debossed with "J" on one side and contain 210 mg of oprozomib.
- Oprozomib 240 mg tablets are debossed with "K" on one side and contain 240 mg of oprozomib
- Oprozomib 270 mg tablets are debossed with "L" on one side and contain 270 mg of oprozomib.

The excipients for the drug product are lactose monohydrate, microcrystalline cellulose, sodium lauryl sulfate, magnesium stearate, hydroxy propyl methyl cellulose, and Opadry II White. The drug substance to excipient ratio is the same in all 6 dosage strengths.

8.1.3 OPROZOMIB ER TABLET DRUG PROPERTIES

The Oprozomib ER Tablet has been developed to have a more consistent dissolution profile. There are minimal changes in the tablet coating and ratio of current excipients; however, there is no change to the ratio of active pharmaceutical ingredient to excipients. The Oprozomib ER Tablet is designed to have a dissolution profile with lower variability that targets the current Oprozomib Tablet profile. In addition, multiple tablets make up the current dose levels and the new tablet will be generally administered as a single tablet.

Given the minimal changes, the new Oprozomib ER Tablet is not expected to result in altered exposure or additional adverse events related to formulation.

8.1.4 STORAGE

Oprozomib must be stored at room temperature (15°C–30°C; 59°F–86°F) in a securely locked area to which access is limited to appropriate study personnel.

8.1.5 ACCOUNTABILITY

Onyx and the investigator will maintain records of each shipment of investigational product. The records will document shipment dates, method of shipment, batch numbers, and number of bottles contained in the shipment. On receipt of the investigational product, the designated recipient at the study site will inspect the shipment, verify the number and condition of the drug product, and prepare an inventory or drug accountability record. Drug accountability records must be readily available for inspection by representatives of Onyx and by regulatory authorities. Further instructions are provided in the Pharmacy Manual.

Instructions for the destruction and return of unused drug supply are also provided in the Pharmacy Manual.

8.2 LENALIDOMIDE

Lenalidomide, a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic and antineoplastic properties. The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the molecular weight is 259.3 (Revlimid Prescribing Information, Appendix H).

8.2.1 PHYSICAL DESCRIPTION

Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/mL. Lenalidomide has an asymmetric carbon atom, can exist as the optically active forms S(–) and R(+), and is produced as a racemic mixture with a net optical rotation of zero. Lenalidomide is available in 5 mg, 10 mg, 15 mg, and 25 mg capsules for oral administration. Each capsule contains lenalidomide as the active

ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The 5 mg and 25 mg capsule shells contain gelatin, titanium dioxide and black ink. The 10 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink. The 15 mg capsule shell contains gelatin, FD&C blue #2, titanium dioxide and black ink (Appendix H).

8.2.2 PACKAGING AND LABELING

Revlimid (lenalidomide) is a commercially available drug supplied as 5 mg, 10 mg, 15 mg, and 25 mg capsules for oral administration only (Appendix H).

8.2.3 STORAGE

Store at 25°C (77°F); excursions permitted to 15°C–30°C (59°F–86°F) (Appendix H).

8.2.4 ACCOUNTABILITY

Bottles of lenalidomide will contain a sufficient number of capsules to last for 1 cycle of dosing. Sites will be required to record and document patient compliance regarding lenalidomide dosing. Please refer to the Pharmacy Manual for additional details.

8.3 CYCLOPHOSPHAMIDE

8.3.1 PHYSICAL DESCRIPTION AND FORMULATION

Cyclophosphamide is an alkylating agent (Cyclophosphamide Prescribing Information, Appendix I).

8.3.2 PACKAGING AND LABELING

Cyclophosphamide is a commercially available drug, available both as tablets for PO administration and as various sterile formulations for parenteral administration (Appendix I). Only the tablet formulation will be used in this protocol.

8.3.3 STORAGE

Cyclophosphamide is to be stored at controlled room temperature. Do not store above 25°C. Consult the package insert for additional storage and usage instructions (Appendix I).

8.3.4 ACCOUNTABILITY

Sites will be required to record and document patient compliance regarding cyclophosphamide dosing. Please refer to the Pharmacy Manual for additional details.

8.4 DEXAMETHASONE

8.4.1 PHYSICAL DESCRIPTION

Dexamethasone, a synthetic adrenocortical steroid, is a white to practically white, odorless, crystalline powder (Dexamethasone Prescribing Information, Appendix J). The empirical formula and molecular weight is $C_{22}H_{29}FO_5$ and 392.5, respectively.

8.4.2 PACKAGING AND LABELING

Dexamethasone is a commercially available drug, available both as tablets for oral administration and as various sterile formulations for parenteral administration (Appendix J).

8.4.3 STORAGE CONDITION

Dexamethasone is to be stored at controlled room temperature 20°C–25°C (68°F–77°F). Consult the package insert of the respective product for additional storage and usage instructions (Appendix J).

8.4.4 ACCOUNTABILITY

Sites will be required to record and document subject compliance regarding dexamethasone dosing. Please refer to the Pharmacy Manual for additional details.

9 DOSAGE AND TREATMENT ADMINISTRATION

9.1 OPROZOMIB

9.1.1 TREATMENT ADMINISTRATION

Oprozomib ER Tablets will be administered in single daily doses (Table 3, Table 4 and Table 5 in the following manner:

It is recommended that subjects take oprozomib with approximately 8 ounces of water at approximately the same time of day with food. When oprozomib is given on the same day

with other treatments, dexamethasone should be administered 30 minutes before oprozomib, lenalidomide and cyclophosphamide. Subjects may take lenalidomide or cyclophosphamide following oprozomib administration at investigator's discretion; however it is recommended that they take their study drugs at approximately the same time each day. On days when oprozomib is not administered, subjects should take lenalidomide or cyclophosphamide at approximately the same time of the day for consistency.

For subjects receiving the ORd treatment regimen under Amendment 1, oprozomib will be administered orally, once daily for 5 consecutive days every other week; specifically on Days 1 through 5, and 15 through 19 (5/14 schedule) of each 28-day treatment cycle. Subjects receiving ORd under Amendment 2 will receive oprozomib 2 consecutive days every 7 days; specifically on Days 1, 2, 8, 9, 15, 16, 22, and 23 (2/7 schedule) of each 28-day treatment cycle (Figure 1).

For subjects receiving the OCyd treatment regimen, oprozomib will be administered orally, once daily on 2 consecutive days every 7 days; specifically on Days 1, 2, 8, 9, 15, 16, 22, and 23 (2/7 schedule) of each 28-day treatment cycle (Figure 1).

Treatment with oprozomib will continue until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason (see Section 11).

Subjects who permanently discontinue lenalidomide or cyclophosphamide for reasons other than disease progression may continue treatment with oprozomib and dexamethasone until disease progression as described above. After 24 months, the dose of dexamethasone will be decreased to premedication doses (4 mg). A dexamethasone taper may be utilized as per institutional guidelines.

Subjects receiving the ORd treatment regimen, who permanently discontinue oprozomib for reasons other than disease progression following the completion of Cycle 1, may continue treatment with lenalidomide and dexamethasone until disease progression or for a maximum of 24 months, whichever occurs first. Subjects who discontinue both lenalidomide and oprozomib may not continue treatment with dexamethasone alone. Subjects receiving the OCyd treatment regimen who permanently discontinue oprozomib for reasons other than

disease progression following the completion of Cycle 1, may continue treatment with cyclophosphamide and dexamethasone until disease progression or for a maximum of 8 months, whichever occurs first. Subjects who discontinue both cyclophosphamide and oprozomib may not continue treatment with dexamethasone alone.

Guidelines for dose modification are provided in Section 9.3. Details on the study design are provided in Section 4.1.

9.1.2 DOSE-ESCALATION RULES

The planned and contingent dose levels are provided in Section 4.2 (Table 3, Table 4, and Table 5 and dose-escalation rules are provided in Table 6. Additional details can be found in the Cohort Management Plan.

Table 6 Dose-escalation Rules

No. of Evaluable Subjects with Treatment-related DLT at a Given Dose Level	Dose-Escalation Rules
0 of 3	New cohort of 3 subjects treated at the next higher dose level.
1 of 3	Up to 3 more subjects are treated at that same dose level.
≥ 2 of 3	Dose escalation stops. Three more subjects will be added to the preceding dose level, unless 6 subjects have already been treated at that dose level.
1 of 6	New cohort of 3 subjects treated at the next higher dose level.
≥ 2 of 6	Dose escalation stops. Additional subjects may be treated at the preceding dose level, for a minimum of 6 subjects treated at that dose level.
Highest dose with < 2 of 6	Maximum tolerated dose

DLT = dose limiting toxicity.
Source: Modified from Simon 1997.

Intrasubject dose escalation to the MTD or RP2D may be permitted once that dose has been determined and after a discussion has occurred between the treating physician and Onyx study medical monitor.

9.1.3 DEFINITION OF DOSE-LIMITING TOXICITY

Subjects will be evaluated for DLT according to the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03 (see Appendix D).

During the Phase 1b portion, assessment of DLTs will occur during the first 28 days of treatment (Cycle 1). For the purposes of this study, a DLT is defined as any of the following treatment-related events occurring in the first 28 days of treatment:

Nonhematologic DLT:

- Any ≥ Grade 3 nonhematologic toxicity with the following exceptions or qualifications:
  - ≥ Grade 3 nausea, vomiting, diarrhea, or constipation will be considered a DLT only if lasting > 7 days, despite optimal supportive care, including (at a minimum), a 5-hydroxytryptamine type-3 (5-HT3) antagonist and aprepitant for nausea/ vomiting and (e.g., Imodium), and diphenoxylate/atropine (e.g., Lomotil) for diarrhea
  - Asymptomatic Grade 3 hypophosphatemia is not considered a DLT
  - ≥ Grade 3 hyperglycemia or toxicity solely due to dexamethasone is not considered a DLT (see dose reduction guidelines for dexamethasone in Section 9.3.2)
  - Grade 3 fatigue lasting < 14 days is not considered a DLT
  - ≥ Grade 3 rash attributed specifically to lenalidomide is not a DLT

Hematologic DLT:

- Grade 4 neutropenia: ANC < 0.5×10^9/L lasting ≥ 7 days, despite myeloid growth factor support
- Febrile neutropenia: Any single temperature ≥ 38.3°C or a sustained temperature of ≥ 38.0°C for over 1 hour with ≥ Grade 3 neutropenia (ANC < 1.0×10^9/L)
- Grade 4 thrombocytopenia lasting ≥ 7 days or
- Grade 4 thrombocytopenia lasting < 7 days with ≥ Grade 2 clinically significant bleeding or < 10,000 platelets requiring platelet transfusion, or
- Grade ≥ 3 thrombocytopenia with clinically significant bleeding or requiring platelet transfusion.

Note: Grade 4 anemia will ***not*** be considered a DLT, but should be treated with supportive measures in accordance with institutional guidelines.

9.1.4 SUBJECT REPLACEMENT

In the Phase 1b portion of the study, subjects must meet the following criteria to be considered evaluable for MTD determination during the 4-week DLT evaluation period:

- A minimum of 8 of 10 planned doses of oprozomib must be received on the 5/14 schedule
- A minimum of 7 of 8 planned doses of oprozomib must be received on the 2/7 schedule
- A minimum of 6 of 8 planned doses of dexamethasone must be received
- All 3 planned doses of cyclophosphamide must be received (OCyd combination regimen only)
- A minimum of 17 of 21 planned doses of lenalidomide must be received (ORd combination regimen only)

Subjects not meeting all of the above criteria or assessed as unevaluable will be replaced. Subjects who do not meet the criteria above because of a DLT will be considered DLT-evaluable. Subjects who discontinue study treatment for any reason after Cycle 1 will not be replaced.

Guidelines for withholding study treatment, including treatment delays, reintroduction, and discontinuation, are described in Section 9.3.

9.2 LENALIDOMIDE, CYCLOPHOSPHAMIDE, AND DEXAMETHASONE ADMINISTRATION

9.2.1 LENALIDOMIDE ADMINISTRATION

Lenalidomide will be administered orally at a dose of 25 mg with or without food at investigator and subject discretion, on Days 1 through 21 of each 28-day cycle for a maximum of 24 cycles (approximately 24 months). Subjects may take lenalidomide following oprozomib, however, it is recommended that they take lenalidomide at approximately the same time each day (Refer to Section 9.1.1 for details on oprozomib treatment administration). On days when oprozomib is not administered, subjects should take lenalidomide at approximately the same time of the day for consistency.

9.2.2 CYCLOPHOSPHAMIDE ADMINISTRATION

Cyclophosphamide will be administered orally at 300 mg/m^2 (up to a maximum of 600 mg) with or without food at investigator and subject discretion, on Days 1, 8, and 15 of each 28-day cycle for a maximum of 8 cycles of therapy (approximately 8 months). Subjects may take cyclophosphamide following oprozomib, however it is recommended that they take

cyclophosphamide at approximately the same time each day (Refer to Section 9.1.1 for details on oprozomib treatment administration). On days when oprozomib is not administered, subjects should take cyclophosphamide at approximately the same time of the day for consistency.

9.2.3 DEXAMETHASONE ADMINISTRATION

Dexamethasone will be administered at 20 mg, orally, on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day cycle. On days when both oprozomib and dexamethasone are administered (i.e., on Days 1, 2, 8. 9, 15, 16, 22, and 23), dexamethasone should be taken at least 30 minutes prior to oprozomib.

Note: Dexamethasone will be taken at a dose of 20 mg/day through the first cycle, after which the dose may be decreased to 10 mg/day in subjects > 75 years of age, at the discretion of the investigator. Dexamethasone dosing (premedication and low-dose) as per the schedule above in combination with oprozomib should be continued for subjects who demonstrate a response of stable disease or better for 24 cycles for both the ORd and OCyd treatment regimens. After 24 cycles, this treatment may be continued or tapered at the discretion of the investigator and per institutional guidelines.

9.3 DOSE-MODIFICATION GUIDELINES

The following sections and tables summarize dose modifications for oprozomib, lenalidomide, cyclophosphamide, and dexamethasone to manage possible toxicity. Administration of oprozomib, lenalidomide, or cyclophosphamide will be discontinued in the event of a treatment-related toxicity that, in the opinion of the investigator, warrants permanent discontinuation. Interruption of oprozomib dosing for > 4 weeks for any reason will result in permanent discontinuation of oprozomib. No dose reductions of oprozomib are allowed in Cycle 1. The subject will remain on protocol treatment as long as oprozomib, lenalidomide, or cyclophosphamide is being administered (either alone or in combination with dexamethasone). Monotherapy with dexamethasone is not allowed.
Dose modifications made during the first cycle of treatment for either combination regimen in the Phase 1b portion of this study should be discussed with the Onyx study medical monitor.

Dose reduction levels for oprozomib, lenalidomide, and cyclophosphamide are provided in Table 7, Table 8, and Table 9, respectively.

Table 7 Dose Decrements for Oprozomib (5/14 Schedule, Original Protocol Amendment 1)

Nominal Dose	Reduced Oprozomib Doses	
	Dose -1	Dose -2
Assigned Cohort Dose	Nominal dose – 30 mg	Nominal dose – 60 mg

Table 8 Dose Decrements for Oprozomib (2/7 Schedule, Amendment 2)

Nominal Dose	Reduced Oprozomib Doses	
	Dose -1	Dose -2
Assigned Cohort Dose	Nominal dose – 30 mg	Nominal dose – 60 mg

Table 9 Dose Decrements for Lenalidomide

Nominal Dose	Reduced Lenalidomide Doses		
	Dose -1	Dose -2	Dose -3
25 mg	15 mg	10 mg	5 mg

Note: Dose adjustments should, in general, follow the Revlimid Prescribing Information (Appendix H).

Table 10 Dose Decrements for Cyclophosphamide

Nominal Dose	Reduced Cyclophosphamide Doses	
	Dose -1	Dose -2
300 mg/m^2	200 mg/m^2	100 mg/m^2

Note: Dose adjustments should, in general, follow the Cyclophosphamide Prescribing Information (Appendix I).

Dose-modification guidelines for specific hematologic toxicities are outlined in Section 9.3.1 and for nonhematologic toxicities in Section 9.3.2. In addition to dose reductions,

administration of oprozomib, lenalidomide, and cyclophosphamide may be temporarily interrupted in the event of a treatment-related toxicity, at the investigator's discretion.

If the dose of lenalidomide, cyclophosphamide, or oprozomib is reduced, the reduced dose level will be continued on Day 1 of the next, new cycle. If the reduced dose level is well-tolerated for a complete cycle, the subject may, at the investigator's discretion, be rechallenged with the dose level prior to the reduction at the start of the next cycle.

Dose reduction levels are defined for dexamethasone in Table 11.

Table 11 Dose Decrements for Dexamethasone

Nominal Dose	Reduced Dexamethasone Doses	
	Dose -1	Dose -2
20 mg	12 mg	8 mg
Cycle 2: Age > 75 and nominal dose is 10 mg post-Cycle 1	8 mg	4 mg

Dexamethasone will be permanently discontinued after 2 dose reductions in the event of continued, unacceptable, dexamethasone-related toxicity. At the investigator's discretion, dexamethasone may be tapered prior to complete discontinuation according to institutional practice. The subject may continue on treatment with the other protocol-specified drug(s). Guidelines for dexamethasone dose modifications are summarized in Table 11.

9.3.1 DOSE-MODIFICATION GUIDELINES FOR HEMATOLOGIC TOXICITIES

Dose-modification guidelines for hematologic toxicities are outlined in Table 12.

Table 12 Dose-Modification Guidelines for Oprozomib-, Lenalidomide-, and Cyclophosphamide-related Hematologic Toxicities Post-Cycle 1

Toxicity	Recommended Action[a]		
	Oprozomib	Lenalidomide	Cyclophosphamide
Toxicity on Day 1 of Cycle			
Platelets < 25×10^9/L	Hold dose until recovery to ≥ 25×10^9/L restart at previous dose	Hold dose, follow CBC 3 times per week Hold prophylactic anticoagulation until platelets return to ≥ 30×10^9/L[a], then resume at 1 dose decrement	Hold dose until recovery to ≥ 25×10^9/L restart at 1 dose decrement
ANC < 1.0×10^9/L	Hold dose Add myeloid growth factor[b] With resolution to ≥ 1.0×10^9/L, restart at previous dose	Hold dose Add myeloid growth factor[b] With resolution to ≥ 1.0×10^9/L, restart at previous dose	Hold dose Add myeloid growth factor[b] With resolution to ≥ 1.0×10^9/L, restart at 1 dose decrement
Toxicity on Subsequent Days of Cycle			
Neutropenic fever (ANC < 1.0×10^9/L and single temperature > 38.3°C or temperature > 38.0°C sustained for more than 1 hour)	Hold dose; follow CBC 3 times per week Add myeloid growth factor[b] With resolution of fever and ANC ≥ 1.0×10^9/L, restart at 1 dose decrement		
ANC < 0.75×10^9/L (Grade 3)	Hold dose Add myeloid growth factor[b] With resolution to ≥ 1.0×10^9/L, restart at previous dose	Hold dose; follow CBC 3 times per week Administer myeloid growth factor[b] Resume at full dose when ANC ≥ 1.0×10^9/L (Resume at 1 dose decrement for each subsequent decrease to < 0.75×10^9/L)	Hold dose Add myeloid growth factor[b] With resolution to ≥ 1.0×10^9/L, restart at 1 dose decrement
ANC < 0.5×10^9/L (Grade 4)	Hold dose; follow CBC 3 times per week Add myeloid growth factor[b] Resume at full dose if ANC rises to ≥ 0.5×10^9/L within 7 days Resume at 1 dose decrement if ANC returns to ≥ 0.5×10^9/L after ≥ 7 days.		Hold dose; follow CBC 3 times per week Add myeloid growth factor[b] When ANC ≥ 1.0×10^9/L, resume at 1 dose decrement

Table 12 Dose-Modification Guidelines for Oprozomib-, Lenalidomide-, and Cyclophosphamide-Related Hematologic Toxicities Post-Cycle 1 (cont'd)

Toxicity	Recommended Action[a]		
	Oprozomib	Lenalidomide	Cyclophosphamide
Toxicity on Subsequent Days of Cycle (continued)			
Platelets 25 to < 50 × 10^9/L without ≥ Grade 2 bleeding/hemorrhage	Full dose	Hold dose, follow CBC weekly Hold prophylactic anticoagulation until platelets return to ≥ 30 × 10^9/L. When platelets reach 50 x 10^9/L, then resume at 1 dose decrement.	Hold dose until platelets return to ≥ 50 × 10^9/L, then resume at 1 dose decrement
Platelets 25 to < 50 × 10^9/L with ≥ Grade 2 bleeding/hemorrhage	Hold dose until platelets return to ≥ 50 × 10^9/L and/or bleeding is controlled, then resume at 1 dose decrement	Hold dose, follow CBC weekly Hold prophylactic anticoagulation until platelets return to ≥ 30 × 10^9/L. When platelets reach 50 × 10^9/L, then resume at 1 dose decrement.	Hold dose until platelets return to ≥ 50 × 10^9/L and/or bleeding is controlled, then resume at 1 dose decrement
Platelets < 25 × 10^9/L or any degree of thrombocytopenia with ≥ Grade 2 bleeding/hemorrhage	Hold dose until platelets return to ≥ 50 × 10^9/L and/or bleeding is controlled, then resume at 1 dose decrement	Hold dose, follow CBC weekly Hold prophylactic anticoagulation until platelets return to ≥ 30 × 10^9/L. When platelets reach 50 × 10^9/L, then resume at 1 dose decrement	Hold dose until platelets return to ≥ 50 × 10^9/L and/or bleeding is controlled, then resume at 1 dose decrement

ANC = absolute neutrophil count; CBC = complete blood count.

[a] The maximum allowed dose interruption is 4 weeks.

[b] Myeloid growth factors include filgrastim or sargramostim.

9.3.2 DOSE-MODIFICATION GUIDELINES FOR NONHEMATOLOGIC TOXICITIES

Dose-modification guidelines for nonhematologic toxicities are outlined below in Table 13.

Table 13 Dose-Modification Guidelines for Oprozomib-, Lenalidomide-, and Cyclophosphamide-Related Nonhematologic Toxicities Post-Cycle 1

Nonhematologic Toxicities, All Days and Cycles				
		Recommended Action[a]		
Symptom	Findings	Oprozomib	Lenalidomide	Cyclophosphamide
Tumor Lysis Syndrome (TLS)	Generally recognized as 3 or more of the following categories: (1) increase in creatinine, uric acid, or phosphate of ≥ 50% (2) increase in potassium of ≥ 30% (3) decrease in calcium of ≥ 20%, or (4) increase in LDH ≥ 2-fold from baseline	Hold both oprozomib and lenalidomide/cyclophosphamide until all abnormalities in serum chemistries have resolved to baseline; resume at full doses. See Section 9.8.1.2 for specific prophylaxis and treatment guidelines for TLS.		
Neuropathy	Grade 2 neuropathy with pain or > Grade 3 neuropathy	Hold dose until toxicity resolve to ≤ Grade 1 or has returned to baseline. Resume study drug at 1 dose decrement.	Hold dose until toxicity resolve to ≤ Grade 1 or has returned to baseline. Resume study drug at 1 dose decrement.	Full dose
Infection	Grade 3 or 4	Hold both oprozomib and lenalidomide/cyclophosphamide until systemic treatment for infection complete. If ANC > 1.0×10^9/L, resume both drugs at full dose. If ANC < 1.0×10^9/L, follow hematologic toxicities dose reduction guidelines.		
Nausea, vomiting, diarrhea, or constipation	> Grade 3 without optimal supportive care as defined by use of both a $5HT_3$ antagonist and antiemetic (aprepitant)	Continue full-dose therapy. Institute optimal supportive care.		
	> Grade 3 with optimal supportive care as defined by use of both a $5HT_3$ antagonist and antiemetic (aprepitant)	Oprozomib-related: Hold dose until toxicity resolve to < Grade 1 or has returned to baseline. Resume study drug at 1 dose decrement.	Hold dose until toxicity resolve to < Grade 1 or has returned to baseline. Resume study drug at full dose. If recurs after oprozomib dose reduction, hold dose until toxicity resolve to < Grade 1 or has returned to baseline. Resume study drug at 1 dose decrement.	
Fatigue	Grade 3 fatigue lasting < 14 days	Full dose	If recurs after oprozomib dose reduction, hold dose until toxicity resolves to < Grade 1 or has returned to baseline. Resume study drug at 1 dose decrement.	Full dose
	Grade 3 fatigue lasting >14 days	Hold dose until toxicity resolves to < Grade 1 or has returned to baseline. Resume study drug at 1 dose decrement.		

Table 13 Dose-Modification Guidelines for Oprozomib-, Lenalidomide-, and Cyclophosphamide-Related Nonhematologic Toxicities Post-Cycle 1 (cont'd)

Nonhematologic Toxicities, All Days and Cycles				
		Recommended Action[a]		
Symptom	Findings	Oprozomib	Lenalidomide	Cyclophosphamide
Renal Dysfunction	CrCl 30 to < 50 mL/min (Grade 2)	Full dose	Reduce dose to 10 mg once daily.	Full dose
	CrCl 15 to < 30 mL/min (Grade 3)	Hold dose. When CrCl recovers to ≤ Grade 2, resume at 1 dose decrement.	Hold dose. When CrCl recovers to ≤ Grade 2, resume dose at 1 dose decrement. If Grade 3 reduction in CrCl reappears, then hold dose until CrCl recovers to ≤ Grade 2 and reduce dose to 15 mg every 48 hours.	Hold dose until resolution to ≤ Grade 2 or baseline, then resume at full dose
	CrCl 0 to <15 mL/min (Grade 4)	Discontinue	Discontinue	Discontinue
Elevation in Liver Function Tests (LFTs)	≥ Grade 3 (AST, ALT, or total bilirubin)[b]	Hold dose until resolves to baseline. Resume at one dose decrement.	Hold dose until resolution, then resume at full dose	Hold dose until resolution to ≤ Grade 1 or baseline, then resume at full dose
Hemorrhagic Cystitis	Grade 1 or 2	Continue full dose	Continue full dose	Hold dose until resolution, then resume at 1 dose decrement
	Grade 3 or 4	Continue full dose	Continue full dose	Discontinue; do not resume.
Other Nonhematologic Toxicity	Assessed as cyclophosphamide-related and ≥ Grade 3	Full dose	Not Applicable	Hold cyclophosphamide dose Follow at least weekly If the toxicity resolves to ≤ Grade 1 or baseline, restart at 1 dose decrement
Other Nonhematologic Toxicity	Assessed as oprozomib-related and ≥ Grade 3	Hold oprozomib dose until toxicity resolves to ≤ Grade 1 or baseline; restart at 1 dose decrement	Full dose	Full dose
Other Nonhematologic Toxicity	Assessed as lenalidomide-related and ≥ Grade 3	Full dose	Hold lenalidomide dose until toxicity resolves to ≤ Grade 1 or baseline; restart at 1 dose decrement	No Applicable
Grades 1 or 2 GI hemorrhage	Assessed as oprozomib-related	DELAY until Grade 0 DECREASE one dose level for Grade 2	Hold lenalidomide dose until toxicity resolves to ≤ Grade 1 or baseline	Hold lenalidomide dose until toxicity resolves to ≤ Grade 1 or baseline

Table 13 Dose-Modification Guidelines for Oprozomib-, Lenalidomide-, and Cyclophosphamide-Related Nonhematologic Toxicities Post-Cycle 1 (cont'd)

Nonhematologic Toxicities, All Days and Cycles				
		Recommended Action[a]		
Symptom	Findings	Oprozomib	Lenalidomide	Cyclophosphamide
Grades 3 or 4 GI Hemorrhage[c]	Assessed as oprozomib-related	Discontinue.	Full dose when AE resolves to < Grade 2 at physician discretion.	Full dose when AE resolves to < Grade 2 at physician discretion.

5-HT_3 = 5-hydroxytryptamine type-3; adverse events = AE; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CrCl = creatinine clearance; eCRF = electronic case report form; GI = gastrointestinal; LDH = lactate dehydrogenase; LFTs = liver function tests; TLS = tumor lysis syndrome; ULN = upper limit of normal

[a] The maximum allowed dose interruption is 4 weeks.

[b] If AST, or ALT is ≥ 3 × ULN, the "evaluation of treatment emergent liver abnormalities" eCRF should be completed.

[c] Subjects who develop Grade 4 GI hemorrhage should not be rechallenged with oprozomib. Oprozomib should be permanently discontinued. Endoscopy should be strongly considered for any subject with GI hemorrhage.

Table 14 Treatment Guidelines for Dexamethasone-related Toxicity

Body System	Symptom	Recommended Action
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1 or 2 (requiring medical management)	Treat with H_2 blockers, sucralfate, and/or a proton pump inhibitor such as omeprazole (if not already on proton pump inhibitor therapy). If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
Gastrointestinal	> Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms are adequately controlled. Restart dexamethasone at 1 dose decrement along with concurrent therapy with H_2 blockers, sucralfate, and/or a proton pump inhibitor such as omeprazole. If symptoms persist despite above measures, discontinue dexamethasone permanently.
Gastrointestinal	Acute pancreatitis	Discontinue dexamethasone permanently.
Cardiovascular	Edema > Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and restart dexamethasone at 1 dose decrement; if edema persists despite above measures, decrease dose another level. Discontinue dexamethasone permanently if symptoms persist despite second reduction.
Neurology	Confusion or mood alteration > Grade 2 (interfering with function ± interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Restart dexamethasone at 1 dose decrement. If symptoms persist despite above measures, reduce by another dose decrement.
Musculoskeletal	Muscle weakness > Grade 2 (symptomatic and interfering with function ± interfering with activities of daily living)	Decrease dexamethasone by 1 dose level. If weakness persists, decrease dose by 1 more dose level. Discontinue dexamethasone permanently if symptoms persist.
Metabolic	Hyperglycemia ≥ Grade 3	Treatment with insulin or other hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by 1 dose level until levels are satisfactory.
All Other	Other nonhematologic toxicity ≥ Grade 3 felt related to dexamethasone	Hold dexamethasone dose. Resume at 1 dose decrement when toxicity has resolved to Grade 2 or less or to baseline. If toxicity recurs, discontinue dexamethasone permanently.

9.3.3 CONDITIONS NOT REQUIRING DOSE REDUCTION

The following conditions are exceptions to the above-described dose-modification guidelines. Oprozomib, lenalidomide, cyclophosphamide, and dexamethasone do not need to be held in the following cases:

- Grade 3 nausea, vomiting, or diarrhea (unless persisting more than 3 days with optimal treatment with antiemetics or antidiarrheal agents)
- Grade 3 fatigue (unless persisting for > 14 days)
- Alopecia
- Asymptomatic Grade 3 hypophosphatemia lasting less than 24 hours
- Grade 3 dexamethasone-related hyperglycemia

9.4 DOSE DELAYS

Dosing delays are not permitted in Cycle 1. If the initiation of Cycle 2 or later must be adjusted for reasons unrelated to toxicity (e.g., holidays or subject requests), the cycle should be started no later than 7 days after the originally scheduled next cycle. Schedule adjustments can only be made at the beginning of each cycle and cannot be made midcycle.

9.5 INTERRUPTION OF TREATMENT FOR HEMATOPOIETIC STEM CELL HARVEST

Subjects who complete at least 4 cycles of study treatment and achieve confirmed response (i.e., a PR, VGPR, CR, or sCR may, after discussion with the Onyx study medical monitor), suspend study treatment for up to 6 weeks to undergo a hematopoietic stem cell harvest. See Section 4.1 for additional information.

9.6 MISSED DOSES

Subjects in the Phase 1b portion of the study may not miss any of the planned doses of cyclophosphamide, or more than 4 planned doses of lenalidomide, or 2 planned doses of oprozomib for the 5/14 schedule or 1 planned dose of oprozomib for the 2/7 schedule, or 2 planned doses of dexamethasone in Cycle 1. Subjects who miss more doses than allowed during Cycle 1 will not be evaluable and will be replaced. A missed dose occurs when the subject does not take the dose on the planned calendar day. The missed dose will not be made

up. If a subject misses more than 28 consecutive days after completing Cycle 1 for reasons other than a hematopoietic stem cell harvest, the subject will permanently discontinue study treatment (see Section 9.3 for interrupted oprozomib dosing > 4 weeks).

9.7 SAFETY GUIDANCE FOR INVESTIGATORS

Additional guidance regarding nonhematologic toxicities and dosing actions is as follows:

- Nontreatment-related events: If the toxicity resolves to ≤ Grade 1 or baseline and the toxicity is not treatment-related, oprozomib may be restarted at the same dose level.
- Subjects who develop Grade 3 or 4 GI hemorrhage should not be rechallenged with oprozomib. Oprozomib should be permanently discontinued. Endoscopy should be strongly considered for any subject with GI hemorrhage.
- Syncope, hypotension (including orthostatic hypotension), and dehydration have been reported for subjects treated with oprozomib. Blood pressure monitoring as detailed in Appendix A and Appendix B is required.
- Tumor lysis syndrome has been reported for subjects treated with oprozomib. Hydration and allopurinol prophylaxis is recommended for renally impaired subjects and those with a high tumor burden. For specific recommendations, see Section 9.8.1.

See Section 9.3 for additional dose adjustment guidelines required for specific hematologic and nonhematologic toxicities.

9.7.1 LENALIDOMIDE

See lenalidomide prescribing information for additional details (Appendix H).

9.7.2 CYCLOPHOSPHAMIDE

See cyclophosphamide prescribing information for additional details (Appendix I)

9.7.3 DEXAMETHASONE

See dexamethasone prescribing information for additional details (Appendix J).

9.8 CONCOMITANT MEDICATIONS

A concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. All concomitant medications must be recorded on the subject's electronic case report form (eCRF) from informed consent to 30 days following the

last dose of study drug. Blood or blood products are not considered concomitant medications and must be recorded on the appropriate eCRF.

In vitro tests indicating that the time-dependent inhibitory effect of oprozomib on human cytochrome P450 3A (CYP3A) is weak (K_{inact} to K_I was only 1.4 mL/min/mcmol). However, concomitant use of drugs that are CYP3A substrates with narrow therapeutic range should be avoided within 2 weeks of Day 1 of Cycle 1 and during treatment with oprozomib as a precaution. Cytochrome P450 3A substrates with narrow therapeutic range refer to drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of CYP3A inhibitors may lead to serious safety concerns. Examples of sensitive CYP3A substrates with narrow therapeutic range can be found in Appendix E. Investigators should consider switching to an alternative drug, or be alert to the need for dose adjustment.

9.8.1 REQUIRED CONCOMITANT MEDICATIONS

Required medications are: TLS prophylaxis, proton pump inhibitors such as omeprazole or lansoprazole, anti-thrombotic agents for those on the ORd arm such as aspirin (or other anticoagulant or antiplatelet medication such as clopidogrel bisulfate, low-molecular-weight heparin, or warfarin) while taking lenalidomide.

Supportive medications for nausea, vomiting and diarrhea are strongly recommended; details are provided in Section 9.8.2.

9.8.1.1 Acid-related Medications

Lansoprazole or another oral proton-pump inhibitor is required (unless subject has intolerance or hypersensitivity) for the duration of treatment to prevent peptic disease or other GI toxicities.

9.8.1.2 Tumor Lysis Syndrome

For subjects at risk for TLS (Sezer 2006), the following are required:

Monitoring and Prophylaxis Guidelines: Oral hydration of 1.5 to 2 liters per 24 hours should be instituted in all subjects 24 to 48 hours prior to initiation of therapy in every cycle,

and continued throughout days of dosing. Premedication with allopurinol or other approved uric acid lowering agents is highly recommended for subjects with high tumor burden (i.e., for multiple myeloma: Durie-Salmon or ISS Stage II/III or rapidly increasing M-protein or light chains) or compromised renal function (CrCl < 50 cc/min). These subjects may be at elevated risk for TLS and should be closely monitored. Uric acid levels should be normalized prior to initiation of treatment, if appropriate.

Subjects with laboratory abnormalities prior to dosing that are consistent with lysis of tumor cells should not receive the scheduled dose prior to institution of the aforementioned preventative measures.

TLS Laboratory Abnormalities: Subjects with laboratory abnormalities prior to dosing that are consistent with lysis of tumor cells (e.g., as defined by increases of 3 of the 4 categories: [1] a 2-fold increase of lactate dehydrogenase [LDH] above the ULN, [2] increases in serum creatinine, uric acid, or phosphorus > 50% over baseline, [3] potassium > 30% above the ULN; or [4] decreases from baseline of calcium > 20% in the absence of concomitant bisphosphonate therapy) (Sezer 2006) should not receive the scheduled dose prior to institution of the aforementioned preventative measures.

Treatment Guidelines: If TLS occurs, cardiac rhythm, fluid and serial laboratory monitoring should be instituted. Correction of electrolyte abnormalities, monitoring of renal function and fluid balance, administration of therapeutic and supportive care, including dialysis, should be done as clinically indicated. In the setting of TLS, oprozomib treatment will be interrupted until resolution of all clinical and laboratory abnormalities consistent with TLS. Once TLS has resolved, subject can resume treatment at the initial dose level.

All cases of TLS must be reported to Onyx Therapeutics as an SAE as outlined in the protocol.

9.8.1.3 Anti-thrombotic Agents

Antithrombitic agents are required for those on the ORd arm such as aspirin (or other anticoagulant or antiplatelet medication such as clopidogrel bisulfate, low-molecular-weight

heparin, or warfarin) while taking lenalidomide is required (refer to the Revlimid Prescribing Information, Appendix H for more information).

9.8.2 OPTIONAL AND ALLOWED CONCOMITANT MEDICATIONS

At least 24 hours prior to Cycle 1 Day 1 and for the duration of the study, the following medications are strongly recommended per published guidelines and institutional standards of care (Bhatt 2008; Bladé 2011; Lonial 2005; Palumbo 2011; Zangari 2008).

- Herpes zoster prophylaxis, with acyclovir, valacyclovir, or equivalent antiviral while taking oprozomib
- Bisphosphonate therapy such as pamidronate or zoledronic acid for skeletal prophylaxis

9.8.2.1 Antinausea and Antiemetics

It is strongly recommended that subjects be premedicated with a 5-HT_3 inhibitor, such as ondansetron or granisetron, at the first onset of nausea and/or vomiting prior to oprozomib dosing each day and throughout the day as needed to prevent nausea and vomiting. If nausea/vomiting at any grade persists, aprepitant, is recommended if needed. Additional antiemetics may be used if needed.

9.8.2.2 Antidiarrheals

Grade 1 diarrhea is defined as an increase over baseline of < 4 stools per day or mild increase in ostomy output compared with baseline. For subjects developing any grade of diarrhea, Imodium is strongly recommended at the onset of symptoms. For subjects with persistent diarrhea despite the use of Imodium, the addition of Lomotil is strongly recommended. Other antidiarrheal agents may be used if necessary; a work-up for other etiologies is suggested if diarrhea continues despite the prior 2 agents.

9.8.2.3 Antihypertensives

Dehydration, hypotension and syncope have been reported in subjects treated with oprozomib monotherapy and combination therapy. It is strongly recommended that subjects utilizing antihypertensives have their volume status, blood pressure, and antihypertensive therapy dosing monitored closely while on protocol directed therapy (see Appendix A and Appendix B).

9.8.3 EXCLUDED CONCOMITANT MEDICATIONS

Concurrent therapy with an approved or investigative anticancer therapeutic is not allowed.

During the study, concurrent glucocorticoid therapy (in addition to dexamethasone) is only permitted to treat a concurrent medical condition (e.g., asthma, inflammatory bowel disease, or as an antiemetic, etc.) after consultation with the Onyx study medical monitor.

10 STUDY PROCEDURES

All protocol-required tests and observations, along with their chronology, are outlined in the Schedule of Assessments (Appendix A and Appendix B). On-treatment tests and observations are summarized below.

10.1 STUDY-SPECIFIC PROCEDURES

10.1.1 VITAL SIGNS

Vital signs measurements include blood pressure, pulse rate, and temperature. Orthostatic blood pressure (BP) should be assessed for subjects with evidence of dehydration. At the investigator's discretion, vital signs monitoring may be extended beyond the time periods specified in the Schedules of Assessments (Appendix A and Appendix B).

10.1.2 PHYSICAL EXAMINATION

A complete physical examination will include examination of the skin, head and neck, chest (heart and lungs), abdomen, extremities, and a brief neurological exam including an assessment for peripheral neuropathy (Appendix G). Rectal and pelvic examinations are optional. Eastern Cooperative Oncology Group Performance Status (assessed at the time of the physical exam) will be collected (Appendix C).

A limited physical examination will include an examination of the chest (heart and lungs), and abdomen, with additional examinations as clinically indicated or directed by AEs.

10.1.3 ELECTROCARDIOGRAM

Twelve-lead electrocardiograms (ECGs) including corrected QT interval (QTc) will be performed locally.

10.2 LABORATORY EVALUATIONS FOR SAFETY

The schedule for laboratory evaluations for safety is outlined in Appendix A and Appendix B. The laboratory tests included in the full chemistry panel are defined in Table 15.

Table 15 Full Chemistry Panels

Full Chemistry Panel
Sodium
Potassium
Calcium
Alkaline phosphatase
Blood urea nitrogen
Uric acid
Lactate dehydrogenase
Creatinine
Chloride
Bicarbonate
Glucose
Total protein
Albumin
Total bilirubin
Alanine aminotransferase
Aspartate aminotransferase
Phosphorous
Magnesium
Calculate or measure creatinine clearance rate

The complete blood count (CBC) with differential includes the following: hemoglobin, hematocrit, white blood cell (WBC) count with complete manual or automated differential (total neutrophils, lymphocytes, monocytes, eosinophils, basophils; reported as absolute counts), RBC count, and platelet count.

Coagulation tests include the following: prothrombin time, activated partial thromboplastin time, and international normalized ratio.

An assessment of platelet adherence, activation, aggregation, and interaction with coagulation factors will be conducted utilizing the platelet function analyzer (PFA-100) and flow cytometry. These assessments will be conducted in a subgroup of subjects enrolled in the OCyd arm of the Phase 1 or Phase 2 trial. See Section 10.6 for details of the assessment and eligible subject requisites. See Appendix A and Appendix B for the schedule of these assessments.

For both treatment regimens (ORd and OCyd), a serum pregnancy test must be performed within 1 day prior to dosing for females of childbearing potential only. Results must be negative prior to dosing.

10.3 DISEASE RESPONSE ASSESSMENTS

The schedule of disease assessments is provided in Appendix A and Appendix B. Disease response will be assessed by the investigator. Disease response assessments will be performed at the end of every 4-week cycle for 24 cycles of ORd or OCyd treatment, and will continue every 8 weeks thereafter, until confirmed progressive disease (PD) (see Figure 1, Figure 2, and Figure 4 for details on the duration of cyclophosphamide dosing) or the start of alternative, nonprotocol antimyeloma therapy. Response assessment will be according to the International Myeloma Working Group - Uniform Response Criteria (IMWG-URC) (Appendix F).

10.3.1 TUMOR RESPONSE ASSESSMENT

The following confirmation assessments are required for all response categories (sCR, CR, VGPR, and PR; refer to definitions in Appendix F):

- All response categories require 2 consecutive assessments made at any time before initiation of any new therapy
- All response categories require no evidence of progression including new bone lesions if radiographic studies were performed
- Confirmation of CR or sCR requires bone marrow biopsy or aspirate slides (a confirmatory bone marrow sample is not required)
- Extramedullary plasmacytoma evaluation (if present at screening)

10.4 PHARMACOKINETIC AND PHARMACODYNAMIC MEASUREMENTS

A sparse sampling strategy will be employed for PK sample collection from all subjects for both study phases. Blood samples for determination of plasma concentrations of oprozomib and metabolite(s) will be collected from subjects at 2 postdose time points in Cycle 1 Day 1, and 1 predose and 2 postdose time points on Cycle 3 Day 1 and Cycle 5 Day 1. Specific sampling times and volumes are detailed in the Laboratory Manual. On the PK collection days, dosing of oprozomib in relation to the meal intake (within 2 hours before and 1 hour after dose) will be recorded. Samples may also be used for biomarker assessment. Population-based PK analyses will be performed for oprozomib, and may include its metabolite(s). The following PK parameters may be calculated: apparent clearance and volume of distribution.

Blood samples for the measurement of proteasome activity in whole blood and peripheral blood mononuclear cells (PBMCs) will be collected for all subjects in the Phase 1b portion of the study predose and 2 at postdose time points on Cycle 1 Day 1 and Cycle 2 Day 1, and predose on Cycle 1 Day 2. Please refer to the Laboratory Manual for collection times and volumes, and processing and shipping of PDn samples. A fluorogenic substrate assay or enzyme-linked immunosorbent assay will be used to measure proteasome activity in whole blood and PBMCs.

10.5 GENOMIC EVALUATIONS

Analysis of genomic biomarkers that may predict for response and resistance following treatment with proteasome inhibitors will be performed on all subjects from both phases of the study who consent to optional genomic biomarker analysis. Analysis of biomarkers will include analysis of saliva, blood, and a bone marrow aspirate sample at Baseline, prior to dosing on Cycle 1 Day 1. Additional bone marrow samples for biomarkers may be collected at the End of Study Treatment visit from all subjects who consent. End of Study Treatment is defined as at disease progression or the end of protocol-defined therapy if end of treatment is due to PD.

Bone marrow samples will be collected at Baseline, prior to dosing on Cycle 1 Day 1 for isolation of $CD138^{+}$ cells. One bone marrow aspirate can be split and used for both a) the

central verification of diagnosis and FISH studies (clinical assessment), and b) $CD138^+$ cell isolation (biomarker assessment). Saliva and a blood sample will also be collected at Baseline and will serve as a source of normal deoxyribonucleic acid (DNA) for determination of tumor-specific genomic alterations. In addition, a bone marrow aspirate will be collected at disease progression for isolation of $CD138^+$ cells.

Whole genome sequencing (WGS), whole exome sequencing (WES), whole transcriptome sequencing (RNA-Seq), and/or other forms of nucleic acid and protein quantification will be conducted on isolated tumor ($CD138^+$) cells from bone marrow samples taken at Basline and disease progression. In addition, WGS or WES will be performed on a normal tissue sample (e.g., saliva or $CD3^+$ T-cells isolated PBMCs) in order to distinguish germline from somatic mutations in tumor cell samples. Data will be analyzed to examine specific hypotheses about whether drug response is related to alterations in genes regulated by or involved in immunoglobulin production and protein homeostasis, i.e., IGH, as well as in genes regulated by or involved in the activation of nuclear factor kappa light chain enhancer of activated B cells (NF-Kappa B) transcription factors.

Immunoglobulin levels in tumor cells will be quantified by qPCR, or immunocytochemistry, and/or other protein or gene expression quantification methods. These data will also be used to derive new hypotheses about mechanisms of drug response, resistance and safety.

The schedule for genomic sampling is outlined in Appendix A and Appendix B.

10.6 PLATELET FUNCTION ASSESSMENT

Platelet function assessments will be conducted in the 10 to 20 subjects enrolled in the OCyd arm for whom the platelet function tests below may be performed. Assessments of platelet adherence, activation, aggregation, and interaction with coagulation factors will be conducted utilizing the PFA-100 (N = 10).

Subjects participating in this study component:

- May not be treated with antiplatelet agents, aspirin or nonsteroidal anti-inflammatory drugs in the 2 weeks prior to assessment.
- Must have a screening and pretest value for platelets of $\geq 100{,}000/mm^3$.

- Must have hematocrit of 28%

The PFA-100 test will be conducted according to the sites' SOPs on Cycle 1 Day 1 (C1D1) (prior to protocol mandated dosing), Cycle 1 Day 2 (C1D2), Cycle 4 Day 1 (C4D1), and 30 days after the completion of oprozomib therapy.

11 STUDY TREATMENT DISCONTINUATION AND DISCONTINUATION FROM THE STUDY

11.1 STUDY TREATMENT DISCONTINUATION

Subjects will be monitored for AEs for 30 days after the last dose of study treatment (i.e., oprozomib, lenalidomide/cyclophosphamide or dexamethasone).

Subjects may discontinue study treatment for the following reasons:

- Disease progression
- Unacceptable toxicity
- Noncompliance with study procedures
- Treatment with prohibited concomitant medications; details provided in Section 9.8.3
- Intercurrent illness that interferes with study assessments
- Female subject who becomes pregnant, in which case treatment must be immediately discontinued

Onyx Therapeutics, or designee must be notified within 24 hours if a subject discontinues all study treatment.

If the reason for discontinuation is the occurrence of an AE, the subject will be followed by the investigator until such event(s) resolve, stabilize, and according to the investigator's judgment, there is no need for further follow-up. Subjects who discontinue study treatment for reasons other than disease progression may continue on study until disease progression or death. The reason for discontinuation from study treatment will be documented on the eCRF.

In the Phase 1b portion of the study, additional subjects may be enrolled to account for subjects who have not had adequate safety evaluations.

11.1.1 ASSESSMENTS AT END OF STUDY TREATMENT OR EARLY DISCONTINUATION

For subjects who discontinue treatment before PD occurs (such as for an AE, noncompliance, etc.), disease response assessments will be performed every 4 weeks during the first 24 months of the study and every 8 weeks thereafter, until confirmed PD, or the start of alternative, nonprotocol antimyeloma therapy.

11.1.2 FOLLOW-UP FOR SUBJECTS WHO END STUDY TREATMENT WITHOUT DOCUMENTED PROGRESSIVE DISEASE

Subjects who have ended study therapy without evidence of progression enter active follow-up after completing their End of Study Treatment visit. They will be followed for progression-free survival.

- Disease response assessments will be performed every 4 weeks through 24 months post C1D1, and then every 8 weeks thereafter, until progression or initiation of new antimyeloma therapy whichever occurs first
- Subjects who have consented to evaluate their genomic biomarkers and End of Study Treatment prior to progression will have a bone marrow aspirate collected for genomic analysis at the time of progression or the start of new antimyeloma therapy, whichever comes first

Active follow-up will continue until the subject has withdrawn consent for further participation, is lost to follow-up, has died, or the sponsor makes a decision to close the study.

11.2 ASSESSMENTS AT END OF STUDY TREATMENT OR EARLY DISCONTINUATION

For subjects who discontinue treatment before PD occurs (such as for an AE, noncompliance, etc.), disease response assessments will be performed every 4 weeks during the first 24 months of the study and every 8 weeks thereafter, until confirmed PD, or the start of alternative, nonprotocol antimyeloma therapy.

12 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

12.1 ADVERSE EVENT REPORTING

12.1.1 DEFINITIONS

An AE is any untoward medical occurrence in a study subject administered an investigational product(s) regardless of the causal relationship with treatment.

An AE, therefore, can be any unfavorable and unintended sign (including laboratory finding), symptom or disease temporally associated with participation in an investigational study, whether or not considered drug-related. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the subject signs the ICF for participation is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction. All reported AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA).

Whenever possible, the NCI-CTCAE, Version 4.03 should be used to describe the event and for assessing the severity of AEs. For AEs not adequately addressed in the NCI-CTCAE Version 4.03, Table 16 below should be used.

Table 16 Toxicity Grading for Adverse Events not Covered in the NCI-CTCAE (Version 4.03)

Severity	Description
GRADE 1 – Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
GRADE 2 – Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
GRADE 3 – Severe	Medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
GRADE 4 – Life-threatening	Life-threatening consequences; urgent intervention indicated
GRADE 5 – Fatal	Death related to AE

AE = Adverse event; NCI CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the current IB or prescribing information for a marketed compound or is not listed at the specificity or severity that has been observed. Adverse events or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with particular study drug are considered "unexpected." For example, an event more specific or more severe than described in the IB would be considered "unexpected." Any condition, laboratory abnormality, or physical finding with an onset date prior to the subject signing the ICF is considered to be pre-existing in nature and part of the subject's medical history.

Abnormal laboratory findings should be reported as AEs if medical intervention or corrective action (e.g., transfusions, initiation of antibiotics or other treatment regimens, hydration, study drug placed on hold) is required or the event is deemed clinically significant by the treating physician.

12.2 CAUSALITY

A suspected adverse reaction means any AE for which there is reasonable possibility that the study drug caused the AE. "Reasonable possibility" means that there is evidence to suggest a causal relationship between the drug and the AE. An adverse reaction means any AE caused by a drug. The relationship of the AE to the study drug should be assessed using the following criteria:

YES: The event is suspected to be related if:

- There is a clinically plausible time sequence between the AE onset and administration of study treatment; and/or
- There is a biologically plausible mechanism for the study treatment to cause or contribute to the AE; and/or
- The event improves or diminishes upon withdrawal of the study drug without the initiation of any specific treatment for the event (dechallenge) and/or recurs or worsens with rechallenge (when clinically feasible); and/or
- The AE cannot be reasonably attributed to concurrent or underlying illness, other drugs, or procedures.

NO: The event is not suspected to be related if:

- The AE is more likely to be explained by the subject's clinical state, underlying disease, concomitant medical, study or nonstudy procedure; and/or
- The time occurrence of the AE is not reasonably related to administration of study treatment; and/or
- The event is not related to the investigational product(s)

In the event of a possible drug-related AE, the investigator should, to the best of his/her ability assess its relationship to each of the study drugs: oprozomib, lenalidomide, cyclophosphamide, and dexamethasone.

12.3 ADVERSE EVENTS REPORTING PROCEDURES

12.3.1 GENERAL

All AEs (e.g., any new event or worsening in severity or frequency of a pre-existing condition or laboratory finding) with an onset date after the subject signs the informed consent for participation in the clinical trial must be promptly documented on the AE eCRF via the electronic data capture (EDC) system. Details of the event must include severity, relationship to study drug(s), duration, action taken, and outcome. Whenever possible, reporting specific diagnosis is preferred when reporting AEs in the AE eCRF rather than reporting individual signs and symptoms.

All AEs will be collected from the time the subject signs the informed consent through 30 days after receiving the last dose of study drug(s). If initiation of new anticancer therapy occurs within 30 days following the last dose of study drug(s), the date of new anticancer therapy will be recorded on the appropriate eCRF. In addition, the investigator should report any AEs that may occur after this time period which are assessed to have a reasonable possibility of being associated with study drug. If the subject discontinues participation in the study prior to receiving study drug, AEs will not be reported through the End of Study Treatment visit as the subject will not be completing the End of Study Treatment visit.

All AE severity changes will be recorded on the AE CRF as separate events.

All AEs that are considered related to study drug and all SAEs regardless of relationship to study drug, must be followed to resolution or stabilization if improvement is not expected.

AEs which completely resolve and then recur should be recorded as a new AE. For subjects who complete the End of Study Treatment visit less than 30 days following the last dose of study drug, a follow-up of ongoing AEs should be attempted by telephone and documented in the subject's source file. Adverse events continuing at 30 days after the last dose of study treatment should have a comment in the source file by the investigator that the event has stabilized or is not expected to improve.

The investigator is responsible for evaluating all AEs, obtaining supporting source documents, and determining that documentation of the event is adequate. The investigator may delegate these duties to subinvestigators and must ensure that these subinvestigators are qualified to perform these duties under the supervision of the investigator and that they are listed on the Food and Drug Administration (FDA) Form 1572.

12.3.2 DISEASE PROGRESSION

Signs and symptoms related to disease progression (e.g., pathologic fracture in a subject with progressive multiple myeloma) should be reported in the appropriate case report form as an AE or as an SAE (if the event in question meets the criteria for seriousness). Verbatim terms such as "disease progression", "progressive disease", etc., should not be reported as AEs or SAEs unless the investigator considers the progression to be atypical and/or accelerated.

Similarly, deaths occurring as a result of disease progression or until 30 days after the last dose of study drug should be reported on the eCRF intended to capture death information and should not be reported as SAEs. In cases of clinical deterioration due to the primary hematologic malignancy, every effort should be made to document disease progression in accordance with IMWG-URC (Appendix F).

12.4 LONG-TERM FOLLOW-UP

After completion of the End-of-Study-Treatment visit, subjects who have ended study therapy prior to progression enter long-term follow-up. They will be followed for progression-free survival.

- Disease response assessments will be performed every 4 weeks through 24 months post C1D1, and then every 8 weeks thereafter, until progression or initiation of next therapy, whichever occurs first.
- Subjects who have consented to evaluate their genomic biomarkers and End of Study Treatment prior to progression will have a bone marrow aspirate collected for genomic analysis at the time of progression or the start of new antimyeloma therapy, whichever comes first.

Long-term follow-up will continue until the subject has withdrawn consent for further participation, is lost to follow-up, has died, or the sponsor makes a decision to close the study.

12.5 SERIOUS ADVERSE EVENTS DEFINITIONS

An SAE is an AE that meets 1 or more of the following criteria:

- Death
- Life-threatening experience defined as any adverse experience that places the subject, in the view of the sponsor or investigator, at immediate risk of death at the time of occurrence (i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death)
- Requires inpatient hospitalization or prolongation of an existing hospitalization (except scheduled hospitalizations for a nonacute, unrelated cause such as elective surgery)
- Results in persistent or significant disability/incapacity (i.e., substantial disruption in a subject's ability to conduct normal activities of daily living)
- Is a congenital anomaly birth defect in the offspring of an exposed female subject or offspring of a female partner of a male subject
- Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, jeopardizes the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.

12.6 SERIOUS ADVERSE EVENT REPORTING AND DOCUMENTATION REQUIREMENTS

Onyx Drug Safety must be notified of the occurrence of any SAE within 24 hours of the investigator, designee, or site personnel's knowledge of the event. The SAE will be reported by completing and submitting the SAE report form through the EDC system. In the event that the EDC system is not available, paper SAE report forms may be used to report the SAE to Onyx Drug Safety. Please refer to the SAE Reporting Guidelines in the Study Reference Manual.

Follow-up reports must be submitted in a timely fashion as additional information becomes available.

The investigator is responsible for notifying the Institutional Review Board (IRB) or Independent Ethics Committees (IEC) in accordance with local regulations, of all SAEs. The sponsor may request for additional source documentation pertaining to the SAE from the investigational site. If a subject is permanently withdrawn from the study due to an SAE, this information must be included in the initial or follow-up SAE report in the eCRF.

The sponsor is responsible for notifying the appropriate global health authorities of SAEs, when required, and in accordance with applicable laws and regulations.

12.7 PREGNANCY REPORTING

Pregnancy occurring in a female subject or in a male subject's partner while enrolled in this clinical trial through 30 days after the last dose of study drug received, although not considered an SAE, must be reported to Onyx Drug Safety within 24 hours of the investigator, designee, or site personnel learning of the event on a Pregnancy Reporting Form. If the subject is pregnant, all study treatment must be discontinued immediately and the pregnancy must be reported to the investigator and sponsor within 24 hours.

In the event of a pregnancy in the partner of a male subject, the pregnant partner will be asked to complete an informed consent/authorization form for the pregnant partner prior to the collection of any pregnancy data. The investigator will follow the subject or the partner of the male subject's pregnancy until completion or termination of the pregnancy.

Any abnormal maternal, fetal, or neonatal outcomes must be reported to Onyx Drug Safety as a follow-up on the Pregnancy Reporting Form within the same time parameters as above. If the outcome of the pregnancy meets an SAE criterion (e.g., spontaneous abortion, stillbirth, neonatal death, or fetal or neonatal congenital anomaly), the investigator will report the SAE through the EDC system.

A fetus exposed to study drug by a parent (female subject or male subject's partner) will be followed until a minimum of 12 weeks after birth. Follow-up may be extended at the discretion of the study medical monitor. All findings inclusive of SAEs will be reported to Onyx Drug Safety within 24 hours of the investigator, designee, or site personnel learning of the event. Serious AEs that may occur for these infants will be reported to Onyx Drug Safety.

13 STATISTICS

The final analysis will be based upon subject data collected through study discontinuation or at the end of maximal treatment duration plus 30 days of safety follow-up, whichever occurs first. Analyses will be based upon the Safety population, defined as subjects receiving treatment with any amount of the treatment regimen (oprozomib and dexamethasone with either lenalidomide or cyclophosphamide) under study. Additional efficacy analyses will be performed using the Response Evaluable population, defined as subjects who are included in the Safety population, and have a baseline disease assessment and at least 1 post-baseline disease assessment, or dropped out due to AE or other reasons prior to first post-baseline tumor assessment.

All summaries will be presented for each combination regimen by the assigned dose cohort level, the combined MTD dose level, as well as for the overall safety population (i.e., subjects who elect to escalate to the RP2D will be analyzed according to their original cohort assignment).

13.1 STUDY ENDPOINTS

13.1.1 PRIMARY ENDPOINTS

The safety endpoints for the Phase 1b and Phase 2 portions of this study are:

- Incidence, nature, and severity of AEs, SAEs, and DLTs (Phase 1b only) of oprozomib, given in combination with dexamethasone, and either lenalidomide or cyclophosphamide, as well as changes from baseline in selected laboratory analytes, vital signs and ECG findings.

The primary efficacy endpoints for the Phase 2 portion of this study are:

- Overall response, defined as a best overall response of sCR, CR, VGPR, or PR according to the IMWG-URC (see Appendix F).
- Complete response, defined as a best overall response of either sCR or CR.

13.1.2 SECONDARY ENDPOINTS

The secondary endpoints of this study are:

- Population-based PK parameters including, but not limited to, clearance and volume of distribution will be determined.
- Duration of response, defined as the time from first evidence of PR or better to confirmation of disease progression or death due to any cause.
- PFS, defined as the time from the start of treatment to disease progression or death (due to any cause), whichever comes first.

13.1.3 EXPLORATORY ENDPOINTS

The exploratory endpoints of this study are:

- Pharmacodynamic analyses of proteasome inhibition will be determined.
- Analyses to potentially identify genetic and gene expression biomarkers that may predict response and will be conducted.

13.2 ANALYSIS OF STUDY CONDUCT

Enrollment, major protocol violations, and discontinuations from the study will be summarized for each combination regimen by the assigned dose cohort, the combined MTD dose level, and for all subjects.

Demographic and baseline characteristics, such as age, sex, race, weight, number of prior therapies, and baseline ECOG PS, will be summarized using means, standard deviations,

medians, and ranges for continuous variables, and proportions for categorical variables. All summaries will be presented for each combination regimen by the assigned dose cohort, the combined MTD dose level, and for all subjects.

13.3 INDEPENDENT REVIEW COMMITTEE

An independent review committee will not be employed for this study.

13.4 DATA MONITORING COMMITTEE

A formal data monitoring committee will not be employed for this study. However, a CSRC will review safety and tolerability data prior to each dose escalation (see Section 4 for more details).

13.5 ANALYSIS OF TREATMENT GROUP COMPARABILITY

No analyses of treatment group in terms of demographic and baseline characteristics will be performed.

13.6 STATISTICAL METHODS

13.6.1 EFFICACY ANALYSES

Response assessment data, PFS, and DOR will be summarized for each combination regimen by the assigned dose cohort, the combined MTD dose level, and for all subjects.

Further details on efficacy analysis populations are provided in Section 13. Definitions of study endpoints are provided in Section 13.1.

The lower 1-sided exact Clopper-Pearson 90% confidence intervals will be calculated for both the ORR and CRR. In addition, exact Clopper-Pearson 95% confidence intervals will be calculated for estimated ORR and CRR.

Summary statistics for DOR and PFS will be calculated using the Kaplan-Meier method. For purposes of calculating PFS, the start date for PD is the date at which progression is first observed. For such subjects, the primary analysis of PFS and DOR will be right-censored according to the conventions described in Table 17.

Table 17 Date of Progression or Censoring for Progression-free Survival and Duration of Response

Situation	Date of Progression or Censoring	Outcome
No baseline disease assessments	Date of first study drug	Censored
New anticancer treatment started before documentation of PD or death[a]	Date of last disease assessment prior to start of a new anticancer treatment	Censored
Death or PD immediately after more than 1 consecutively missed disease assessment visits	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[a] or PD between planned disease assessments	Date of death or first disease assessment showing PD, whichever occurs first	Progressed
Death[a] before first disease assessment	Date of death[a]	Progressed

DOR = duration of response; PD = progressive disease; PFS = progression-free survival.
[a] For DOR, death must be due to disease progression, otherwise, both outcomes will be censored at the date of last disease assessment. For PFS, death due to any cause is counted as an event.

The follow-up time for PFS will be summarized by reverse Kaplan-Meier method (Schemper 1996).

13.6.2 SAFETY ANALYSES

All subjects who receive any amount of oprozomib, dexamethasone, lenalidomide, or cyclophosphamide will be included in the safety analyses.

Safety and tolerability will be assessed through summaries of study drug administration, DLTs (Phase 1b only), AEs, changes in selected laboratory analytes, ECGs, and vital signs, by dose cohort, the combined MTD dose level, and for all subjects.

Study drug administration data will be listed by combination regimen and dose cohort, and any dose modifications will be flagged. Means and standard deviations will be used to summarize the total dose for each component of study drug received. All summaries will be presented for each combination regimen by the assigned dose cohort, the combined MTD dose level, and for all subjects.

All AE data will be listed by study site, treatment regimen, dose cohort, subject number, and study day. All AEs occurring on or after treatment on Cycle 1 Day 1 will be summarized by mapped term, appropriate thesaurus levels, and NCI-CTCAE (Version 4.03) toxicity grade. In addition, all SAEs, including deaths, will be listed separately and summarized.

Relevant laboratory and vital sign (temperature, heart rate, and blood pressure) data will be displayed by visit and time (when available), with NCI-CTCAE (Version 4.03) Grade 3 and 4 values identified where appropriate. Additionally, all laboratory data will be summarized by NCI-CTCAE grade.

13.6.3 PHARMACOKINETIC ANALYSES

Plasma samples for determination of PK will be collected as outlined in the Laboratory Manual. A population PK software program will be used to fit a nonlinear, mixed effects model to estimate PK parameters (clearance and volume of distribution), the inter- and intrapatient variability and the population variability in the parameter estimates for oprozomib and, if deemed necessary, its metabolite(s). The sparse sampling approach in this study, along with results from oprozomib studies with intensive sampling, will be used in the development of a structural model. The best model will be evaluated by goodness-of-fit statistics, reduction in the objective function and posterior predictive checks. Potential covariates impacting PK of oprozomib including formulation (Oprozomib Tablet versus Oprozomib ER Tablet), age, gender and body weight, will be assessed. Potential correlations of relevant PK parameters with dose, safety or efficacy outcomes, and other covariates will be explored.

13.6.4 EXPLORATORY ANALYSES

Exploratory analyses of the correlation between PDn, genomic biomarkers, and antitumor activity may be conducted.

The extent of inactivation of proteasome activity after oprozomib dosing in RBCs and PBMCs will be monitored as a PDn parameter. Pharmacodynamic inhibition will be listed by dose cohort, exposure, and response status. Additional PK and PDn analyses will be conducted as appropriate.

13.7 HANDLING OF MISSING DATA

Missing data for partial dates on AEs or concomitant medication may be imputed according to prespecified, conservative imputation rules. Censoring rules for PFS and DOR and details about the handling of missing data are described in Section 13.6.1.

Details on the Response Evaluable population are provided in Section 13.

13.8 DETERMINATION OF SAMPLE SIZE

The estimated sample size for the dose-escalation portion of the study of up to 24 subjects per combination regimen is based upon standard 3 + 3 dose-escalation rules (see Section 9.1.2) and the expectation that 2 to 6 dosing cohorts of 3 to 6 subjects per cohort will be required to establish the MTD. Enrollment of up to 35 additional subjects per combination regimen during the Phase 2 portion of the study is based upon the goal of ruling out an ORR < 85% and a CRR < 50% based upon the lower 1-sided 90% confidence interval for each parameter. This sample size is based on a simulation of a multinomial outcome of CR, PR, or PD for various cohort sizes. With 35 subjects per combination regimen, and an assumed true ORR and CRR of 95% and 75%, respectively, the probability of ruling out an ORR < 85% and a CRR < 50% with 90% confidence is approximately 88%, from the simulation described above. The same assumptions for ORR and CRR are used in determining the sample size for each combination regimen. Thus, in total, the study will enroll up to a sample size of 118 subjects (up to 48 subjects for the Phase 1b portion of the study and 70 subjects for the Phase 2 portion of the study).

13.9 INTERIM ANALYSIS

No formal interim analyses will be conducted for this study.

14 ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

14.1 COMPLIANCE STATEMENT

This study will be conducted in accordance with the protocol and with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, as well as all applicable country and regional regulatory requirements. The investigator is responsible for ensuring that this protocol, the site's ICF, and any other information that will be presented to

potential subjects are reviewed and approved by the appropriate IRB or IEC prior to the enrollment of any study subjects.

14.2 INSTITUTIONAL REVIEW BOARD OR INDEPENDENT ETHICS COMMITTEE

The investigator will submit this protocol, the ICF, IB, and any other relevant supporting information to the appropriate IRB or IEC for review and approval prior to study initiation.

Amendments to the protocol must also be approved by the IRB/IEC, as appropriate, prior to the implementation of changes in this study. No protocol violations are allowed. However, the investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the study subjects without prior IRB/IEC/Onyx approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment, should be submitted to the IRB/IEC/Onyx. Any deviations from the protocol must be fully explained and documented by the investigator.

14.3 INFORMED CONSENT AND HUMAN SUBJECT PROTECTION

No investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the subject's legally authorized representative sufficient opportunity to consider whether or not to participate, and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in a language understandable to the subject or representative.

Onyx or its designated representative will provide the investigator with a sample consent form. Local and/or institutional requirements may require disclosure of additional information in the ICF. Any changes to the consent form must be submitted to Onyx or its designated representative for approval, prior to submission to the IRB/IEC. The IRB/IEC will review the consent form for approval. A copy of the approved form must be submitted to Onyx or its designated representative prior to initiation of the study. Before implementing any study procedure, informed consent shall be documented in the subject case histories and

by the use of a written consent form approved by the IRB/IEC and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy of the signed informed consent will be given to the subject or subject's legally authorized representative. The original signed consent must be maintained by the investigator and available for inspection by Onyx, its designated representative, or regulatory authority at any time.

14.4 DIRECT ACCESS TO SOURCE DATA, SOURCE DOCUMENTS, AND STUDY RECORDS

The study will be carried out in keeping with applicable local laws and regulations. This may include an inspection by Onyx representatives/designees, and/or regulatory authority representatives at any time. The investigator/institution must agree to the inspection of study-related records by the regulatory authority/Onyx representatives/designees, and must allow direct access to source documents to the regulatory authority/Onyx representatives/ designees/IRB/IEC. The investigator must allocate time (investigator and study staff) to discuss findings and relevant issues with the regulatory authority/Onyx representatives.

14.5 DATA COLLECTION AND HANDLING

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include subject diaries, laboratory reports, and other documents. Onyx will supply the eCRF, which will be completed in English.

Data collection will involve the use of the EDC system, to which only authorized personnel will have access.

The investigator or designee must enter all results collected during the clinical study into eCRFs. Guidelines for completion of eCRFs will be reviewed with study site personnel at the site initiation visits. Investigators are responsible for approval of the entered/corrected data. Detailed instructions may be found in the other study-specific documents.

All entries made on the eCRF must be verifiable against source documents. In addition to periodic monitoring occurring within the system by study monitors, programmatic edit checks and data listings will be used to review the data for completeness, logic, and adherence to study protocol. As a result of this monitoring and these checks, queries may be electronically issued to the clinical study sites and electronically resolved by those sites.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to assure subject confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (e.g., copies of eCRFs, regulatory documents) will be retained at the study site, along with adequate source documentation. The study file and all source data should be retained until written notification is given by the sponsor or designee for destruction.

14.6 CONFIDENTIALITY

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded on the eCRF. If the subject name appears on any other document (e.g., pathologist report) or study materials (e.g., biopsy tissue slides), then that information must be deleted before a copy of the document is supplied to the sponsor. Study data stored on a computer will be stored in accordance with local data protection laws. Subjects will be informed in writing that representatives of the sponsor, IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects' records to be identified.

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APPENDIX A SCHEDULE OF STUDY ASSESSMENTS FOR 5/14 DOSING SCHEDULE

Visit	Screening	Baseline	Cycle 1										Cycle 2–24				Cycle 25+		End of Study Treatment[b]
	Day -21 to -1	(pre-C1D1 dose)	Day 1	Day 2	Day 3, 4	Day 5	Day 6, 7	Day 8 ± 1	Day 9–14	Day 15 ± 1	Day 16–21	Day 22–28	Day 1	Day 2–14	Day 15 ± 1	Day 22–28	Day 1	Day 22–28[a]	
Written Informed Consent	X																		
Inclusion/Exclusion Criteria	X																		
Medical History	X																		
Previous Treatment History	X																		
Physical Examination[c]	X		X					X		X		X	X		X		X		X
Height	X																		
Weight	X		X										X						X
Neurological Assessment (BPNS and CTCAE Grading)[d]	X												X						X
Vital Signs		X	X[e]	X[e]		X[e]		X		X[e]		X	X[f]		X[f]				X
12–lead ECG (Local)	X	X																	X
Urinalysis[g]	X																		X
Serum Chemistry[h]	X		X[i]			X		X		X		X	X[i]		X		X[i]		X
CBC with Diff and Platelets[j]	X		X[j]			X		X		X		X	X[j]		X		X[j]		X
Coagulation Tests[k]	X		X[k]										X[k]				X[k]		
Pregnancy Test[l]	X		X					X		X		X	X		X		X		X
SPEP/UPEP/Immunofixation[m]	X											X				X		X	X
β2 Microglobulin	X																		
SFLC assay and ratio[n]	X											X				X		X	X
Skeletal Survey[o]		X										X				X		X	X
Plasmacytoma Evaluation[p]		X										X				X		X	X
Bone Marrow Aspirate[q]	X																		
Biopsy (FISH Analyses)[q]		X																	
Optional– Genomic Biomarker Assessment: Bone Marrow Aspirate[r]		X																	X
Optional – Genomic Biomarker Assessment: Blood[r]		X																	
Optional – Genomic Biomarker Assessment: Saliva[r]		X																	

APPENDIX A SCHEDULE OF STUDY ASSESSMENTS FOR 5/14 DOSING SCHEDULE (CONT'D)

Visit	Screening	Baseline	Cycle 1										Cycle 2–24				Cycle 25+		End of Study Treatment[b]
	Day -21 to -1	(pre-C1D1 dose)	Day 1	Day 2	Day 3, 4	Day 5	Day 6, 7	Day 8 ± 1	Day 9-14	Day 15 ± 1	Day 16–21	Day 22–28	Day 1[a]	Day 2–14	Day 15 ± 1	Day 22–28	Day 1	Day 22–28[a]	
Blood for PK[s]			X										X						
Blood for PDn Assay[t]			X	X									X						
Treatment Regimen 1 (ORd) Dosing[u]:																			
Oprozomib			X	X	X	X				X	X		X	X	X		X		
Lenalidomide			X	X	X	X	X	X	X	X	X		X	X	X				
Dexamethasone			X	X				X	X	X	X	X	X	X	X	X			
Review Patient Diary			X	X		X		X		X		X	X		X	X	X	X	X
AEs and Con Meds[v]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cycle 1 Follow-up Telephone Call to Subject					X[w]														

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BPNS = Brief Peripheral Neuropathy Screen; CBC = complete blood count; CR = complete response; CrCl = creatinine clearance; CRF = case report form; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; eCRF = electronic case report form; FCBP = females of child-bearing potential; FISH = fluorescent in-situ hybridization; MRI = magnetic resonance imaging; ORd = oprozomib, lenalidomide, and dexamethasone; PD = progressive disease; PDn = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; SFLC = serum free light chain; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

[a] Following completion of 24 cycles of ORd or OCyd treatment, disease response assessments will continue every 8 weeks until confirmed PD. For subjects who discontinue treatment before PD occurs (such as for an AE, noncompliance, etc.), disease response assessments will be performed every 4 weeks during the first 24 months of the study and every 8 weeks thereafter, until confirmed PD, or the start of alternative, non-protocol antimyeloma therapy.

[b] All End of Study Treatment/Early Discontinuation Assessments must be performed within 30 days following the subject's last administration of study drug and prior to initiation of any other treatment. The same methods of disease assessment must be used throughout the study. If disease assessments show disease progression, assessments do not need to be repeated with End of Study Treatment Assessments.

[c] Complete physical exams will be performed during Screening and at the End of Study Treatment visit. All other physical exams will be limited physical exams. A complete physical examination will include examination of the skin, head and neck, chest (heart and lungs), abdomen, extremities, and a brief neurological exam including an assessment for peripheral neuropathy. Rectal and pelvic examinations are optional. Eastern Cooperative Oncology Group performance status (assessed at the time of the physical exam) will be collected during a complete physical exam. A limited physical examination will include an examination of the chest (heart and lungs) and abdomen, with additional examinations as clinically indicated or directed by AEs.

[d] Neurological assessments (BPNS, and if applicable, record adverse events with CTCAE grading; Refer to Appendix G), and if applicable, record adverse events with CTCAE grading) will be performed at Screening, on Day 1 for Cycles 2+ until oprozomib is discontinued and at the End of Study Treatment.

[e] Measure on day of dosing, prior to the administration of oprozomib dose and at 30 minutes +/- 10 min, 1 hour +/- 15 min, and 2 hours +/- 15 min after each oprozomib dose (Cycle 1 Days 1 through 5 and Day 15). On days when oprozomib is not administered, vital signs will be measured anytime during the clinic visit. At the investigator's medical discretion, vital signs monitoring may be extended beyond the time periods specified above. Orthostatic BP should be assessed for subjects with evidence of dehydration during site visits.

[f] Cycles 2 and higher, vital signs are required on the day of dosing, prior to the administration of oprozomib dose. Orthostatic BP should be assessed for subjects with evidence of dehydration during site visits.

APPENDIX A SCHEDULE OF STUDY ASSESSMENTS FOR 5/14 DOSING SCHEDULE (CONT'D)

[g] Subjects with urine positive for protein (> than trace) will need to collect a 24-hour urine sample for creatinine and protein.

[h] Full chemistry panel (sodium, potassium, calcium, alkaline phosphatase, blood urea nitrogen, uric acid, lactate dehydrogenase, creatinine, chloride, bicarbonate, glucose, total protein, albumin, total bilirubin, ALT, AST, phosphorous, and magnesium). Calculate or measure CrCl.

[i] Day 1 labs can be drawn up to 3 days prior to Day 1.

[j] Complete blood count (CBC) with differential includes the following: hemoglobin, hematocrit, white blood cell (WBC) count with complete manual or automated differential (total neutrophils, lymphocytes, monocytes, eosinophils, basophils; reported as absolute counts), red blood cell count, and platelet count.

[k] Coagulation tests include the following: prothrombin time, activated partial thromboplastin time, and international normalized ratio.

[l] For both treatment regimens (ORd and OCyd): Screening pregnancy testing for females of childbearing potential (FCBP) must have a sensitivity of at least 25 mIU/mL with 2 medically supervised tests performed before lenalidomide or cyclophosphamide dosing starts. One test must be obtained within 10 through 14 days and 1 test within 24 hours prior to the start of lenalidomide or cyclophosphamide on Cycle 1 Day 1 (C1D1). A medically supervised negative serum pregnancy test will be done within 24 hours **prior to each cycle of lenalidomide or cyclophosphamide dosing**. Negative serum pregnancy tests will also be performed on Day 8, Day 15, and between Days 22 through 28 of **Cycle 1**; on Day 1 for **Cycles 2 through 24**; and at the **End of Study Treatment** visit, in FCBP only. Pregnancy tests will be repeated on Day 1 and Day 15 of Cycle 2 through 24 if menses are irregular or not present in FCBP. A medically supervised serum pregnancy test for FCBP must be obtained during Cycle 26 at 4 weeks after the last dose of lenalidomide or cyclophosphamide.

[m] SPEP and UPEP (24-hour assessment, no substitute method is acceptable) is required for all subjects at Screening before study drug treatment. Thereafter, SPEP is to be done at each assessment for all subjects. Obtain blood for SPEP, serum immunofixation, serum immunoglobulin levels, and serum FLCs and urine sample for UPEP and immunofixation. UPEP with 24-hour urine collection is required at each assessment only if screening UPEP shows measurable paraprotein in the urine. If screening UPEP is negative, spot urine is required at each assessment. If positive for paraprotein, a 24 hour urine collection with UPEP must be done at the next assessment and at each subsequent assessment unless the UPEP shows the absence of paraprotein. Immunofixation is required at next assessment only if SPEP or UPEP results are zero/undetectable. Subjects with negative serum and urine M-proteins are required to complete FLC at each time point.

[n] Serum free light chain: Only in subjects without measurable serum and urine M-protein levels (serum M-protein < 0.5 g/dL or urine M-protein < 200 mg/24 hours) at Screening will SFLC assays be used to determine eligibility and response.

[o] Baseline skeletal survey does not need to be repeated if previously done within 6 weeks of consent. Skeletal survey will include lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. If present at screening, bone lesion(s) must be monitored throughout the study per IMWG response criteria and the skeletal survey will be only repeated if worsening clinical symptoms suggest PD, or as clinically indicated.

[p] Extramedullary plasmacytoma evaluation will be conducted at Screening only if a lesion is suspected clinically. Baseline plasmacytoma assessment does not need to be repeated if previously done within 6 weeks of consent. Only measurable plasmacytomas will be followed for response and progression. Measurable lesions must have a longest diameter of at least 1 cm and the product of cross diameter is at least 1 cm^2. Plasmacytomas of lessor size are considered non measurable. If an extramedullary plasmacytoma is detected, evaluation will be repeated during treatment as clinically indicated, or to confirm a response of PR or better, or to confirm PD. The same technique (which may include clinical evaluation by palpation, ultrasound, x-ray, CT scan, MRI, or PET) should be employed for each measurement of plasmacytoma dimensions as clinically appropriate (Appendix F). Bi-dimensional lesion measurements must be performed and recorded in the designated eCRF.

[q] Bone marrow aspiration and/or biopsy are required for all subjects at Screening to confirm diagnosis and eligibility. Bone marrow aspiration can be collected up to 8weeks prior to C1D1 in Phase 1b and can be collected up to 21 days prior to C1D1 in Phase 2. In Phase 1, the FISH assessment on the Screening bone marrow may be performed locally. Subsequent FISH assessments must be performed locally and assessed centrally. In Phase 2 all FISH assessments, including the baseline assessment, performed prior to dosing on C1D1, must be assessed centrally. Please see the lab manual for processing information. Central FISH assessment reports will not be provided to sites. Additional bone marrow aspirates will need to be obtained and submitted for local assessment.

[r] Optional genomic biomarker samples: For subjects who consent to participate and who are eligible for the study, bone marrow aspirate (obtained from the bone marrow aspirate for FISH analysis; no new bone marrow sample is required at baseline), blood, and saliva samples will be collected at baseline prior to dosing on C1D1. Bone marrow aspirate will also be collected for isolation of CD138+ cells at the end of protocol-defined therapy if end of treatment is due to PD; bone marrow will be collected only from subjects consenting to genomic biomarker analyses.

APPENDIX A SCHEDULE OF STUDY ASSESSMENTS FOR 5/14 DOSING SCHEDULE (CONT'D)

[s] Blood for PK for subjects will occur at two postdose time points on C1D1, and one predose and two postdose time points on Cycle 3 Day 1 (C3D1) and Cycle 5 Day 1 (C5D1). Sampling times and volumes are provided in the Laboratory Manual. On the PK collection days, dosing of oprozomib in relation to the meal intake (within 2 hours before and 1 hour after dose) will be recorded.

[t] Blood for measurement of proteasome activity in whole blood and PBMCs will only be collected in Phase 1b. Samples will be collected predose and at 2 at postdose time points on C1D1 and Cycle 2 Day 1 (C2D1), and predose on Cycle 1 Day 2 (C1D2). Sampling times and volumes are provided in the Laboratory Manual.

[u] Treatment Regimen 1 (ORd): Oprozomib treatment will be administered on Days 1 through 5 and 15 through 19 during 28-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason. Subjects will receive 20 mg of dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day treatment cycle up to Cycle 24. After Cycle 1, the dexamethasone dose may be decreased to 10 mg/day in subjects > 75 years of age, at the discretion of the investigator. On days when both oprozomib and dexamethasone are administered (i.e., on Days 1, 2, 15, and 16 of each cycle), dexamethasone should be taken at least 30 minutes prior to oprozomib. Lenalidomide will be administered orally at a dose of 25 mg, on Days 1 through 21 of each 28 day cycle up to Cycle 24. Subjects may take lenalidomide following oprozomib administration; however it is recommended that they take lenalidomide at approximately the same time each day. On days when oprozomib is not administered, subjects should take lenalidomide at approximately the same time in the day for consistency.

[v] Record all AEs from time of consent through 30 days after the last dose of study drug. Start to record concomitant medications from 30 days prior to Day 1 until 30 days after the last dose of study drug. If there is any change in the subject's concomitant medications during the study, it must be recorded on the eCRF.

[w] For subjects in the Ph 1b portion: The study nurse (or designee) will call the subject on Cycle 1 Days 3 and 4, approximately 6-10 hours after the expected study drug dosing time to follow up on dosing compliance and to collect start, stop, and duration times as well as severity of any AEs, if applicable.

APPENDIX B SCHEDULE OF STUDY ASSESSMENTS FOR 2/7 DOSING SCHEDULE

Visit	Screening	Baseline	Cycle 1										Cycle 2–24				Cycle 25+		End of Study Treatment[b]
	Day -21 to -1	(pre-C1D1 dose)	Day 1	Day 2	Day 3, 4	Day 5	Day 6, 7	Day 8	Day 9	Day 15	Day 16	Day 22–28	Day 1	Day 2–14	Day 15	Day 22–28	Day 1	Day 22–28[a]	
Written Informed Consent	X																		
Inclusion/Exclusion Criteria	X																		
Medical History	X																		
Previous Treatment History	X																		
Physical Examination[c]	X		X					X		X		X	X		X		X		X
Height	X																		
Weight	X		X										X						X
Neurological Assessment (BPNS and CTCAE Grading)[d]	X												X						X
Vital Signs		X	X[e]	X[e]		X[e]		X[e]	X[e]	X[e]	X[e]	X	X[f]		X[f]				X
12–lead ECG (Local)	X																		X
Urinalysis[g]	X																		X
Serum Chemistry[h]	X		X[i]			X		X		X		X	X[i]		X		X[i]		X
CBC with Diff and Platelets[j]	X		X[j]			X		X		X		X	X[j]		X		X[j]		X
Coagulation Tests[k]	X		X[k]										X[k]				X[k]		
Pregnancy Test[l]	X		X					X		X		X	X		X		X		X
SPEP/UPEP/Immunofixation[m]	X											X				X		X	X
β2 Microglobulin	X																		
SFLC assay and ratio[n]	X											X				X		X	X
Skeletal Survey[o]	X											X				X		X	X
Plasmacytoma Evaluation[p]	X											X				X		X	X
Bone Marrow Aspirate[q]	X																		
Biopsy (FISH Analyses)[q]		X																	
Optional– Genomic Biomarker Assessment: Bone Marrow Aspirate[r]		X																	X
Optional – Genomic Biomarker Assessment: Blood[s]		X																	
Optional – Genomic Biomarker Assessment: Saliva[r]		X																	

APPENDIX B SCHEDULE OF STUDY ASSESSMENTS FOR 2/7 DOSING SCHEDULE (CONT'D)

Visit	Screening[a]	Baseline	Cycle 1										Cycle 2–24				Cycle 25+		End of Study Treatment[b]
	Day -21 to -1	(pre-C1D1 dose)	Day 1	Day 2	Day 3, 4	Day 5	Day 6, 7	Day 8	Day 9	Day 15	Day 16	Day 22–28	Day 1[a]	Day 2–14	Day 15	Day 22–28	Day 1	Day 22–28[b]	
Blood for PK[s]			X										X						
Blood for PDn Assay[t]			X	X									X						
Blood for Platelet Assessment (OCyd arm only)[u]			X	X		X		X					X						X
Treatment Regimen 1 (ORd) Dosing[v]:																			
Oprozomib			X	X				X	X	X	X	X	X	X	X		X		
Lenalidomide			X	X	X	X	X	X	X	X	X		X	X	X				
Dexamethasone			X	X				X	X	X	X	X	X	X	X	X			
Treatment Regimen 2 (OCyd) Dosing[w]:																			
Oprozomib			X	X				X	X	X	X	X	X	X	X		X		
Cyclophosphamide			X					X		X			X	X	X				
Dexamethasone			X	X				X	X	X	X	X	X	X	X	X			
Review Patient Diary			X	X		X		X	X	X	X	X	X		X	X	X	X	X
AEs and Con Meds[x]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cycle 1 Follow-up Telephone Call to Subject					X[y]														

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BPNS = Brief Peripheral Neuropathy Screen; CBC = complete blood count; CR = complete response; CrCl = creatinine clearance; CRF = case report form; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; eCRF = electronic case report form; FCBP = females of child-bearing potential; FISH = fluorescent in-situ hybridization; MRI = magnetic resonance imaging; OCyd = oprozomib, cyclophosphamide, and dexamethasone; ORd = oprozomib, lenalidomide, and dexamethasone; PD = progressive disease; PDn = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; SFLC = serum free light chain; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

[a] Following completion of 24 cycles of ORd or OCyd treatment, disease response assessments will continue every 8 weeks until confirmed PD. For subjects who discontinue treatment before PD occurs (such as for an AE, noncompliance, etc.), disease response assessments will be performed every 4 weeks during the first 24 months of the study and every 8 weeks thereafter, until confirmed PD, or the start of alternative, non-protocol antimyeloma therapy.

[b] All End of Study Treatment/Early Discontinuation Assessments must be performed within 30 days following the subject's last administration of study drug and prior to initiation of any other treatment. The same methods of disease assessment must be used throughout the study. If disease assessments show disease progression, assessments do not need to be repeated with End of Study Treatment Assessments.

[c] Complete physical exams will be performed during Screening and at the End of Study Treatment visit. All other physical exams will be limited physical exams. A complete physical examination will include examination of the skin, head and neck, chest (heart and lungs), abdomen, extremities, and a brief neurological exam including an assessment for peripheral neuropathy. Rectal and pelvic examinations are optional. Eastern Cooperative Oncology Group performance status (assessed at the time of the physical exam) will be collected during a complete physical exam. A limited physical examination will include an examination of the chest (heart and lungs) and abdomen, with additional examinations as clinically indicated or directed by AEs.

[d] Neurological assessments (BPNS, and if applicable, record adverse events with CTCAE grading; [Appendix G]) will be performed at Screening, on Day 1 for Cycles 2+ until oprozomib is discontinued and at the End of Study Treatment.

APPENDIX B SCHEDULE OF STUDY ASSESSMENTS FOR 2/7 DOSING SCHEDULE (CONT'D)

[e] Measure on day of oprozomib dosing prior to the administration of oprozomib dose and at 30 minutes +/- 10 min, 1 hour +/- 15 min, and 2 hours +/- 15 min after each oprozomib dose (Cycle 1 Days 1 and 2, 7, and 8, 15, and 16). On days when oprozomib is not administered (Cycle 1 Days 3, 4, and 5), vital signs will be measured anytime during the clinic visit. At the investigator's medical discretion, vital signs monitoring may be extended beyond the time periods specified above. Orthostatic BP should be assessed for subjects with evidence of dehydration during site visits.

[f] Cycles 2 and higher, vital signs are required on the day of dosing, prior to the administration of oprozomib dose. Orthostatic BP should be assessed for subjects with evidence of dehydration during site visits.

[g] Subjects with urine positive for protein (> than trace) will need to collect a 24-hour urine sample for creatinine and protein.

[h] Full chemistry panel (sodium, potassium, calcium, alkaline phosphatase, blood urea nitrogen, uric acid, lactate dehydrogenase, creatinine, chloride, bicarbonate, glucose, total protein, albumin, total bilirubin, ALT, AST, phosphorous, and magnesium). Calculate or measure CrCl.

[i] Day 1 labs can be drawn up to 3 days prior to Day 1.

[j] Complete blood count (CBC) with differential includes the following: hemoglobin, hematocrit, white blood cell (WBC) count with complete manual or automated differential (total neutrophils, lymphocytes, monocytes, eosinophils, basophils; reported as absolute counts), red blood cell count, and platelet count.

[k] Coagulation tests include the following: prothrombin time, activated partial thromboplastin time, and international normalized ratio.

[l] For both treatment regimens (ORd and OCyd): Screening pregnancy testing for females of childbearing potential (FCBP) must have a sensitivity of at least 25 mIU/mL with **2** medically supervised tests performed before lenalidomide or cyclophosphamide dosing starts. One test must be obtained within 10 through 14 days and one test within 24 hours prior to the start of lenalidomide or cyclophosphamide on C1D1. A medically supervised negative serum pregnancy test will be done within 24 hours **prior to each cycle of lenalidomide or cyclophosphamide dosing**. Negative serum pregnancy tests will also be performed on Day 8, Day 15, and between Days 22 through 28 of **Cycle 1**; on Day 1 for **Cycles 2 through 24**; and at the **End of Study Treatment** visit, in FCBP only. Pregnancy tests will be repeated on Day 1 and Day 15 of Cycle 2 through 24 if menses are irregular or not present in FCBP. A medically supervised serum pregnancy test for FCBP must be obtained during Cycle 26 at 4 weeks after the last dose of lenalidomide or cyclophosphamide.

[m] SPEP and UPEP (24-hour assessment, no substitute method is acceptable) is required for all subjects at Screening before study drug treatment. Thereafter, SPEP is to be done at each assessment for all subjects. Obtain blood for SPEP, serum immunofixation, serum immunoglobulin levels, and serum FLCs and urine sample for UPEP and immunofixation. UPEP with 24-hour urine collection is required at each assessment only if screening UPEP shows measurable paraprotein in the urine. If screening UPEP is negative, spot urine is required at each assessment. If positive for paraprotein, a 24 hour urine collection with UPEP must be done at the next assessment and at each subsequent assessment unless the UPEP shows the absence of paraprotein. Immunofixation is required at next assessment only if SPEP or UPEP results are zero/undetectable. Subjects with negative serum and urine M-proteins are required to complete FLC at each time point.

[n] Serum free light chain: Only in subjects without measurable serum and urine M-protein levels (serum M-protein < 0.5 g/dL or urine M-protein < 200 mg/24 hours) at Screening will SFLC assays be used to determine eligibility and response.

[o] Baseline skeletal survey does not need to be repeated if previously done within 6 weeks of consent. Skeletal survey will include lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. If present at screening, bone lesion(s) must be monitored throughout the study per IMWG response criteria and the skeletal survey will be only repeated if worsening clinical symptoms suggest PD, or as clinically indicated.

[p] Extramedullary plasmacytoma evaluation will be conducted at Screening only if a lesion is suspected clinically. Baseline plasmacytoma assessment does not need to be repeated if previously done within 6 weeks of consent. Only measurable plasmacytomas will be followed for response and progression. Measurable lesions must have a longest diameter of at least 1 cm and the product of cross diameter is at least 1 cm^2. Plasmacytomas of lessor size are considered non measurable. If an extramedullary plasmacytoma is detected, evaluation will be repeated during treatment as clinically indicated, or to confirm a response of PR or better, or to confirm PD. The same technique (which may include clinical evaluation by palpation, ultrasound, x-ray, CT scan, MRI, or PET) should be employed for each measurement of plasmacytoma dimensions as clinically appropriate (refer to Appendix F). Bi-dimensional lesion measurements must be performed and recorded in the designated eCRF.

APPENDIX B SCHEDULE OF STUDY ASSESSMENTS FOR 2/7 DOSING SCHEDULE (CONT'D)

[q] Bone marrow aspiration and/or biopsy are required for all subjects at Screening to confirm diagnosis and eligibility. Bone marrow aspiration can be collected up to 8 weeks prior to C1D1 in Phase 1b and can be collected up to 21 days prior to C1D1 in Phase 2. In Phase 1, the FISH assessment on the Screening bone marrow may be performed locally. Subsequent FISH assessments must be performed locally and assessed centrally. In Phase 2 all FISH assessments, including the baseline assessment, performed prior to dosing on C1D1, must be assessed centrally. Please see the lab manual for processing information. Central FISH assessment reports will not be provided to sites. Additional bone marrow aspirates will need to be obtained and submitted for local assessment.

[r] Optional genomic biomarker samples: For subjects who consent to participate and who are eligible for the study, bone marrow aspirate (obtained from the bone marrow aspirate for FISH analysis; no new bone marrow sample is required at baseline), blood, and saliva samples will be collected at baseline prior to dosing on C1D1. Bone marrow aspirate will also be collected for isolation of CD138+ cells at the end of protocol-defined therapy if end of treatment is due to PD; bone marrow will be collected only from subjects consenting to genomic biomarker analyses.

[s] Blood for PK for subjects will occur at 2 postdose time points on C1D1, and one predose and two postdose time points on C3D1 and C5D1. Sampling times and volumes are provided in the Laboratory Manual. On the PK collection days, dosing of oprozomib in relation to the meal intake (within 2 hours before and 1 hour after dose) will be recorded.

[t] Blood for measurement of proteasome activity in whole blood and PBMCs will only be collected in Phase 1b. Samples will be collected predose and at 2 postdose time points on C1D1 and C2D1, and predose on C1D2. Sampling times and volumes are provided in the Laboratory Manual.

[u] For OCyd subjects participating in the assessment of platelet function, samples for the assessment of platelet adherence, activation, aggregation, and interaction with coagulation factors will be conducted utilizing the platelet function analyzer (PFA-100 on C1D1 prior to protocol mandated therapy, C1D2, C1D5, C1D8, C4D1 and End of Study Treatment.

[v] Treatment Regimen 1 (ORd): Oprozomib treatment will be administered on Days 1, 2, 8, 9, 15, 16, 22, and 23 during 28-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason. Subjects will receive 20 mg of dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day treatment cycle up to Cycle 24. After Cycle 1, the dexamethasone dose may be decreased to 10 mg/day in subjects > 75 years of age, at the discretion of the investigator. On days when both oprozomib and dexamethasone are administered (i.e., on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each cycle), dexamethasone should be taken at least 30 minutes prior to oprozomib. Lenalidomide will be administered orally at a dose of 25 mg on Days 1 through 21 of each 28 day cycle up to Cycle 24. Subjects may take lenalidomide following oprozomib administration; however it is recommended that they take lenalidomide at approximately the same time each day. On days when oprozomib is not administered, subjects should take lenalidomide at approximately the same time in the day for consistency.

[w] Treatment Regimen 2 (OCyd): Oprozomib treatment will be administered on Days 1, 2, 8, 9, 15, 16, 22, and 23 during 28-day cycles for up to 8 cycles or until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason. Subjects will receive 20 mg of dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day treatment cycle up to Cycle 8. After Cycle 1, the dexamethasone dose may be decreased to 10 mg/day in subjects > 75 years of age, at the discretion of the investigator. On days when both oprozomib and dexamethasone are administered (i.e., on Days 1, 2, 8, 9, 15, 16, 22, and 23 during of each cycle), dexamethasone should be taken at least 30 minutes prior to oprozomib. Cyclophosphamide will be administered orally at 300 mg/m^2 (up to a maximum of 600 mg) on Days 1, 8, and 15 of each cycle for a total of 8 cycles. Subjects may take cyclophosphamide following oprozomib administration; however it is recommended that they take cyclophosphamide concurrently with oprozomib at approximately the same time each day. On days when oprozomib is not administered, subjects should take cyclophosphamide at approximately the same time in the day for consistency.

[x] Record all AEs from time of consent through 30 days after the last dose of study drug. Start to record concomitant medications from 30 days prior to Day 1 until 30 days after the last dose of study drug. If there is any change in the subject's concomitant medications during the study, it must be recorded on the eCRF.

[y] For subjects in the Ph 1b portion: The study nurse (or designee) will call the subject on Cycle 1 Days 3 and 4, approximately 6–10 hours after the expected study drug dosing time to follow up on dosing compliance and to collect start, stop, and duration times as well as severity of any AEs, if applicable.

APPENDIX C EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE SCALE

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Death

Source: Oken 1982.
Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair

APPENDIX D NCI-CTCAE VERSION 4.03

Common Terminology Criteria for Adverse Events (CTCAE)
of the National Cancer Institute (NCI) v4.03

Publish Date: 14 June 2010

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

APPENDIX E CYTOCHROME P450 3A4 (CYP3A4) SUBSTRATES WITH NARROW THERAPEUTIC RANGE

CYP3A4 substrates with narrow therapeutic range refers to drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of CYP3A4 inhibitors may lead to serious concerns. Investigators should seriously consider switching to an alternative agent whenever possible, or exercise caution and be alert for signs requiring dose modification. The following list provides examples of CYP3A4 substrates with narrow therapeutic range (note that this is not an exhaustive list):

Alfentanil	Diergotamine	Quinidine
Astemizole[a]	Ergotamine	Sirolimus
Cisapride[1]	Fentanyl	Tacrolimus
Cyclosporine	Pimozide	Terfenadine[1]

[a] Not available in the United States.

APPENDIX F RESPONSE CRITERIA FOR MULTIPLE MYELOMA

Summary of International Myeloma Working Group - Uniform Response Criteria (IMWG-URC)

Response Subcategory[a]	Response Criteria
sCR[b]	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow and • Normal SFLC ratio and • Absence of clonal cells in bone marrow[c]
CR[b]	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow
VGPR[b, d]	• Serum and urine M-protein detectable by immunofixation, but not on electrophoresis or • ≥ 90% reduction in serum M-component with urine M-component < 100 mg per 24 hours
PR[b, d]	• ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours • If the serum and urine M-protein are not measurable, a decrease ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • If the serum and urine M-protein are not measurable, a decrease ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • If present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required[d, e]
Stable	• Not meeting criteria for sCR, CR, VGPR, PR, or PD

Summary of International Myeloma Working Group - Uniform Response Criteria (IMWG-URC) (cont'd)

Response Subcategory[a]	Response Criteria
PD[e]	Any one or more of the following: • Increase of ≥ 25% from lowest response value in: o Serum M-component (absolute increase must be ≥ 0.5 g/dL) and/or o Urine M-component (absolute increase must be ≥ 200 mg per 24 hours) and/or o Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) o Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥ 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in size of existing bone lesions or soft tissue plasmacytomas[f, g, h] • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.87 mmol/L) attributed solely to the plasma cell proliferative disorder

Sources: Durie 2006; Rajkumar 2011.

CR = complete response; sCR = stringent complete response; FLC = serum free light chain; PD = progressive disease; PR = partial response; SFLC = serum free light chain; VGPR = very good partial response.

[a] Subjects with measurable disease in both serum (SPEP) and urine (UPEP) at study entry are required to meet response criteria in both UPEP and SPEP in order to qualify for a PR or better. Conversely, it should be noted that criteria for PD only need to be met and confirmed in 1 parameter.

[b] All response categories (CR, sCR, VGPR, PR) require 2 consecutive assessments made at any time before the institution of any new therapy, as well as no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments are not required to be confirmed by repeat testing.

[c] Presence/absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of > 4:1 or < 1:2.

[d] Response criteria for all categories and subcategories of response except CR and VGPR are applicable only to subjects that have "measurable" disease defined by at least one of SPEP ≥ 0.5 g/dL) or UPEP ≥ 200 mg per 24 hours; except for assessment of sCR, CR, or VGPR, subjects with measurable disease restricted to SPEP will need to be followed only by SPEP. Correspondingly, subjects with measurable disease restricted to UPEP will need to be followed only by UPEP.

[e] Determination of PD while on study requires 2 consecutive assessments made at any time before classification of PD and/or the institution of new therapy. Serum M-component increases of ≥ 1 g/dL is sufficient to define progression if starting M-component is ≥ 5 g/dL.

[f] Plasmacytomas: A definite increase in the size is defined as a ≥ 50% increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion. A plasmacytoma is considered measurable if the longest diameter is at least 1 cm and the product of the cross diameters is at least 1 cm^2. Plasmacytomas of lesser size will be considered nonmeasurable.

[g] The requirement for bi-directional measurements will only be applied to plasmacytomas.

[h] The plasmacytoma specifications for PD are based on the sponsor's interpretation of the IMWG-URC and practical considerations for study execution.

APPENDIX G ACTG BRIEF PERIPHERAL NEUROPATHY SCREENING TOOL

Source: NIAID Adult AIDS Clinical Trials Group

1. Elicit Subjective Symptoms

Ask the subject to rate the severity of each symptom listed in Question 1 on a scale of 01 (mild) to 10 (most severe) for right and left feet and legs. Enter the score for each symptom in the columns marked R (right lower limb) and L (left lower limb). If a symptom has been present in the past, but not since the last visit, enter "00 - Currently Absent." If the symptom has never been present, enter "11 - Always Been Normal."

Always Been Normal	**Currently Absent**	**Mild ⟷ Severe**									
11	00	01	02	03	04	05	06	07	08	09	10

Symptoms	**R**	**L**
a. Pain, aching, or burning in feet, legs		
b. "Pins and needles" in feet, legs		
c. Numbness (lack of feeling) in feet, legs		

2. Grade Subjective Symptoms

Use the single highest severity score from Question 1 above to obtain a subjective sensory neuropathy score. If all severity scores are "00" or "11," the subjective sensory neuropathy score will equal "0."

Subjective Sensory Neuropathy Score (based on highest severity rating)

01−03 = grade of 1
04−06 = grade of 2
07−10 = grade of 3
11 or 00 = grade of 0

R	**L**

3. Evaluate Perception of Vibration

Compress the ends of a 128-Hz tuning fork just hard enough that the sides touch. Place the vibrating tuning fork on a bony prominence on the subject's wrist or hand to be sure that he/she can recognize the vibration or "buzzing" quality of the tuning fork. Again, compress the ends of the tuning fork just hard enough that the sides touch. Immediately place the vibrating tuning fork gently but firmly on the top of the distal interphalangeal (DIP) joint of one great toe and begin counting the seconds. Instruct the subject to tell you when the "buzzing" stops. Repeat for the other great toe.

APPENDIX H REVLIMID PRESCRIBING INFORMATION

http://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=5fa97bf5-28a2-48f1-8955-f56012d296be&type=pdf&name=5fa97bf5-28a2-48f1-8955-f56012d296be

APPENDIX I CYCLOPHOSPHAMIDE PRESCRIBING INFORMATION

http://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=367b47d7-c4de-4b39-bd3a-69c29d80396f&type=pdf&name=367b47d7-c4de-4b39-bd3a-69c29d80396f

APPENDIX J DEXAMETHASONE PRESCRIBING INFORMATION

http://dailymed.nlm.nih.gov/dailymed/getFile.cfm?id=5672&type=pdf&name=537b424a-3e07-4c81-978c-1ad99014032a

APPENDIX K REVLIMID RISK EVALUATION AND MITIGATION STRATEGY (REMS)™ PROGRAM

http://www.revlimidrems.com/pdf/REV_Prescriber_Guide.pdf

APPENDIX K: SUMMARY OF CHANGES IN PROTOCOL OPZ003 AMENDMENT 1

Study OPZ003 was amended to add a treatment regimen of oprozomib, cyclophosphamide, and dexamethasone (OCyd), in addition to the existing treatment regimen of oprozomib, lenalidomide, and dexamethasone (ORd). This and other key changes in Amendment 1 are listed below:

1. Global change: The study/protocol title was updated to reflect the addition of the OCyd combination regimen.
2. Global change: "Cyclophosphamide" was added as appropriate throughout the protocol to reflect the addition of the cyclophosphamide (in the OCyd treatment regimen) to the study design.
3. Global change: References to "each combination regimen", "each treatment regimen", "ORd", and "OCyd" were added to distinguish and further clarify between the two treatment regimens.
4. Study Synopsis (Objectives) and Section 3: Changed "safety and tolerability of oprozomib" secondary objective to primary objective for both phases of the study. Revised text to provide clarification on the study objectives.
5. Study Synopsis (Study Design) and Section 4: Added text to provide details regarding the OCyd treatment regimen, and added a study schema for additional clarity on the study design.
6. Study Synopsis (Study Design) and Section 9.1.3: Updated text to provide additional clarification on missed doses of study drug and subject replacement, and to reflect the addition of the OCyd treatment regimen.
7. Study Synopsis (Study Design; Duration of Study/Treatment Periods; Criteria for evaluation: Efficacy variables), Section 4.2, Section 4.6, Section 9.1.3, and Section 10.3: Updated schedule for disease response assessments to reflect the addition of the OCyd treatment regimen, and for consistency between the two combination regimens.
8. Study Synopsis (Number of Investigational Sites) and Section 4.4: Updated the number of investigational sites to reflect the addition of the OCyd treatment regimen.
9. Study Synopsis (Planned Number of Subjects) and Section 4.5: Updated the sample sizes to reflect the addition of the OCyd treatment regimen.
10. Study Synopsis (Duration of Study/Treatment Periods) and Section 4.6: Updated the estimated study duration and treatment periods to reflect the addition of the OCyd treatment regimen.

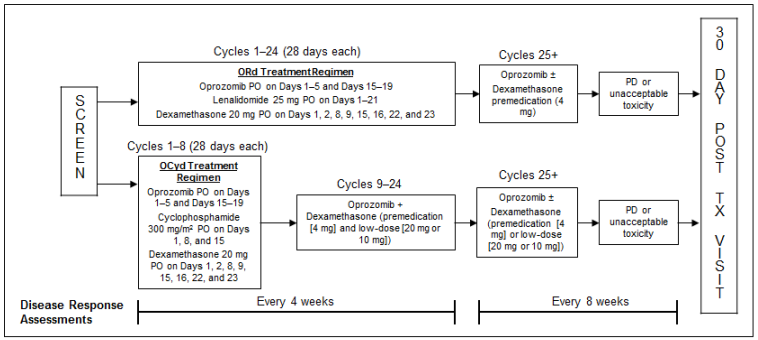
11. Study Synopsis (Inclusion Criteria) and Section 5.1: Text was added to clarify that the inclusion criteria for females and males of reproductive potential are applicable to both treatment regimens. References were changed to the Revlimid REMS guide (added as Appendix J). Added text to clarify for both treatment regimens, contraception is to be used for 3 months following the discontinuation of oprozomib.
12. Study Synopsis (Exclusion Criteria) and Section 5.2: Added lenalidomide-specific exclusion criteria "A history of deep vein thrombosis or pulmonary embolism, with contraindication to anticoagulation and antiplatelet options", and renumbered subsequent exclusion criteria.
13. Study Synopsis (Statistical Methods and Analyses) and Section 13.1: Updated text to reflect the addition of the OCyd treatment regimen, and to provide clarification on the Phase 1b and Phase 2 primary endpoints, and populations for the safety and efficacy analyses.
14. Section 2.1: Revised text to reflect current treatment options for relapsed/refractory multiple myeloma, and updated median OS estimates (based on risk stratification).
15. Section 2.3.2.1: Updated text with the current efficacy and safety data from Study 2009-003.
16. Section 2.3.2.2: Updated text to reflect the current status of, and data from, Study 2011-001.
17. Section 2.3.4: Added new subsection to provide background information on cyclophosphamide.
18. Section 2.4: Revised text to provide updated dose rationale.
19. Section 2.5: Updated text for study rationale to reflect the addition of the OCyd treatment regimen. Added text to provide results from a Phase 2 study of the CRd treatment regimen in subjects with newly diagnosed multiple myeloma (Korde 2012); deleted text as a clarification.
20. Section 4.2: Added dose escalation table for the OCyd treatment regimen.
21. Section 9.1: Revised text to provide additional clarification regarding oprozomib treatment administration in relation to PK sample collection. Deleted redundant text and added a cross-reference to Section 4.1, Study Design.
22. Section 9.3: Added table of dose decrements for cyclophosphamide, and revised table of dose decrements for dexamethasone to include dose reduction details for subjects > 75 years old.
23. Section 9.3.1: Updated table of dose modification guidelines for hematologic toxicities to include guidance for cyclophosphamide-related hematologic toxicities.
24. Section 9.3.2: Updated table of dose modification guidelines for nonhematologic toxicities to include guidance for cyclophosphamide-related nonhematologic toxicities.

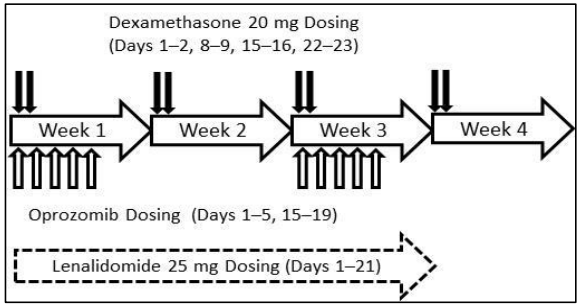
25. Section 9.8.1: Added text to provide specific guidance for the treatment of tumor lysis syndrome. A cross-reference to this section was added in Section 9.7, Safety Guidance for Investigators.
26. Section 9.8.2: Added text to provide specific guidance for antinausea and antiemetics, and antidiarrheals.
27. Section 10.6: Revised text to provide clarification regarding disease assessments for subjects who discontinue treatment before PD occurs.
28. Appendix H: Added cyclophosphamide prescribing information as an appendix, reflecting the addition of the OCyd treatment regimen.
29. Appendix J: Added Revlimid REMS Guide as an appendix to provide guidance for females and males of reproductive potential. This change was applied to both treatment regimens to minimize the risk for confusion around the guidance.

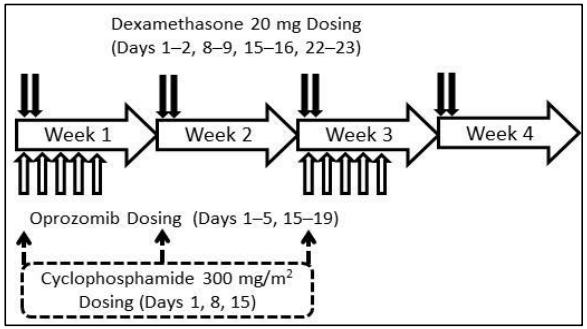
Administrative updates, editorial changes, and style and formatting revisions have been made to improve clarity and consistency throughout the document. Significant changes are described in the table below. Changes in sections of the protocol body were also made in the protocol synopsis and elsewhere in the document, as applicable. Deletions of text are presented in strikethrough format. Added text is presented in bold format.

Section Number	Changed from	Changed to	Rationale
Cover Page Signature Page Protocol Acceptance Page	Phase 1b/2, Multicenter, Open-label Study of Oprozomib, Lenalidomide, and Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma	Phase 1b/2, Multicenter, Open-label Study of Oprozomib and **Dexamethasone in Combination With** Lenalidomide~~, and Dexamethasone~~ **or Oral Cyclophosphamide** in Patients with Newly Diagnosed Multiple Myeloma	Revised study title to reflect the addition of the OCyd treatment regimen.
Cover Page	[redacted], MD, PhD Senior Medical Director, Clinical Science 249 E. Grand Avenue South San Francisco, CA 94080 USA [redacted] Email: [redacted]	[redacted]**, MD** Senior Medical Director, Clinical Science 249 E. Grand Avenue South San Francisco, CA 94080 USA [redacted] Email: [redacted]	Updated.
Cover Page Signature Page Protocol Acceptance Page		**Amendment 1: 19 September 2013**	Added.
Signature Page	[redacted], PhD Vice President, Global Regulatory Affairs [redacted], MD Vice President, Clinical Science [redacted], PhD Senior Director, Biometrics [redacted], MD, PhD Senior Medical Director, Clinical Science	[redacted]**MD** **Executive Vice President, Global Research & Development and Technical Operations** [redacted]**MD** **Vice President of Clinical Science and Biometrics** [redacted]~~MD~~ ~~Senior Vice President, Clinical Development~~ [redacted]PhD Vice President, Global Regulatory Affairs [redacted]~~MD~~ ~~Vice President, Clinical Science~~ [redacted]~~PhD~~ ~~Senior Director, Biometrics~~ [redacted]~~MD, PhD~~ ~~Senior Medical Director, Clinical Science~~	Updated per Sponsor's new approval process, and to reflect proxy approval for Barbara Klencke by Natalie Sacks.

Section Number	Changed from	Changed to	Rationale
Synopsis – Study Objectives 3 Study Objectives	Primary Objectives: Phase 1b: •To establish the maximum tolerated dose (MTD) of oprozomib administered orally in combination with lenalidomide and dexamethasone Phase 2: • To estimate the overall response rate (ORR) and complete response rate (CRR) Secondary Objectives: • To evaluate the safety and tolerability of oprozomib administered in combination with lenalidomide and dexamethasone • To evaluate population pharmacokinetic (PK) parameter estimates of oprozomib and variability in these estimates when administered in combination with lenalidomide and dexamethasone • To estimate the duration of response (DOR) • To estimate progression-free survival (PFS) Exploratory Objectives: • To evaluate pharmacodynamic (PDn) biomarkers that may correlate with antitumor activity • To evaluate genomic biomarkers that may predict response and resistance following treatment with proteasome inhibitors	Primary Objectives: Phase 1b: • To establish the maximum tolerated dose (MTD) of oprozomib **given in combination with lenalidomide and dexamethasone (ORd) or with cyclophosphamide and dexamethasone (OCyd)** ~~administered orally in combination with lenalidomide and dexamethasone~~ • **To evaluate the safety and tolerability of the ORd and OCyd combination regimens, as assessed by the type, incidence, severity and seriousness of adverse events [AEs], and abnormalities in selected laboratory analytes)** Phase 2: • To estimate the **antitumor activity of the ORd and OCyd combination regimens, as measured by** overall response rate (ORR) and complete response rate (CRR) • **To evaluate the safety and tolerability of the ORd and OCyd combination regimens, as assessed by the type, incidence, severity and seriousness of adverse events [AEs], and abnormalities in selected laboratory analytes)** Secondary Objectives: ~~• To evaluate the safety and tolerability of oprozomib administered in combination with lenalidomide and dexamethasone~~ • To evaluate population pharmacokinetic	Updated text to change "safety and tolerability of oprozomib" from a secondary objective to a primary objective for both phases of the study, to reflect the addition of the OCyd treatment regimen, and to provide clarification on the study objectives.

Section Number	Changed from	Changed to	Rationale
		(PK) parameter estimates of oprozomib and **the** variability in these estimates ~~when administered in combination with lenalidomide and dexamethasone~~ • To estimate the duration of response (DOR) • To estimate progression-free survival (PFS) Exploratory Objectives**:** • To evaluate pharmacodynamic (PDn) biomarkers that may correlate with antitumor activity • To evaluate genomic biomarkers that may predict response and resistance following treatment with proteasome inhibitors	
Synopsis – Study Design 4 Study Design Appendix A Schedule of Assessments	This is an open-label, Phase 1b/2, ~~single~~ **two-combination regimen**, non-randomized, multicenter study **(see study schema below).** **Study Schema for OPZ003**  **In one combination regimen (ORd),** ~~in which~~ subjects will receive Oprozomib Tablets (hereafter referred to as oprozomib) administered orally, once daily on Days 1–5 and on	Added text to provide details regarding the OCyd treatment regimen. Added a study schema for additional clarity on the study design.

Section Number	Changed from	Changed to	Rationale
	Days 15–19 in combination with lenalidomide **at a dose of** 25 mg on Days 1–21, and dexamethasone **at a dose of** 20 mg on Days 1, 2, 8, 9, 15, 16, 22, and 23 of 28-day cycles (see **dose administration** schema below). ~~Alternative dosing schedules may be evaluated during the Phase 1b portion of this study, if deemed necessary due to the observed toxicity profile.~~ **Dose Administration Schema for Oprozomib, Lenalidomide, and Dexamethasone (ORd)**  The ORd combination will be administered until progression of disease, unacceptable toxicity, or **for** 24 cycles (approximately 24 months), whichever occurs first. Subjects who complete 24 cycles of treatment and ~~who~~ have stable disease or better will continue on oprozomib, with or without dexamethasone premedication (~~e.g.,~~ 4 mg/day) until progression of disease or unacceptable toxicity. Lenalidomide will be administered for a maximum of 24 cycles. Dexamethasone will be **administered** ~~taken~~ at a dose of 20 mg/day, as described above, through the first cycle, after which the dose may be decreased to 10 mg/day in subjects > 75 years of age, at the discretion of the investigator. **In the second combination regimen (OCyd), subjects will receive oprozomib administered orally, once daily on Days 1–5 and on Days 15–19 in combination with oral cyclophosphamide at a dose of 300 mg/m^2 on Days 1, 8, and 15, and dexamethasone at a dose of 20 mg on Days 1, 2, 8, 9, 15, 16, 22, and 23 of 28-day cycles (See dose administration schema below). Dexamethasone will be administered at a dose of 20 mg/day, as described above, through the first cycle, after which the dose may be decreased to 10 mg/day in subjects > 75 years of age, at the discretion of the investigator.**		

Section Number	Changed from	Changed to	Rationale
	Dose Administration Schema for Oprozomib, Cyclophosphamide, and Dexamethasone (OCyd)  **The OCyd combination will be administered until progression of disease, unacceptable toxicity, or for 8 cycles (approximately 8 months), whichever occurs first. Subjects who complete 8 cycles of treatment and who have stable disease or better will continue on oprozomib, with dexamethasone premedication. Dexamethasone dosing, premedication and low-dose (e.g., 20 mg or 10 mg), should continue for a total of 24 cycles, or until progression of disease or unacceptable toxicity. Subjects who complete 24 cycles of oprozomib therapy (total) without evidence of progression, may continue therapy with or without dexamethasone, premedication or low-dose. A taper of dexamethasone after 24 cycles may be utilized as per institutional guidelines. Cyclophosphamide will be administered for a maximum of 8 cycles.** Note: Subjects **receiving either treatment regimen,** who complete at least 4 cycles of study treatment and achieve a~~n~~ **confirmed** ~~objective~~ response (i.e., ~~a~~ partial response [PR], very good partial response [VGPR], complete response [CR], or stringent complete response [sCR]) may, after discussion with the Onyx study medical monitor, suspend study treatment for up to 6 weeks to undergo a hematopoietic stem cell harvest. Stem cell mobilization will be conducted using a noncytotoxic regimen such as granulocyte colony–stimulating factor (G-CSF). These subjects may then **resume** ~~continue~~ study treatment until progression of disease, unacceptable toxicity, or for a total of 24 cycles of treatment with lenalidomide **or a total of 8 cycles of treatment with cyclophosphamide**, **followed by** ~~along with continued~~ oprozomib treatment **with low-dose dexamethasone (20 mg or**		

Section Number	Changed from	Changed to	Rationale
	10 mg) for subjects free from progression, as described above. Phase 1b: The Phase 1b portion of the study will identify any dose-limiting toxicities (DLTs) and **determine** the MTD, evaluate the safety and tolerability, and assess PK/PDn of oprozomib when administered as described above in subjects with newly diagnosed symptomatic multiple myeloma (see the Study Population section below for details). A standard 3 + 3 dose-escalation scheme will be used. **For each combination regimen**, ~~O~~**o**prozomib doses will be escalated in sequential cohorts of 3 subjects with expansion **to** up to 6 subjects if a DLT is observed in one of the first 3 subjects. **The doses of lenalidomide, cyclophosphamide, and dexamethasone will remain fixed in all dose cohorts.** The initial cohort **for each combination regimen** will be entered at a **daily** dose level of 210 mg oprozomib~~, 25 mg lenalidomide, and 20 mg dexamethasone. The lenalidomide and dexamethasone doses will remain fixed while~~ The dose of oprozomib for subsequent cohorts will be escalated in 30- mg increments until the MTD is established**. In the Phase 1b portion of the study, dose cohorts will be enrolled sequentially, alternating between the ORd and OCyd treatment regimens across sites.** There will not be a predefined maximum dose to be studied. Subjects will be evaluated for DLTs according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03. In the event that the initial cohort**s** at the 210 mg dose ~~is~~ **are** found to exceed the MTD, dosing will proceed at 180 mg or a lower dose as agreed to by the Cohort Safety Review Committee (CSRC), comprised of the Onyx study medical monitor, Onyx safety representative, and the active investigators). Intrasubject dose escalation to the **MTD or** recommended Phase 2 dose may be permitted once that dose has been determined and after a discussion has occurred between the treating physician and Onyx study medical monitor. **Maximum Tolerated Dose** **For each dosing schedule, the MTD will be defined as the highest dose at which a DLT is observed in fewer than 2 of 6 patients. At least 6 patients must be treated at the MTD for a minimum of 1 cycle to establish this dose as tolerated.**		
Synopsis – Study Design 9.1.3 Definition of Dose-limiting Toxicity	Dose-Limiting Toxicities: During the Phase 1b portion, assessment of DLTs will occur during the first cycle of combination therapy (first 4 weeks). For the purposes of this study, a DLT is defined as any of the following treatment-related events occurring in the first 28 days	Dose-Limiting Toxicities: During the Phase 1b portion, assessment of DLTs will occur during the first cycle of combination therapy (first 4 weeks). For the purposes of this study, a DLT is defined as any of the following treatment-related events occurring in the first 28 days	The definition of a DLT for use in the Phase 1b component of the study was modified to accommodate FDA's requested changes to another oprozomib protocol; text regarding Grade ≥ 3 rash and Grade 4 neutropenia was

Section Number	Changed from	Changed to	Rationale
	of treatment: Nonhematologic DLT: • Any ≥ Grade 3 nonhematologic toxicity with further clarifications as described below: o ≥ Grade 3 acute kidney injury (creatinine > 3 × baseline or > 4.0 mg/dL) must last > 72 hours to be a DLT o Grade 3 nausea, vomiting, diarrhea, or constipation will be a DLT only if occurring despite optimal supportive care, which at a minimum, must include a 5–hydroxytryptamine type–3 (5-HT3) antagonist and aprepitant for nausea and vomiting o Asymptomatic Grade 3 hypophosphatemia is not considered a DLT o Grade 3/4 hyperglycemia or toxicity solely due to dexamethasone is not considered a DLT (see dose reduction guidelines for dexamethasone in Section 9.3.2) o Grade 3 fatigue lasting < 14 days is not considered a DLT Hematologic DLT: • Grade 4 neutropenia: Absolute neutrophil count (ANC) < 0.5×10^9/L lasting ≥ 7 days	of treatment: Nonhematologic DLT: • Any ≥ Grade 3 nonhematologic toxicity with ~~further clarifications as described below~~ **the following exceptions or qualifications**: ~~o ≥ Grade 3 acute kidney injury (creatinine > 3 × baseline or > 4.0 mg/dL) must last > 72 hours to be a DLT~~ o **≥** Grade 3 nausea, vomiting, diarrhea, or constipation will be **considered** a DLT only if **lasting > 7 days** ~~occurring~~ despite optimal supportive care, **including** ~~which~~ **(**at a minimum**)**, ~~must include~~ a 5-hydroxytryptamine type-3 (5-HT_3) antagonist and aprepitant for nausea ~~and~~/vomiting **and (e.g., Imodium), and diphenoxylate/atropine (e.g., Lomotil) for diarrhea** o Asymptomatic Grade 3 hypophosphatemia is not considered a DLT o **≥** Grade 3 hyperglycemia or toxicity solely due to dexamethasone is not considered a DLT (see dose reduction guidelines for dexamethasone in Section 9.3.2) o Grade 3 fatigue lasting < 14 days is not considered a DLT o **Grade ≥ 3 rash attributed specifically to lenalidomide is not a DLT** Hematologic DLT:	added for clarification.

Section Number	Changed from	Changed to	Rationale
		• Grade 4 neutropenia: Absolute neutrophil count (ANC) < 0.5 × 109/L lasting ≥ 7 days**, despite myeloid growth factor support**	
Synopsis – Study Design 4.2 Dose Escalation Plan 9.1.3 Definition of Dose-limiting Toxicity	Subject Replacement: In the Phase 1b portion of the study, subjects who miss more than 1 planned dose of oprozomib, 2 planned doses of lenalidomide, or 1 planned dose of dexamethasone during Cycle 1 for reasons other than a DLT, will be unevaluable and replaced for the purpose of MTD determination. Subjects who discontinue study treatment for any reason after Cycle 1 will not be replaced.	Subject Replacement **In the Phase 1b portion of the study, subjects must meet the following criteria to be considered evaluable for MTD determination during the 4 week DLT evaluation period:** • **A minimum of 8 of 10 planned doses of oprozomib must be received** • **A minimum of 6 of 8 planned doses of dexamethasone must be received** • **All 3 planned doses of cyclophosphamide must be received (OCyd combination regimen only)** • **A minimum of 17 of 21 planned doses of lenalidomide must be received (ORd combination regimen only)** **Subjects not meeting all of the above criteria or assessed as unevaluable by the CSRC will be replaced. Subjects who do not meet the criteria above because of a DLT will be considered DLT-evaluable.** ~~In the Phase 1b portion of the study, subjects who miss more than 1 planned dose of oprozomib, 2 planned doses of lenalidomide, or 1 planned dose of dexamethasone during Cycle 1 for reasons other than a DLT, will be unevaluable and replaced for the purpose of MTD determination. Subjects who discontinue study treatment for any reason after Cycle 1 will not be replaced.~~	Updated text to reflect the addition of the OCyd treatment regimen, and to provide additional clarification on missed doses of study drug and subject replacement.

Section Number	Changed from	Changed to	Rationale
Synopsis – Study Design 4.1 Type/Design of Study	The Phase 2 portion of the study will include up to 35 additional subjects with the same disease characteristics as those in Phase 1b. Phase 2 subjects will be treated at the recommended Phase 2 dose and schedule of oprozomib identified during the Phase 1b portion of the study in order to better characterize the safety and tolerability, antimyeloma activity, and PK.	The Phase 2 portion of the study will include up to 35 additional subjects **in each of the two combination regimens,** with the same **eligibility criteria** ~~disease characteristics~~ as those in Phase 1b. Phase 2 subjects will be treated at the recommended Phase 2 dose and schedule of oprozomib identified during the Phase 1b portion of the study in order to better characterize the safety and tolerability, antimyeloma activity, and PK. **The recommended Phase 2 dose may or may not be the same as the MTD, and will be assessed on the basis of the totality of safety and PK/PDn data. In the Phase 2 portion of the study, subjects will be enrolled alternately between the OCyd and ORd treatment regimens at each site.**	Updated text to reflect the addition of the OCyd treatment regime, and for further clarification on the dose of oprozomib and method of treatment regimen assignment to be used in the Phase 2 portion of the study.
Synopsis – Study Design 10.4 Pharmacokinetic and Pharmacodynamic Measurements	Pharmacokinetics: A sparse sampling strategy will be employed for PK sample collection.	Pharmacokinetics: A sparse sampling strategy will be employed for PK sample collection **from all subjects for both phases of the study**.	Added text to provide clarification regarding PK sample collection.
Synopsis – Study Design 10.5 Genomic Evaluations	Genomics: Analysis of genetic and gene expression biomarkers that may predict response and resistance following treatment with proteasome inhibitors will be conducted on all subjects from both phases of the study who consent to optional genomic biomarker analysis. These analyses will be performed on a baseline bone marrow aspirate (a portion of the bone marrow aspirate sample obtained at baseline will be used; no additional sample is required), blood, and saliva. Additional bone marrow samples for biomarkers may	Genomics: Analysis of genetic and gene expression biomarkers that may predict response and resistance following treatment with proteasome inhibitors will be conducted on all subjects from both phases of the study who consent to optional genomic biomarker analysis. These analyses will be performed on a baseline bone marrow aspirate (a portion of the bone marrow aspirate sample obtained at baseline will be used; no additional sample is required), blood, and saliva. Additional bone marrow samples for biomarkers may	Revised and added text for clarification.

Section Number	Changed from	Changed to	Rationale
	be collected at the time of progression from all subjects who consent.	be collected at the **End of Study Treatment visit** ~~time of progression~~ from all subjects who consent. **End of Study Treatment is defined as the end of protocol-defined therapy.**	
Synopsis – Study Design Synopsis – Criteria for Evaluation	Activity: The International Myeloma Working Group – Uniform Response Criteria (IMWG–URC) will be used to evaluate response. Response assessments will be performed at the end of every 4 week cycle for the first year of study treatment, at the end of every other cycle for the second year of study treatment, and every 12 weeks thereafter. Overall response rate and CRR will be determined based on subjects' best overall response.	Activity: The International Myeloma Working Group – Uniform Response Criteria (IMWG-URC) will be used to evaluate response. **Disease** response assessments will be performed at the end of every 4 week cycle for **24 cycles of ORd or OCyd treatment, and will continue every 8 weeks thereafter, until confirmed PD (See study schema and dose administration schemas for details on the duration of cyclophosphamide dosing).** ~~the first year of study treatment, at the end of every other cycle for the second year of study treatment, and every 12 weeks thereafter.~~ Overall response rate and CRR will be determined based on subjects' best overall response.	Updated schedule for disease response assessments to reflect the addition of the OCyd treatment regimen, and for consistency between the two combination regimens.
Synopsis – Number of Investigational Sites 4.4 Number of Centers	Up to 12 sites in the United States (US) will participate in this study.	Up to ~~12~~ **20** sites in the United States (US) will participate in this study.	Updated text to reflect the addition of the OCyd treatment regimen.
Synopsis – Planned Number of Subjects 4.5 Number of Subjects	Enrollment of up to 59 subjects is planned for this study (up to 24 subjects for the Phase 1b portion of the study and 35 subjects for the Phase 2 portion of the study).	**Total** enrollment of up to ~~59~~ **118** subjects is planned for this study; (**including** up to ~~24~~ **48** subjects for the Phase 1b portion of the study **(24 for each combination regimen [ORd and OCyd])** and ~~35~~ **70** subjects for the Phase 2 portion of the study **(35 subjects for each combination regimen)**.	Updated text to reflect the addition of the OCyd treatment regimen.
Synopsis – Sample Size Justification 4.5.1 Phase 1b 4.5.2 Phase 2	The estimated sample size for the dose-escalation portion of the study is based upon standard 3 + 3 dose-escalation rules and the expectation that 2–6 dosing cohorts of 3–6	The estimated sample size for the dose-escalation portion of the study **of up to 24 subjects for each combination regimen** is based upon standard 3 + 3 dose-escalation	Added text to provide clarification following the addition of the OCyd treatment regimen.

Section Number	Changed from	Changed to	Rationale
13.8 Determination of Sample Size	subjects per cohort will be required to establish the MTD. Enrollment of 35 additional subjects during the Phase 2 portion of the study is based upon the goal of ruling out an ORR < 85% and a CRR < 50% based upon the approximate lower 1-sided 90% confidence interval. With 35 subjects, and an assumed true ORR and true CRR of 95% and 75%, respectively, the probability of ruling out an ORR < 85% and a CRR < 50% with 90% confidence is approximately 88%.	rules and the expectation that 2–6 dosing cohorts of 3–6 subjects per cohort will be required to establish the MTD **for each treatment regimen**. Enrollment of 35 additional subjects **in each combination regimen** during the Phase 2 portion of the study is based upon the goal of ruling out an ORR < 85% and a CRR < 50% based upon the approximate lower 1-sided 90% confidence interval **for each parameter**. **This sample size is based upon a simulation of a multinomial outcome of CR, PR, or PD for various cohort sizes.** With 35 subjects **per combination regimen** and an assumed true ORR and true CRR of 95% and 75%, respectively, the probability of ruling out an ORR < 85% and a CRR < 50% with 90% confidence is approximately 88%, **from the simulation described above. The same assumptions for ORR and CRR are used in determining the sample size for each combination regimen.**	
Synopsis – Duration of Study/Treatment Periods 4.6 Estimated Study Duration	The total study duration is expected to be approximately 36 months. The estimated study duration is based upon the assumption that approximately 10–12 months may be required to enroll all subjects (4–6 months to enroll Phase 1b subjects and 6 months to enroll Phase 2 subjects) and that the average time on study will be approximately 24 months. Subjects must complete an End of Study visit approximately 4 weeks after the last study treatment for safety follow-up. Subjects with disease progression will be considered to have completed the study 30 days after the last dose of study drug(s).	The total study duration is expected to be approximately ~~36~~ **39** months~~. The estimated study duration is~~ based upon the assumption that approximately 10–~~12~~ **15** months may be required to enroll all subjects (~~4–6~~ **6–9** months to enroll Phase 1b subjects and 6 months to enroll Phase 2 subjects) and that the average time on study will be approximately 24 months. **Following completion of 24 cycles of ORd or OCyd treatment, disease response assessments will continue every 8 weeks until confirmed progressive disease (PD). For subjects who discontinue treatment**	Updated text to reflect the addition of the OCyd treatment regimen and the revised schedule for disease response assessments.

Section Number	Changed from	Changed to	Rationale
		before PD occurs (such as for an AE, noncompliance, etc.), disease response assessments will be performed every 4 weeks during the first 24 months of the study and every 8 weeks thereafter, until confirmed PD, or the start of alternative, non-protocol antimyeloma therapy. Subjects must complete an End of Study **Treatment** visit approximately 4 weeks after the last study treatment for safety follow-up. ~~Subjects with disease progression will be considered to have completed the study 30 days after the last dose of study drug(s).~~	
Synopsis – Test Product, Dose, and Mode of Administration	Oral oprozomib with tablet strengths of 60, 90, and 120 mg Oral lenalidomide with capsule strengths of 5, 10, 15, and 25 mg Oral dexamethasone with tablet strengths of 4 and 6 mg	~~Oral~~ **O**prozomib with tablet strengths of 60, 90, and 120 mg to be given PO ~~Oral~~ **L**enalidomide ~~with capsule strengths of 5, 10, 15, and 25~~ **25 mg to be given PO** **Cyclophosphamide 300 mg/m^2 (up to 600 mg) to be given PO** ~~Oral~~ **D**examethasone ~~with tablet strengths of 4 and 6 mg~~ **20 mg to be given PO**	Added and revised text to reflect the addition of the cyclophosphamide (in the OCyd treatment regimen) to the study design.
Synopsis – Treatment Regimen(s) Appendix A, Schedule of Assessments	Oprozomib will be administered in a 28 day cycle at the assigned dose in combination with ~~lenalidomide and~~ dexamethasone **and either lenalidomide (ORd) or cyclophosphamide (OCyd)**: • Oprozomib administered on Days 1–5 and Days 15–19, **for all subjects in the study** • Lenalidomide administered on Days 1–21 **for those subjects receiving the ORd combination regimen** • **Cyclophosphamide administered on Days 1, 8, and 15, for those subjects receiving the OCyd combination regimen** • Dexamethasone administered on Days 1, 2, 8, 9, 15, 16, 22, and 23 **for all subjects in the study** Oprozomib doses may be reduced in 30-mg decrements for up to 2 dose reductions for toxicities per the discretion of the investigator. **Interruption of oprozomib dosing for > 4 weeks for any reason will result in permanent discontinuation of oprozomib. No dose reductions of oprozomib are allowed in Cycle 1.**		Updated text to reflect the addition of the OCyd treatment regimen.

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	~~Note:~~ Subjects who permanently discontinue lenalidomide **or cyclophosphamide** ~~during the study~~ for reasons other than disease progression may continue treatment with oprozomib and dexamethasone, ~~and will be followed~~ until disease progression **as described above. After** ~~or for a maximum of~~ 24 months **the dose of dexamethasone may be decreased to premedication doses (4 mg) with allowances for a taper as clinically indicated.** ~~whichever occurs first~~. ~~Subjects who permanently discontinue oprozomib for any reason prior to the completion of Cycle 1 will be removed from the study and will not be followed for disease progression.~~ Subjects receiving the **ORd treatment regimen** who permanently discontinue oprozomib for reasons other than disease progression following the completion of Cycle 1, may continue treatment with lenalidomide and dexamethasone, ~~and will be followed~~ until disease progression or for a maximum of 24 ~~months~~ **cycles**, whichever occurs first. Subjects who discontinue both lenalidomide and oprozomib may not continue treatment with dexamethasone alone. **Subjects receiving the OCyd treatment regimen who permanently discontinue oprozomib for reasons other than disease progression following the completion of Cycle 1, may continue treatment with cyclophosphamide and dexamethasone until disease progression or for a maximum of 8 cycles, whichever occurs first. Subjects who discontinue both cyclophosphamide and oprozomib may not continue treatment with dexamethasone alone.**		
Synopsis – Inclusion Criteria 5.1 Inclusion Criteria	Main inclusion criteria are: 1. Newly diagnosed, symptomatic multiple myeloma patients for whom a hematopoietic stem cell transplant is not planned or scheduled during the study or are considered ineligible for hematopoietic stem cell transplant, with measurable disease as indicated by one or more of the following: a. Serum M-protein ≥ 500 mg/dL b. Urine M-protein ≥ 200 mg/24 hour c. Serum free light chain (FLC): Involved FLC level ≥ 10 mg/dL provided serum FLC ratio is abnormal	Main inclusion criteria are: 6. Newly diagnosed ~~symptomatic multiple myeloma patients~~ **multiple myeloma patients for whom treatment is indicated per the National Comprehensive Cancer Network (NCCN) guidelines,** and for whom a hematopoietic stem cell transplant is not planned or scheduled during the study or are considered ineligible for hematopoietic stem cell transplant, with measurable disease as indicated by one or more of the following: a. Serum M-protein ≥ 500 mg/dL b. Urine M-protein ≥ 200 mg/24 hour c. Serum free light chain (**S**FLC): Involved SFLC level ≥ 10 mg/dL provided serum FLC ratio is	Revised text to provide clarification around term "symptomatic"

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		abnormal	
Synopsis – Inclusion Criteria 5.1 Inclusion Criteria	8. Female patients of childbearing potential (FCBP) must agree to ongoing pregnancy testing and to practice contraception according to, and for the timeframe outlined in the Revlimid Prescribing Information. Postmenopausal females (> 45 years old and without menses for > 24 consecutive months) and surgically sterilized females are exempt from these requirements. Two effective contraceptive methods must be used by FCBP for at least 4 weeks prior to start of lenalidomide therapy, during therapy, and during dose interruptions, and for 4 weeks following discontinuation of lenalidomide therapy. 9. Male subjects must agree to practice contraception according to, and for the timeframe outlined in the Revlimid Prescribing Information. Male subjects receiving lenalidomide must use an effective method of contraception during any sexual contact with FCBP, even if the subject has undergone a successful vasectomy.	8. **For both treatment regimens (ORd and OCyd):** Females of childbearing potential (FCBP) must agree to ongoing pregnancy testing and to practice contraception **as** ~~according to, and for the timeframe~~ outlined in the Revlimid **REMS Guide (Appendix J).** Two effective contraceptive methods must be used by FCBP for at least ~~4 weeks~~ prior to start o**f lenalidomide or cyclophosphamide** therapy, during therapy, and during dose interruptions, and for **3 months following the discontinuation of oprozomib** ~~4 weeks following discontinuation of lenalidomide or cyclophosphamide therapy.~~ Postmenopausal females (> 45 years old and without menses for > 24 consecutive months) and surgically sterilized females are exempt from these requirements. 9. **For both treatment regimens (ORd and OCyd):** Male subjects must agree to practice contraception **as** ~~according to, and for the timeframe~~ outlined in the Revlimid **REMS Guide (Appendix J)** Male subjects receiving lenalidomide **or cyclophosphamide** must use an effective method of contraception during any sexual contact with FCBP **during the study, and for 3 months following the discontinuation of oprozomib,** even if the subject has undergone a successful vasectomy.	Text was added to clarify that inclusion criteria for females and males of reproductive potential are applicable to both treatment regimens; references were changed to the Revlimid REMS Guide (added as Appendix J); added text to clarify for both treatment regimens, contraception is to be used for 3 months following the discontinuation of oprozomib.

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Synopsis – Exclusion Criteria 5.2 Exclusion Criteria	2. Any prior antimyeloma therapy except oral steroids (dexamethasone up to a total dose of 160 mg or equivalent within 14 days prior to the first dose of study treatment). Use of topical or inhaled steroids is acceptable.	2. Any prior **systemic** antimyeloma therapy except oral steroids (dexamethasone up to a total dose of 160 mg or equivalent within 14 days prior to the first dose of study treatment). Use of topical or inhaled steroids is acceptable.	Added text for clarification.
Synopsis – Exclusion Criteria 5.2 Exclusion Criteria		**6. A history of deep vein thrombosis or pulmonary embolism, with contraindication to anticoagulation and antiplatelet options**	Added lenalidomide-specific exclusion criteria, and renumbered subsequent exclusion criteria.
Synopsis – Exclusion Criteria 5.2 Exclusion Criteria	10. Other malignancy within the past 3 years with the exception of adequately treated basal cell carcinoma of the skin, squamous cell skin cancer, thyroid cancer, carcinoma in situ of the cervix, carcinoma in situ of the breast, prostate cancer with Gleason Score 6 or less with stable prostate specific antigen levels, or cancer considered cured by surgical resection	11. Other malignancy within the past 3 years **except those considered cured by surgical resection including some cases of:** • **Adequately treated basal or squamous cell carcinoma of the skin** • **Thyroid cancer** • **Carcinoma in situ of the breast or cervix** • **Prostate cancer with Gleason Score of 6 or less with stable prostate-specific antigen levels**	Revised text to provide additional clarification.
Synopsis – Statistical Methods and Analyses 13 Statistics	The safety evaluable population includes all subjects receiving treatment with any amount of the treatment regimen (oprozomib, lenalidomide, or dexamethasone) under study. Efficacy analyses will also be performed using the safety evaluable population. The primary endpoints of the Phase 1b portion of the study are the safety and assessment of the MTD of oprozomib. The primary efficacy endpoints for the	**Phase 1b:** The safety evaluable population includes all subjects receiving treatment with any amount of the treatment regimen (oprozomib **and dexamethasone with either lenalidomide or cyclophosphamide**) under study. **Phase 2: Safety and** efficacy analyses will be performed using the safety evaluable population. **Additional efficacy analyses will be performed using the response evaluable population, defined as subjects**	Updated text to reflect the addition of the OCyd treatment regimen, and to provide clarification on the Phase 1b and Phase 2 primary endpoints, and populations for the safety and efficacy analyses.

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	Phase 2 portion of the study are overall response and CR for subjects treated at the recommended Phase 2 dose. … Safety will be assessed through summaries of DLTs, AEs, and changes in laboratory test results, ECGs, vital signs, and oprozomib exposure. All collected AE data will be listed by study site, cohort, patient number, and study day.	**who are included in the safety evaluable population, and have a baseline disease assessment and at least one post-baseline disease assessment, or dropped out due to AE prior to first post-baseline disease assessment.** The primary **safety** endpoints **for both combination regimens (ORd and OCyd) in the Phase 1b and Phase 2 portions of the study are the incidence, nature, and severity of AEs, serious adverse events (SAEs), and DLTs (Phase 1b only) of oprozomib, given in combination with dexamethasone, and either lenalidomide or cyclophosphamide, as well as changes from baseline in selected laboratory analytes, vital signs and ECG findings.** … Safety **and tolerability** will be assessed through summaries of **study drug administration**, DLTs **(Phase 1b only),** AEs, and changes in laboratory test ~~results~~ **analytes**, ECGs, and vital signs, and oprozomib exposure **by dose cohort, the combined MTD dose levels, and for all subjects.** All ~~collected~~ AE data will be listed by study site, **treatment regimen, dose** cohort, ~~patient~~ **subject** number, and study day.	

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2.1 Multiple Myeloma	Current treatment options commonly include combination chemotherapy with regimens using melphalan (Alkeran®), bortezomib (Velcade®), thalidomide (Thalomid®), and lenalidomide (Revlimid®) with and without corticosteroids such as dexamethasone or prednisone and other agents. … Median OS from diagnosis was reported at 42 months (Jawed 2007).	Current treatment options for **multiple myeloma** commonly include **combination regimens using alkylators such as** ~~combination chemotherapy with regimens using~~ melphalan (Alkeran~~®~~) **or cyclophosphamide (Cytoxan),** bortezomib (Velcade~~®~~), **carflizomib (Kyprolis), an immunomodulatory agent including** thalidomide (Thalomid~~®~~), ~~and~~ lenalidomide (Revlimid~~®~~), **or pomalidomide (Pomalyst),** with and without corticosteroids such as dexamethasone or prednisone, and other agents. … **Median OS from diagnosis was reported 3 years for high-risk subjects, 4–5 years for intermediate-risk subjects, and 8–20 years for standard-risk subjects (Mikhael 2013).** ~~Median OS from diagnosis was reported at 42 months (Jawed 2007).~~	Revised text to reflect current treatment options for relapsed/refractory multiple myeloma, and updated median OS estimates based on risk stratification.
2.3.2.1 Study 2009-003	At least 1 adverse event (AE) was observed in all 25 subjects treated on the once daily dosing schedule. The most commonly observed study drug-related AEs (≥ 30%) were nausea (92.0%), vomiting (92.0%), diarrhea (76.0%), fatigue (52.0%), abdominal pain (44.0%), and decreased appetite (44.0%). A total of 8 serious adverse events (SAEs) were experienced by 7 of 25 (28.0%) subjects on the once daily dosing schedule. One serious event of confusion in a subject treated at the 180 mg dose level was assessed as related to study drug. … The most commonly observed study	At least 1 **treatment-related** adverse event (AE) was observed in **23 (92.0%) of the** ~~all~~ 25 subjects treated on the once daily dosing schedule. **The most common treatment-related AEs were nausea (92.0%), vomiting (76.0%), fatigue (52.0%), diarrhea (44.0%), and decreased appetite (44.0%).** ~~The most commonly observed study drug-related AEs (≥ 30%) were nausea (92.0%), vomiting (92.0%), diarrhea (76.0%), fatigue (52.0%), abdominal pain (44.0%), and decreased appetite (44.0%).~~ **A total of 7 subjects (28.0%) in the once daily dosing group experienced at least 1 treatment-emergent serious adverse event (SAE).** ~~A total of 8 serious adverse~~	Updated text with current efficacy and safety data from Study 2009-003.

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	drug-related AEs (≥ 30%) were vomiting (94.7%), nausea (89.5%), diarrhea (68.4%), fatigue (36.8%), and decreased appetite (36.8%). A total of 13 SAEs were experienced by 8 of 19 (42.1%) subjects on the twice daily dosing schedule. Of these SAEs, nausea and vomiting (observed in a subject treated at 90 mg/day total dose), and anemia (observed in a subject treated at the 120 mg/day total dose) were assessed as related to study drug.	~~events (SAEs) were experienced by 7 of 25 (28.0%) subjects on the once daily dosing schedule.~~ One serious event of confusion in a subject treated at the 180 mg dose level was assessed as related to study drug. … **All 19 subjects treated on the twice daily dosing schedule experienced at least 1 treatment-related AE.** The most common~~ly observed study drug~~ **treatment-**related AEs ~~(≥ 30%)~~ were vomiting (94.7%), nausea (89.5%), diarrhea (68.4%), fatigue (36.8%), and decreased appetite (36.8%). **A total of 8 subjects (42.1%) in the twice daily dosing group experienced at least 1 treatment-emergent SAE.** ~~A total of 13 SAEs were experienced by 8 of 19 (42.1%) subjects on the twice daily dosing schedule.~~ Of these SAEs, nausea and vomiting (observed in a subject treated at 90 mg/day total dose), and anemia (observed in a subject treated at the 120 mg/day total dose) were assessed as related to study drug.	
2.3.2.2 Study 2011-001	This study has undergone 2 amendments. … Subjects enrolled under Amendment 2 of this study are receiving a new modified-release tablet formulation of oprozomib. … In addition to the new tablet formulation that is being tested under Amendment 2, a second, less-intensive dosing schedule is also being evaluated: treatment on Days 1, 2, 8, and 9 of the 14–day cycle (2 consecutive days weekly). Treatment	This study has undergone ~~2~~ **3** amendments. … Subjects enrolled under **and subsequent to** Amendment 2 of this study are receiving a new modified-release tablet formulation of oprozomib. … In addition to the new tablet formulation ~~that is being tested under Amendment 2~~, a second, less-intensive dosing schedule ~~is also being evaluated~~ **was added with**	Updated text to reflect the current status of Study 2011-001.

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	cycles are being repeated until disease progression, unacceptable toxicity, or discontinuation for any reason occurs. A 3 + 3 dose-escalation scheme using 30 mg increments in daily dose is ongoing in order to determine the recommended Phase 2 dose for each treatment schedule. In Phase 2, the 2 treatment schedules will assess differences in PK, PDn, safety, and efficacy between subjects treated on each schedule.	**Amendment 2**: treatment on Days 1, 2, 8, and 9 of the 14-–day cycle (2 consecutive days weekly). Treatment cycles are being repeated until disease progression, unacceptable toxicity, or discontinuation for any reason occurs. A 3 + 3 dose-escalation scheme using 30-mg increments in daily dose is ongoing in order to determine the recommended Phase 2 dose for each treatment schedule. In Phase 2, the 2 treatment schedules will **be** assess**ed for** differences in PK, PDn, safety, and efficacy ~~between subjects treated on each schedule.~~	
2.3.2.2 Study 2011-001	**2.3.2.2.1 Oprozomib in Capsules (Split Daily Dosing Schedule)** **As of March 2013, thirteen (13) subjects have received Oprozomib in Capsules and were evaluable for safety. Subjects treated with capsules have received between 1–28 cycles of treatment on the split daily dosing schedule (n = 3 for the 120 mg, 150 mg, and 180 mg dose cohorts, and n = 4 for the 210 mg dose cohort). At least 1 study drug-related AE has been observed in all 13 subjects treated with Oprozomib in Capsules. Treatment-related AEs observed in ≥ 25% of subjects include nausea (11 subjects), vomiting (9 subjects), diarrhea (8 subjects), fatigue (7 subjects), anemia (5 subjects), and decreased appetite (4 subjects). Seven subjects have experienced at least one Grade 3 AE, which were diarrhea (n = 3), anemia and nausea (n = 2 each), and thrombocytopenia, abdominal pain, fatigue, herpes zoster ophthalmic, neutropenia, pneumonia, back pain, and vomiting (n = 1 each). No Grade 5 AEs have been reported within 30 days of the last dose of study drug. One death has occurred due to progressive disease (PD), 71 days after the last dose of study drug.** **Three subjects experienced at least 1 treatment-emergent SAE, which were pneumonia (n = 1 in the 120 mg cohort), herpes zoster ophthalmic n = 1 in the 120 mg cohort), and nausea (n = 1 in the 150-mg cohort). The event of pneumonia resolved after 2 days without any action taken with study drug. The herpes zoster event resolved after 2 days and required the subject's oprozomib dose to be held or delayed. The nausea event resolved after 2 days and required dose reduction and concomitant mediation.** **As of March 2013, no DLTs have been observed at doses up to 210 mg in subjects**		Updated text with current data from Study 2011-001

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	treated with Oprozomib in Capsules on a split daily dosing schedule. **2.3.2.2.2 Oprozomib Tablets (5 Consecutive Days, Bimonthly Schedule)** **As of March 2013, eleven (11) subjects have received 1–8 cycles of Oprozomib Tablets on the 5 consecutive days, bimonthly schedule (n = 4 for the 150 mg cohort and n = 7 for the 180 mg cohort) and were evaluable for safety. Treatment-related AEs observed in ≥ 25% of subjects include diarrhea (n = 7), nausea (n = 5), and vomiting (n = 4). Five subjects have experienced at least 1 treatment-emergent Grade 3 AE, including diarrhea (n = 2), and anemia, nausea, vomiting, increased creatinine, acute renal failure, confusional state, and headache (n = 1 each). One subject experienced Grade 4 AEs of anemia and sepsis, which which resolved and subject resumed study drug. No Grade 5 AEs have been reported.** **Two subjects treated on the 5 consecutive days, bimonthly schedule experienced at least 1 treatment-emergent SAE (renal failure and PD in 1 subject, and sepsis in the second subject; both in the 180 mg dose cohort). Study drug was permanently discontinued for the Grade 3 renal failure and PD. The Grade 4 sepsis event was considered unrelated to study drug and resolved when study drug was held.** **2.3.2.2.3 Oprozomib Tablets (2 Consecutive Days, Weekly Schedule)** **As of March 2013, eleven (11) subjects have received 1–7 cycles of Oprozomib Tablets on the 2 consecutive days, weekly schedule (n = 3 for each of the 150, 180, and 210 mg cohorts, n = 2 for the 240 mg cohort) and were evaluable for safety. No DLTs have been observed for subjects who have received Oprozomib Tablets on the 2 consecutive days, weekly schedule.** **At least 1 study drug-related AE has been observed in 10 subjects. The most common treatment-related AEs observed in ≥ 25% of subjects were nausea (n = 9), diarrhea (n = 8), vomiting (n = 4), and fatigue (n = 3). Three subjects experienced at least one study treatment-emergent Grade 3 AE, reported individually as diarrhea (n = 2), and vomiting, upper respiratory tract infection, and neutropenia (n = 1 each). The events of diarrhea, vomiting, and neutropenia were considered related to study drug. No Grade 4 or 5 AE have been reported. No SAEs have been reported.** **2.3.2.2.4 Preliminary Pharmacokinetic and Pharmacodynamic Results** **Plasma concentrations of oprozomib reached a time to maximum plasma concentration (t_{max}) at 75.0–90.0 minutes and were cleared with a terminal half-life ($t_{½}$) of 48.9–82.9 minutes following once daily administration of Oprozomib Tablets under fasted conditions. A trend toward a dose-proportional increase in oprozomib**		

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	area under the plasma concentration-time curve to the last time point (AUC_{last}) and C_{max} exposure was observed with the QD×5 and QD×2 weekly regimens, though the number of subjects evaluated at each dose level and schedule was small (n = 3 to 5). The majority (87% to 100%) of the total AUC exposure was observed within 4 hours of dosing. Rapid and potent proteasome inhibition in whole blood was observed after administration of Oprozomib Tablets on Cycle 1, Day 1. Proteasome inhibition was > 75% at 4 hours postdose for Oprozomib Tablets (150 mg; QD×5 and QD×2 weekly). This inhibition was sustained, and surpassed 95% by Cycle 2. **2.3.2.2.5 Preliminary Efficacy Results** **A total of 25 subjects have been treated with oprozomib in this study and were evaluable for efficacy. Of the 12 subjects treated with Oprozomib in Capsules, 3 subjects with multiple myeloma had a partial response (PR) and 2 subjects with multiple myeloma had a minimal response (MR). Of the 6 subjects treated with Oprozomib Tablets on the 2 consecutive days, weekly schedule, 2 subjects with multiple myeloma had an MR. Of the 7 subjects treated with Oprozomib Tablets for 5 consecutive days, bimonthly, 1 subject with multiple myeloma had a very good partial response (VGPR), 1 subject with Waldenström's macroglobulinemia (WM) had a PR, and 1 subject with WM had an MR.** ~~As of January 2013, 13 subjects receiving Oprozomib in Capsules and 11 subjects receiving Oprozomib Tablets in Study 2011-001 have been evaluated for safety. Subjects treated with capsules have received between 1–25 cycles of treatment on the twice daily dosing schedule (n = 3 for the 120 mg, 150 mg, and 180 mg dose cohorts, and n = 4 for the 210 mg dose cohort).~~ ~~At least 1 AE has been observed in all 13 subjects treated with Oprozomib in Capsules. The most common AEs observed in ≥ 4 subjects thus far have been nausea (n = 11), diarrhea (n = 10), vomiting (n = 9), fatigue (n = 8), anemia (n = 6), and decreased appetite and thrombocytopenia (n = 4 each). The most common study drug–related AEs observed in ≥ 4 subjects have been nausea (n = 11), diarrhea and vomiting (n = 9 each), fatigue (n = 7), anemia (n = 5), and decreased appetite (n = 4). Seven subjects experienced at least one Grade 3 AE. Grade 3 AEs were diarrhea (n = 3), anemia and nausea (n = 2 each), and neutropenia, thrombocytopenia, vomiting, abdominal pain, fatigue, back pain, ophthalmic herpes zoster, and pneumonia (n = 1 each). Three subjects experienced Grade 4 thrombocytopenia. No treatment–related Grade 5 AEs have been observed. One nonrelated Grade 3 pneumonia was observed in one subject. No DLTs have been observed to date at doses up to 210 mg/day in subjects treated with Oprozomib in Capsules after the~~		

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	~~January 2013 data cutoff. Four subjects have received 1-4 cycles of Oprozomib Tablets on the 5 consecutive days, bimonthly schedule (n = 4 for the 150 mg cohort). At least 1 AE has been observed in 3 of the 4 subjects treated. The most common AEs observed thus far have been nausea and diarrhea (n = 3 each), and vomiting and myalgia (n = 2 each). Similarly, the most common study drug-related AEs observed have been diarrhea, nausea, and vomiting (n = 2 each). Two subjects experienced at least one Grade 3 AE of diarrhea (n = 2), and nausea and vomiting (n = 1 each). No Grade 4 or 5 AEs have been observed. One DLT (Grade 3 study drug-related acute renal failure) has been observed in a subject treated with Oprozomib Tablets as of the January 2013 data cutoff.~~ ~~Seven subjects have received 1-5 cycles of Oprozomib Tablets on the 2 consecutive days, weekly schedule (n = 3 for the 150 mg dose cohort, n = 3 for the 180 mg dose cohort, and n = 1 for the 210 mg cohort). At least 1 AE has been observed in all subjects. The most common AEs observed thus far have been nausea (n = 6), diarrhea (n = 5), and vomiting (n = 3). Similarly, the most common study drug-related AEs observed thus far have been nausea (n = 6), diarrhea (n = 5), and vomiting (n = 3). One subject has experienced a Grade 3 AE of diarrhea. No Grade 4 or 5 AEs have been observed. No DLTs have been observed to date (up to 210 mg/day total dose) in subjects treated with Oprozomib Tablets after the January 2013 data cutoff date.~~ ~~The AUC exposures following once daily administration of Oprozomib Tablets appear to be similar to the corresponding exposures following twice daily administration of Oprozomib in Capsules at the same total daily dose in patients with hematological malignancies. Maximum concentration was reached within 120 minutes and half-life was 47.4–96.5 minutes after dosing on Cycle 1 Day 1. There appeared to be no effect of food on AUClast or Cmax following Oprozomib Tablet administration. Whole blood proteasome inhibition > 75% was observed in patients receiving Oprozomib Tablets after the first day of dosing in Cycle 1. This inhibition was sustained and reached levels of proteasome inhibition greater than 95% by Cycle 2.~~ ~~A total of 22 subjects have been treated with oprozomib in this study and were evaluable for efficacy. Of the 13 subjects treated with the powder in capsule formulation on the 5 consecutive days, bimonthly schedule, 4 had a partial response ([PR], 1 subject with chronic lymphocytic leukemia and 3 subjects with multiple myeloma) and 2 subjects with multiple myeloma had a minimal response (MR). None of 5 subjects treated with Oprozomib Tablets on the 2 consecutive days, weekly schedule had an objective response by International Myeloma Working Group (IMWG) criteria. Of the 4 subjects treated with Oprozomib Tablets on the 5 consecutive days, bimonthly schedule, 1 subject with multiple~~		

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	~~myeloma had a PR and 1 subject with Waldenström macroglobulinemia had an MR. Overall, 8 of 22 subjects treated with oprozomib have achieved either MR or PR.~~		
2.3.4 Cyclophosphamide Background	*The following new subsection was added:* **2.3.4 Cyclophosphamide Background** Alkylating agents such as melphalan and cyclophosphamide have been the backbone of multiple myeloma therapy for over 40 years. In current practice they are widely used during induction therapy in newly diagnosed multiple myeloma subjects in combination with steroids and one of the novel agents, particularly a proteasome inhibitor (Dispenzieri 2007). Cyclophosphamide is less stem-cell toxic than other alkylating agents, and has predictable, short duration myelosuppression when administered at doses currently in use in multiple myeloma (300–500 mg/m^2) (Volpe 2003; Morgan 2011). These properties have encouraged the use of oral cyclophosphamide in combination with a steroid and proteasome inhibitor in both front-line and relapsed and/or refractory multiple myeloma (Kropff 2007, Kropff 2009, Reece 2008, Reeder 2009, Reeder 2010). The largest published experience with cyclophosphamide-based induction regimens was reported by Reeder et al. (2010) who combined cyclophosphamide 300 mg/m^2 orally (PO) on Days 1, 8, 15, and 22, with dexamethasone 40 mg PO on Days 1–4, 9–12, and 17–20 or Days 1, 8, 15, and 22 and bortezomib 1.3 mg/m^2 IV on Days 1, 4, 8, and 11 or 1.5 mg/m^2 IV on Days 1, 8, 15, and 22 every 28 days for 4 cycles in transplant-eligible subjects (Reeder 2010). The overall response rate (PR or better) for 63 subjects enrolled in this trial was 90%, with 41% complete response/near complete response (CR/nCR) and 60% VGPR or better. Weekly (Days 1, 8, 15, and 22) bortezomib administration led to reduction in Grade 3-4 toxicity (37% versus 48%), without apparent reduction in efficacy. The safety, tolerability, and efficacy of carfilzomib in combination with cyclophosphamide and dexamethasone is being evaluated in a Phase 2 study (Palumbo 2012). Transplant-ineligible subjects with newly diagnosed multiple myeloma received oral cyclophosphamide 300 mg/m^2 on Days 1, 8, and 15; oral dexamethasone 40 mg on Days 1, 8, 15, and 22; and IV carfilzomib 20 mg/m^2 on Days 1 and 2 and 36 mg/m^2 on Days 8, 9, 15, and 16 in Cycle 1, Cycle 2, and beyond, every 28 days for 9 cycles. Median age of the 34 enrolled subjects was 70years; 46% had International Staging System (ISS) Stage III (Appendix F). Nineteen subjects were evaluable for response and safety after at least 4 cycles. All subjects had achieved at least a PR, 74% at least a VGPR, and 42% CR/nCR including 10% stringent complete response (sCR). Responses were rapid with a median time to PR of 1 month. At least one Grade 3-4 nonhematologic AE was reported in 4 subjects (21%). No subjects discontinued treatment and 4 subjects (21%) required		This new subsection was added to provide background information on cyclophosphamide.

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	carfilzomib dose reduction due to AEs (Grade 4 neutropenia, Grade 3 pneumonia, Grade 3 atrial fibrillation, and Grade 3 renal failure). These results are consistent with the report of the "CYCLONE "Phase 1/2 study in patients with newly diagnosed multiple myeloma investigating a combination of carfilzomib with oral cyclophosphamide 300 mg/m^2 on Days 1, 8, and 15; thalidomide 100 mg Days 1–28, and dexamethasone 40 mg on Days 1, 8, 15, and 22 in transplant-eligible subjects. In this report, doses of carfilzomib up to 45 mg/m^2 were safely delivered without DLTs and with a high ORR of 96% (Mikhael 2012). These data, along with the emerging data that oprozomib has similar activity as carfilzomib, suggest that oprozomib, cyclophosphamide, and dexamethasone may be an active regimen for initial treatment of multiple myeloma regardless of transplant eligibility. However, the safety, tolerability and MTD of oprozomib in this combination have not been evaluated. This study will investigate the MTD for oprozomib when given in combination with cyclophosphamide and dexamethasone.		
2.4 Dose Rationale	**The oprozomib starting dose of 210 mg once daily for 5 consecutive days (QD×5) bimonthly for the Phase 1b component of this study is based on preclinical data that suggests improved antimyeloma activity with consecutive day dosing of epoxyketone proteasome inhibitors (Demo 2007) and clinical data collected for subjects exposed to oprozomib on current and completed clinical studies. In the ongoing, dose-escalation phase of Study 2011-001, antimyeloma activity (confirmed MR or better) was reported with the QD×2 weekly regimen and the QD×5 bimonthly dosing schedule, both beginning at a daily dose of 150 mg (Kaufman 2013).** **Safety results from Study 2011-001 demonstrate similar tolerability profiles for QD×2 weekly and QD×5 bimonthly dosing schedules. The most commonly reported adverse events (nausea, vomiting, and diarrhea), were generally transient, mild to moderate, and manageable with antiemetics and over-the-counter antidiarrheal agents. Preliminary data from this trial suggest that dexamethasone premedication (4–8 mg) may reduce GI toxicity.** **Given the activity against multiple myeloma and the acceptable safety profile demonstrated with QD×5 bimonthly dosing, this schedule was chosen for this study. It is further anticipated that oprozomib may have less GI toxicity in combination with low-dose, therapeutic dexamethasone.** ~~The starting dose of 210 mg given once daily on the 5 consecutive days, bimonthly schedule is based on the clinical data collected for subjects exposed to Oprozomib Tablets on current and completed clinical studies.~~ ~~Preliminary safety results from Study 2011-001 (Phase 1b/2, Multicenter, Open-label Study of the Safety and Activity of Oprozomib in Patients with Hematologic Malignancies)~~		Revised text to provide updated dose rationale.

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	~~demonstrate:~~ ~~• Subjects have tolerated 180 mg tablets in the 5 consecutive days, bimonthly schedule.~~ ~~• Subjects have tolerated up to 240 mg tablets in the 2 consecutive days, weekly schedule without the occurrence of 2 DLTs in 3 treated patients and with no other significant safety concerns.~~ ~~• Subjects were able to tolerate up to 210 mg total daily dose with Oprozomib in Capsules administered on the 5 consecutive days, bimonthly schedule without occurrence of DLTs or the occurrence of other significant safety concerns.~~ ~~In a previous study, the addition of steroids to bortezomib has demonstrated a reduction in GI toxicity when compared to bortezomib alone (Jagannath 2006). Preliminary review of safety data from Study 2011-001 suggests that the addition of low doses of therapeutic dexamethasone may reduce GI toxicity. Given that GI AEs have been the most frequent events observed in subjects treated with oprozomib, it is anticipated that Oprozomib Tablets will have less GI toxicity in combination with dexamethasone and therefore, may be safely dosed at the same level as oprozomib monotherapy.~~		
2.5 Study Rationale	An ongoing, Phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone in patients with newly diagnosed multiple myeloma has demonstrated excellent activity and tolerability with 62% of 53 patients achieving near complete response or better and with only Grade 1/2 peripheral neuropathy in 23% of the patients (Jakubowiak 2012). Based on these results, Onyx is conducting an ongoing pivotal study of carfilzomib in combination with lenalidomide and low-dose therapeutic dexamethasone in patients with relapsed multiple myeloma.	An ongoing, Phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone in ~~patients~~ **subjects** with newly diagnosed multiple myeloma has demonstrated excellent activity and tolerability with 62% of 53 ~~patients~~ **subjects** achieving nCR or better and with only Grade 1/2 peripheral neuropathy reported in 23% of the ~~patients~~ **subjects** (Jakubowiak 2012). **Preliminary results from an ongoing Phase 2 study of CRd in untreated newly diagnosed nontransplant and transplant candidates with multiple myeloma have also been reported. After a median of 4 cycles of CRd completed (range 1–8) in 15 evaluable subjects, 40% of subjects achieved nCR or better (4 sCR and 2 nCR), 33% of subjects had VGPR (n = 5), 20% of subjects had PR (n = 3), and 1 subject had SD (6%). No subjects reported grade ≥ 3 neuropathy**	Added text to provide results from a Phase 2 study of the CRd treatment regimen in subjects with newly diagnosed multiple myeloma (Korde 2012); deleted text as a clarification.

Section Number	Changed from	Changed to	Rationale
		(Korde 2012). ~~Based on these results, Onyx is conducting an ongoing pivotal study of carfilzomib in combination with lenalidomide and low-dose therapeutic dexamethasone in patients with relapsed multiple myeloma.~~	
2.5 Study Rationale	Oprozomib appears to have clinically meaningful, single-agent activity in an ongoing study in patients with hematologic malignancies, including multiple myeloma. These properties make oprozomib a promising proteasome inhibitor to combine with lenalidomide and low dose therapeutic dexamethasone to provide an all oral treatment regimen for the frontline treatment of multiple myeloma. The current study is designed to establish the MTD of oprozomib when combined with standard doses of lenalidomide and low-dose therapeutic dexamethasone and to provide a preliminary assessment of the antimyeloma activity of this combination.	**Likewise, and as described above in Section 2.3.4, the combination of carfilzomib and cyclophosphamide also appears to have good anti-myeloma activity and an acceptable safety profile.** Oprozomib appears to have ~~clinically meaningful,~~ single-agent activity in an ongoing study ~~in~~ of patients with hematologic malignancies, including multiple myeloma**. Combining oprozomib** ~~promising proteasome inhibitor to combine~~ with low-dose therapeutic dexamethasone, **plus either cyclophosphamide or lenalidomide,** to provide an all oral treatment regimen for the frontline treatment of multiple myeloma **has obvious appeal**. The current study is designed to establish the MTD of oprozomib when combined with ~~standard doses of lenalidomide and~~ low-dose therapeutic dexamethasone and **standard doses of either cyclophosphamide or lenalidomide, and** to provide a preliminary assessment of the antimyeloma activity of ~~this~~ **these** combination**s**.	Updated text to reflect the addition of the OCyd treatment regimen.
4.2 Dose Escalation Plan	In the Phase 1b portion of the study, oprozomib doses ~~in combination lenalidomide and dexamethasone~~ will be escalated in sequential groups of 3 subjects **for each combination regimen**, with expansion **to** up to 6 subjects if a DLT is observed in one of the first 3 subjects. **The doses of lenalidomide, cyclophosphamide, and dexamethasone will remain fixed in all dose cohorts**. The initial cohort (Table 1 **and Table 2**) **for each**		Updated text to reflect the addition of the OCyd treatment arm, and added dose escalation table for OCyd.

<table>
<tr><th>Section Number</th><th>Changed from</th><th>Changed to</th><th>Rationale</th></tr>
<tr><td></td><td colspan="2">**combination regimen** will be entered at a **daily** dose level of 210 mg oprozomib, ~~25 mg lenalidomide, and 20 mg dexamethasone.~~ ~~The lenalidomide and dexamethasone doses will remain fixed while~~ The dose of oprozomib for subsequent cohorts will be escalated by 30- mg increments ~~of oprozomib~~ until the MTD is ~~reached~~ **established**. There will not be a predefined maximum dose to be studied. Additional details regarding dose escalation can be found in the Cohort Management Plan. **Details on subject replacement are provided in Section 9.1.3. The MTD will be defined as the highest dose in which a DLT is observed in fewer than 2 of 6 patients (Kummar 2006). At least 6 patients must be treated at the MTD for a minimum of 1 cycle to establish this dose as tolerated.**
Table 1: Dose Escalation Scheme: Using Oprozomib **in Combination With Lenalidomide and Dexamethasone (ORd)** ~~Tablets~~
<table>
<tr><th>Cohorts</th><th>Oprozomib Daily Dose (mg)</th><th>Lenalidomide Doses (mg)</th><th>Dexamethasone Doses (mg)</th></tr>
<tr><td>−101[a]</td><td>180</td><td>25</td><td>20</td></tr>
<tr><td>101</td><td>210</td><td>25</td><td>20</td></tr>
<tr><td>102</td><td>240</td><td>25</td><td>20</td></tr>
<tr><td>103</td><td>270</td><td>25</td><td>20</td></tr>
<tr><td>104[b]</td><td>300</td><td>25</td><td>20</td></tr>
</table>
Note: This table is for illustrative purposes.
[a] If DLTs are observed in 2 or more subjects at the first dose level of 210 mg, dosing of Cohort -101 will proceed at 180 mg, or a lower dose as agreed with the Cohort Safety Review Committee (CSRC) and may be expanded **to include** up to 6 evaluable subjects.
[b] Additionally, subsequent cohorts of 3**–6** subjects will continue to be enrolled with doses escalated by 30 mg until the MTD (the highest dose at which a DLT is observed in less than 2 of 6 evaluable subjects) is defined.</td><td></td></tr>
</table>

<table>
<tr><th>Section Number</th><th>Changed from</th><th>Changed to</th><th>Rationale</th></tr>
<tr><td></td><td>Table 2: Dose Escalation Scheme: Oprozomib in Combination With Cyclophosphamide and Dexamethasone (OCyd)
<table>
<tr><th>Cohorts</th><th>Oprozomib Daily Dose (mg)</th><th>Cyclophosphamide Doses (mg/m^2)</th><th>Dexamethasone Doses (mg)</th></tr>
<tr><td>−201[a]</td><td>180</td><td>300</td><td>20</td></tr>
<tr><td>201</td><td>210</td><td>300</td><td>20</td></tr>
<tr><td>202</td><td>240</td><td>300</td><td>20</td></tr>
<tr><td>203</td><td>270</td><td>300</td><td>20</td></tr>
<tr><td>204[b]</td><td>300</td><td>300</td><td>20</td></tr>
</table>
Note: This table is for illustrative purposes.
[a] If DLTs are observed in 2 or more subjects at the first dose level of 210 mg, dosing of Cohort -201 will proceed at 180 mg, or a lower dose as agreed with the Cohort Safety Review Committee (CSRC) and may be expanded to include up to 6 evaluable subjects.
[b] Additionally, subsequent cohorts of 3–6 subjects will continue to be enrolled with doses escalated by 30 mg until the MTD (the highest dose at which a DLT is observed in less than 2 of 6 evaluable subjects) is defined.</td><td></td></tr>
<tr><td>8 Study Drug</td><td>The following new subsection was added:
8.3 CYCLOPHOSPHAMIDE
8.3.1 PHYSICAL DESCRIPTION AND FORMULATION
Cyclophosphamide is an alkylating agent (Cyclophosphamide Prescribing Information 2011; Appendix H).
8.3.2 PACKAGING AND LABELING
Cyclophosphamide is a commercially available drug, available both as tablets for PO administration and as various sterile formulations for parenteral administration (Cyclophosphamide Prescribing Information 2011). Only the tablet formulation will be used in this protocol.
8.3.3 STORAGE
Cyclophosphamide is to be stored at controlled room temperature. Do not store above 25°C. Consult the package insert for additional storage and usage instructions (Cyclophosphamide Prescribing Information 2011).
8.3.4 ACCOUNTABILITY
Sites will be required to record and document patient compliance regarding</td><td></td><td>This new subsection was added to provide information on cyclophosphamide.</td></tr>
</table>

Section Number	Changed from	Changed to	Rationale
	cyclophosphamide dosing. Please refer to the Pharmacy Manual for additional details.		
9.1 Oprozomib	9.1.1 TREATMENT ADMINISTRATION **Oprozomib Tablets will be administered in single daily doses (Table 1 and Table 2) in the following manner:** **Dosing instructions for days on which PK samples will not be collected (non-PK days): Subjects should take oprozomib with approximately 8 ounces of water at approximately the same time of day, with or without food at their discretion. When oprozomib is given on the same day with other treatments, dexamethasone should be administered 30 minutes before oprozomib, lenalidomide and cyclophosphamide. Subjects may take lenalidomide or cyclophosphamide following oprozomib administration at investigator's discretion, however it is recommended that they take their study drugs at approximately the same time each day.** **Dosing instructions for days on which PK samples will be collected (PK days): Dexamethasone should be administered at least 30 minutes before the other medications. Oprozomib and either lenalidomide or cyclophosphamide will be administered in the clinic. Oprozomib should be administered concurrently (i.e., within 5 minutes of each other) with lenalidomide or cyclophosphamide, with approximately 8 ounces of water, to subjects on an empty stomach (at least 2 hours after and 1 hour before a meal).** ~~Oprozomib Tablets will be administered in single daily doses (Table 1). Subjects should take oprozomib at approximately the same time of day, in the morning , with or without food at their discretion, except on PK sample collection days. On the days on which PK samples are to be collected, the oprozomib, dexamethasone, and either lenalidomide or cyclophosphamide will be administered in the clinic. The dexamethasone should be administered approximately 30 minutes before the other medications. The oprozomib and lenalidomide or oprozomib and cyclophosphamide should be administered to subjects within 5 minutes of each other. Theis should be done with subjects having and on an empty stomach (at least 2 hours after or and 1 hour before a meal) with 8 ounces of water.~~ Oprozomib will be administered orally, once daily for 5 consecutive days every other week (i.e., on Days 1, ~~2, 3, 4,~~ **through** 5, **and** 15, ~~16, 17, 18, and~~ **through** 19) of each 28-day treatment cycle (Figure 1). ~~and~~ Treatment with oprozomib will continue until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason (see Section 11). ~~Lenalidomide will be administered at 25 mg, orally, on Days 1 21, and dexamethasone at 20 mg, orally, on Days 1, 2, 8, 9, 15, 16, 22, and 23. On days when oprozomib and dexamethasone are administered concurrently (i.e., on Days 1, 2, 15, and 16~~		Updated text to reflect the addition of the OCyd treatment regimen, and to provide additional clarification regarding oprozomib treatment administration in relation to PK sample collection. Deleted redundant text and added a cross-reference to Section 4.1, Study Design.

Section Number	Changed from	Changed to	Rationale
	~~of each cycle), dexamethasone should be taken at least 30 minutes prior to oprozomib. Oprozomib and lenalidomide should be taken concurrently, i.e., within 5 minutes of each other.~~ ~~Note:~~ Subjects who permanently discontinue lenalidomide **or cyclophosphamide** ~~during the study~~ for reasons other than disease progression may continue treatment with oprozomib and dexamethasone ~~and will be followed~~ until disease progression ~~or for a maximum of 24 months, whichever occurs first~~ **as described above. After 24 months, the dose of dexamethasone may be decreased to premedication doses (4 mg), with allowances for a taper as clinically indicated.** ~~Subjects who permanently discontinue oprozomib for any reason prior to the completion of Cycle 1 will be removed from the study and will not be followed for disease progression.~~ Subjects **receiving the ORd treatment regimen**, who permanently discontinue oprozomib for reasons other than disease progression following the completion of Cycle 1, may continue treatment with lenalidomide and dexamethasone ~~and will be followed~~ until disease progression or for a maximum of 24 months, whichever occurs first. Subjects who ~~permanently~~ discontinue both lenalidomide and oprozomib may not continue treatment with dexamethasone alone. **Subjects receiving the OCyd treatment regimen, who permanently discontinue oprozomib for reasons other than disease progression following the completion of Cycle 1, may continue treatment with cyclophosphamide and dexamethasone until disease progression or for a maximum of 8 months, whichever occurs first. Subjects who discontinue both cyclophosphamide and oprozomib may not continue treatment with dexamethasone alone.** **Guidelines** ~~Procedures~~ for dose modification are **provided** ~~summarized~~ in Section 9.3. **Details on the study design are provided in Section 4.1.** ~~All subjects will continue on combination therapy until disease progression, unacceptable toxicity, or 24 cycles (approximately 24 months), whichever occurs first. Subjects who complete 24 cycles of treatment and who have stable disease or better will continue on oprozomib, with or without dexamethasone premedication (e.g., 4 mg/day) until progression of disease or unacceptable toxicity. Dexamethasone will be taken at a dose of 20 mg/day, as described above, through the first cycle, after which the dose may be decreased to 10 mg/day in subjects > 75 years of age, at the discretion of the investigator.~~ ~~In the Phase 1b portion, subjects will be enrolled in treatment dose cohorts in escalating order (see Section 4.2 and Table 1 for doses/cohorts, and see Section 9.1.2 for methods of dose escalation to the MTD). Dose escalation will proceed only after the safety and tolerability of the previous dose level have been assessed as acceptable as determined by~~		

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	~~the CSRC (comprised of Onyx's study medical monitor, Onyx's drug safety representative, and the investigators) or until a MTD has been determined.~~ ~~In the Phase 2 portion, oprozomib will be administered in combination with lenalidomide, and dexamethasone at the recommended Phase 2 dose and schedule of oprozomib, as defined in the Phase 1b portion of the study (see Section 4.2 and Table 1 for doses/cohorts, and see Section 9.1.2 for methods of dose escalation to the MTD).~~		
9.2 Lenalidomide, **Cyclophosphamide,** and Dexamethasone Administration	9.2.1 LENALIDOMIDE ADMINISTRATION Lenalidomide will be administered at 25 mg, orally, daily on Days 1–21 of each 28 day cycle for a maximum of 24 cycles of therapy (approximately 24 months). Lenalidomide and oprozomib should be administered concurrently, i.e., within 5 minutes of each other. On days on which oprozomib is not administered, it is suggested that subjects take lenalidomide at approximately the same time in the morning for consistency. 9.2.2 DEXAMETHASONE ADMINISTRATION Dexamethasone will be administered at 20 mg, orally, on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28 day cycle. On days of concurrent oprozomib and dexamethasone administration (i.e., on Days 1, 2, 15, and 16), dexamethasone should be taken at least 30 minutes prior to oprozomib. Note: Dexamethasone will be taken at a dose of 20 mg/day through the first cycle, after which the dose may be decreased to 10 mg/day in subjects > 75 years of age, at the discretion of the investigator. In addition, treatment with dexamethasone premedication (e.g., 4 mg/day) in	9.2.1 LENALIDOMIDE ADMINISTRATION **Except for PK collection days,** lenalidomide will be administered **orally at a dose of 25 mg with or without food at investigator and subject discretion**~~, orally, daily~~ on Days 1–21 of each 28 day cycle for a maximum of 24 cycles ~~of therapy~~ (approximately 24 months). **Subjects may take lenalidomide following oprozomib administration, however it is recommended that they take lenalidomide at approximately the same time each day (Refer to Section 9.1.1 for details on oprozomib treatment administration).** Lenalidomide and oprozomib should be administered concurrently, i.e., within 5 minutes of each other. On days ~~on which~~ when oprozomib is not administered, it is suggested that subjects **should** take lenalidomide at approximately the same time **of** the ~~morning~~ **day** for consistency. **9.2.2 CYCLOPHOSPHAMIDE ADMINISTRATION** **Except for PK collection days, cyclophosphamide will be administered orally at 300 mg/m^2 (up to a maximum of 600 mg), with or without food at**	Revised text on lenalidomide and dexamethasone administration to provide clarity; a section on cyclophosphamide administration was added to (to reflect the addition of the OCyd treatment regimen).

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	combination with oprozomib may continue after if a subject demonstrates stable disease or better after 24 cycles of combination therapy.	**investigator and subject discretion, on Days 1, 8 and 15 of each 28 day cycle for a maximum of 8 cycles of therapy (approximately 8 months). Subjects may take cyclophosphamide following oprozomib administration, however it is recommended that they take cyclophosphamide at approximately the same time each day (Refer to Section 9.1.1 for details on oprozomib treatment administration). On days when oprozomib is not administered, subjects should take cyclophosphamide at approximately the same time of the day for consistency.** 9.2.2 DEXAMETHASONE ADMINISTRATION Dexamethasone will be administered at 20 mg, orally, on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28 day cycle. On days when both oprozomib and dexamethasone are administered (i.e., on Days 1, 2, 15, and 16), dexamethasone should be taken at least 30 minutes prior to oprozomib. Note: Dexamethasone will be taken at a dose of 20 mg/day through the first cycle, after which the dose may be decreased to 10 mg/day in subjects > 75 years of age, at the discretion of the investigator. ~~In addition, treatment with~~ Dexamethasone **dosing (**premedication **and low-dose) as per the schedule above** ~~(e.g., 4 mg/day)~~ in combination with oprozomib ~~may~~ **should** be continued ~~after if a~~ **for** subject**s** who demonstrate~~s~~ **a response of** stable disease or better ~~after~~ **for** 24 cycles ~~of~~ **for both the**	

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		ORd ~~or 8 cycles of~~ **and OCyd treatment regimens. After 24 cycles, this treatment may be continued or tapered at the discretion of the investigator and per institutional guidelines.**	
9.3 Dose Modification Guidelines	The following sections and tables summarize dose modifications for oprozomib, lenalidomide, and dexamethasone to manage possible toxicity. Administration of oprozomib or lenalidomide will be discontinued in the event of a treatment-related toxicity that, in the opinion of the investigator, warrants permanent discontinuation. The subject will remain on protocol treatment as long as either oprozomib or lenalidomide is being administered (either alone or in combination with dexamethasone). Monotherapy with dexamethasone is not allowed. Exceptions to the dose modification guidelines are permitted with written approval from the Onyx study medical monitor. Dose reduction levels for oprozomib and lenalidomide are provided in Table 3 and Table 4, respectively.	The following sections and tables summarize dose modifications for oprozomib, lenalidomide, **cyclophosphamide,** and dexamethasone to manage possible toxicity. Administration of oprozomib, ~~or~~ lenalidomide, **or cyclophosphamide** will be discontinued in the event of a treatment-related toxicity that, in the opinion of the investigator, warrants permanent discontinuation. **Interruption of oprozomib dosing for > 4 weeks for any reason will result in permanent discontinuation of oprozomib. No dose reductions of oprozomib are allowed in Cycle 1.** The subject will remain on protocol treatment as long as ~~either~~ oprozomib, ~~or~~ lenalidomide, **or cyclophosphamide** is being administered (either alone or in combination with dexamethasone). Monotherapy with dexamethasone is not allowed. ~~Exceptions to the dose modification guidelines are permitted with written approval from the Onyx study medical monitor.~~ **Dose modifications made during the first cycle of treatment for either combination regimen in the Phase 1b portion of this study should be discussed with the Onyx medical monitor.** Dose reduction levels for oprozomib ~~and ,~~ lenalidomide, **and cyclophosphamide** are provided in ~~Table 3~~ **Table 4** and , ~~Table 4~~	Revised text to reflect the addition of the dose reduction table for cyclophosphamide and to provide clarification on dose modifications or interruptions.

<table>
<tr><th>Section Number</th><th>Changed from</th><th>Changed to</th><th>Rationale</th></tr>
<tr><td></td><td></td><td>Table 5, and Table 6, respectively.</td><td></td></tr>
<tr><td>9.3 Dose Modification Guidelines</td><td>The following table was revised:
Table ~~3~~ 4: Dose Decrements for Oprozomib<table><tr><th rowspan="2">Nominal Dose</th><th colspan="3">Reduced Oprozomib Doses</th></tr><tr><th>Dose –1</th><th>Dose –2</th><th>~~Dose –3~~</th></tr><tr><td>210 mg</td><td>Nominal dose -30 mg</td><td>Nominal dose -60 mg</td><td>—</td></tr></table></td><td></td><td>The table was revised with the Dose –3 column removed to clarify that there is no third dose decrement of oprozomib</td></tr>
<tr><td>9.3 Dose Modification Guidelines</td><td>The following table was added:
Table 6: Dose Decrements for Cyclophosphamide<table><tr><th rowspan="2">Nominal Dose</th><th colspan="2">Reduced Cyclophosphamide Doses</th></tr><tr><th>Dose –1</th><th>Dose –2</th></tr><tr><td>300 mg/m^2</td><td>200 mg/m^2</td><td>100 mg/m^2</td></tr></table>Note: Dose adjustments should, in general, follow the Cyclophosphamide Prescribing Information 201 (Appendix H).</td><td></td><td>This table was added to provide dose reduction levels for cyclophosphamide (for the OCyd treatment regimen).</td></tr>
<tr><td>9.3 Dose Modification Guidelines</td><td>Table 7: Dose Decrements for Dexamethasone<table><tr><th rowspan="2">Nominal Dose</th><th colspan="2">Reduced Dexamethasone Doses</th></tr><tr><th>Dose –1</th><th>Dose –2</th></tr><tr><td>20 mg</td><td>12 mg</td><td>8 mg</td></tr><tr><td>Cycle 2: Age > 75 and nominal dose is 10 mg post-Cycle 1</td><td>8 mg</td><td>4 mg</td></tr></table></td><td></td><td>This table was revised to include dexamethasone dose reduction details for subjects > 75 years old.</td></tr>
<tr><td>9.3.1 Dose Modification Guidelines for Hematologic Toxicities</td><td>Dose modification guidelines for hematologic toxicities are outlined below in Table 8. ~~Guidelines for the management of thrombocytopenia for lenalidomide and oprozomib are summarized in Table 6 and Table 7, respectively. Guidelines for the management of neutropenia are summarized in Table 8.~~

Table 8: Dose Modification Guidelines for Oprozomib-, Lenalidomide-, and Cyclophosphamide-Related Hematologic Toxicities Post-Cycle 1</td><td></td><td>Updated text and table to include dose modification guidelines for cyclophosphamide-related hematologic toxicities (reflecting the addition of the OCyd treatment regimen).</td></tr>
</table>

Section Number	Changed from		Changed to		Rationale
	Toxicity	Recommended Action[a] Oprozomib	Lenalidomide	Cyclophosphamide	
	Toxicity on Day 1 of Cycle				
	Platelets < 25 × 10^9/L (oprozomib and cyclophosphamide)	**Hold dose until recovery ≥ 25 × 10^9/L restart at previous dose**	**Hold dose, follow CBC 3 times per week; Hold prophylactic anticoagulation until platelets return to ≥ 30 × 10^9/L[a], then resume at 1 dose decrement**	**Hold dose until recovery to ≥ 25 × 10^9/L restart at 1 dose decrement**	
	ANC < 1.0 × 10^9/L	**Hold dose Add myeloid growth factor[b] With resolution to ≥ 1.0 × 10^9/L, restart at previous dose**	**Hold dose Add myeloid growth factor[b] With resolution to ≥ 1.0 × 10^9/L, restart at previous dose**	**Hold dose Add myeloid growth factor[b] With resolution to ≥ 1.0 × 10^9/L, restart at 1 dose decrement**	
	Toxicity on Subsequent Days of Cycle				
	Neutropenic fever (ANC < 1.0 × 10^9/L and single temperature > 38.3°C or temperature > 38.0°C sustained for more than 1 hour)	**Hold dose; follow CBC 3 times per week Add myeloid growth factor[b] With resolution of fever and ANC ≥ 1.0 × 10^9/L, restart at 1 dose decrement**			
	ANC < 0.75 × 10^9/L (Grade 3)	**Hold dose Add myeloid growth factor[b] With resolution to ≥ 1.0 × 10^9/L, restart at previous dose**	**Hold dose; follow CBC 3 times per week Administer myeloid growth factor[b] Resume at full dose when ANC ≥ 1.0 × 10^9/L (Resume at 1 dose decrement for each subsequent decrease to < 0.75 × 10^9/L)**	**Hold dose Add myeloid growth factor[b] With resolution to ≥ 1.0 × 10^9/L, restart at 1 dose decrement**	
	ANC < 0.5 × 10^9/L (Grade 4)	**Hold dose; follow CBC 3 times per week; add myeloid growth factor[b]. Resume at full dose if**		**Hold dose; follow CBC 3 times per week; add myeloid growth factor[b]. When ANC**	

Section Number	Changed from		Changed to		Rationale
		ANC rises to ≥ 0.5 × 10^9/L within 7 days; Resume at 1 dose decrement if ANC returns to ≥ 0.5 × 10^9/L after 7 days.		≥ 1.0 × 10^9/L, resume at 1 dose decrement	
	Platelets 25 to < 50 × 10^9/L without ≥ Grade 2 bleeding/ hemorrhage	Full dose	Hold dose, follow CBC weekly Hold prophylactic anticoagulation until platelets return to ≥ 30 × 10^9/L. When platelets reach 50 × 10^9/L, then resume at 1 dose decrement.	Hold dose until platelets return to ≥ 50 × 10^9/L, and then resume at 1 dose decrement	
	Platelets 25 to < 50 × 10^9/L with ≥ Grade 2 bleeding/ hemorrhage	Hold dose until platelets return to ≥ 50 × 10^9/L and/or bleeding is controlled, then resume at 1 dose decrement	Hold dose, follow CBC weekly Hold prophylactic anticoagulation until platelets return to ≥ 30 × 10^9/L. When platelets reach 50 × 10^9/L, then resume at 1 dose decrement.	Hold dose until platelets return to ≥ 50 × 10^9/L and/or bleeding is controlled, then resume at 1 dose decrement	
	Platelets < 25 × 10^9/L or any degree of thrombocytopenia with ≥ Grade 2 bleeding/ hemorrhage	Hold dose until platelets return to ≥ 50 × 10^9/L and/or bleeding is controlled, then resume at 1 dose decrement	Hold dose, follow CBC weekly Hold prophylactic anticoagulation until platelets return to ≥ 30 × 10^9/L. When platelets reach 50 x 10^9/L, then resume at 1 dose decrement	Hold dose until platelets return to ≥ 50 × 10^9/L and/or bleeding is controlled, then resume at 1 dose decrement	
	ANC = absolute neutrophil count; CBC = complete blood count. [a] The maximum allowed dose interruption is 4 weeks. [b] Myeloid growth factors include filgrastim or sargramostim.				

<table>
<tr><th>Section Number</th><th>Changed from</th><th>Changed to</th><th>Rationale</th></tr>
<tr><td>9.3.2 Dose Modification Guidelines for Nonhematologic Toxicities</td><td>Dose modification guidelines for nonhematologic toxicities are outlined below in Table 11.
Table 11: Dose Modification Guidelines for Oprozomib-, Lenalidomide-, and Cyclophosphamide-Related Nonhematologic Toxicities
<table>
<tr><th colspan="5">Nonhematologic Toxicities, All Days and Cycles</th></tr>
<tr><th>Symptom</th><th>Findings</th><th colspan="3">Recommended Action[a]</th></tr>
<tr><th></th><th></th><th>Oprozomib</th><th>Lenalidomide</th><th>Cyclophosphamide</th></tr>
<tr><td>Tumor Lysis Syndrome (TLS)</td><td>Generally recognized as 3 or more of the following categories: (1) increase in creatinine, uric acid, or phosphate of ≥ 50% (2) increase in potassium of ≥ 30% (3) decrease in calcium of ≥ 20%, or (4) increase in LDH ≥ 2 fold from baseline</td><td colspan="3">Hold both oprozomib and lenalidomide/cyclophosphamide until all abnormalities in serum chemistries have resolved to baseline; resume at full doses. See Section 9.8.1.1 for specific prophylaxis and treatment guidelines for TLS.</td></tr>
<tr><td>Neuropathy</td><td>Grade 2 neuropathy with pain or ≥ Grade 3 neuropathy</td><td>Hold dose until toxicity resolve to ≤ Grade 1 or has returned to baseline. Resume study drug at 1 dose decrement.</td><td>Hold dose until toxicity resolve to ≤ Grade 1 or has returned to baseline. Resume study drug at 1 dose decrement.</td><td>Full dose.</td></tr>
<tr><td>Infection</td><td>Grade 3 or 4</td><td colspan="3">Hold both oprozomib and lenalidomide/cyclophosphamide until systemic treatment for infection complete. If ANC > 1.0 × 10^9/L, resume both drugs at full dose. If ANC < 1.0 × 10^9/L, follow hematologic toxicities dose reduction guidelines.</td></tr>
</table></td><td>Updated text and table to include dose modification guidelines for cyclophosphamide-related nonhematologic toxicities (reflecting the addition of the OCyd treatment regimen).</td></tr>
</table>

Section Number	Changed from		Changed to			Rationale
	Nausea, vomiting, diarrhea, or constipation	> Grade 3 without optimal supportive care as defined by use of both a $5HT_3$ antagonist and antiemetic (aprepitant)	Continue full-dose therapy. Institute optimal supportive care.			
		> Grade 3 with optimal supportive care as defined by use of both a $5HT_3$ antagonist and antiemetic (aprepitant)	Oprozomib related: Hold dose until toxicity resolve to < Grade 1 or has returned to baseline. Resume study drug at 1 dose decrement	Hold dose until toxicity resolve to < Grade 1 or has returned to baseline. Resume study drug at full dose. If recurs after oprozomib dose reduction, hold dose until toxicity resolve to < Grade 1 or has returned to baseline. Resume study drug at 1 dose decrement.		
	Fatigue	Grade 3 fatigue lasting < 14 days	Full dose.	If recurs after oprozomib dose reduction, hold dose until toxicity resolves to < Grade 1 or has returned to baseline. Resume study drug at 1 dose decrement.	Full dose.	
		Grade 3 fatigue lasting ≥ 14 days	Hold dose until toxicity resolves to ≤ Grade 1 or has returned to baseline. Resume study drug at 1 dose decrement.			
	Renal Dysfunction	CrCL 30 to <50 mL/min (Grade 2)	Full dose	Reduce dose to 10 mg once daily.	Full dose	
		CrCl 15 to < 30 mL/min (Grade 3)	Hold dose. When CrCl recovers to ≤ Grade 2, resume at 1 dose	Hold dose. When CrCl recovers to ≤ Grade 2, resume dose at 1 dose	Hold dose until resolution to ≤ Grade 2 or baseline, then	

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			decrement.	decrement. If Grade 3 reduction in CrCl reappears, then hold dose until CrCl recovers to ≤ Grade 2 and reduce dose to 15 mg every 48 hours.	resume at full dose	
		CrCl 0 to <15 mL/min (Grade 4)	Discontinue	Discontinue	Discontinue	
	Elevation in Liver Function Tests (LFTs)	≥ Grade 3 (AST, ALT, or total bilirubin)[b]	Hold dose until resolves to baseline. Resume at one dose decrement.	Hold dose until resolution, then resume at full dose	Hold dose until resolution to ≤ Grade 1 or baseline, then resume at full dose	
	Hemorrhagic cystitis	Grade 1 or 2	Continue full dose	Continue full dose	Hold dose until resolution, then resume at 1 dose decrement	
		Grade 3 or 4	Continue full dose	Continue full dose	Discontinue; do not resume.	
	Other Non-Hematologic Toxicity	Assessed as cyclophosphamide-related and ≥ Grade 3	Full dose	Not Applicable	Hold cyclophosphamide dose Follow at least weekly If the toxicity resolves to ≤ Grade 1 or baseline, restart at 1 dose decrement	
	Other Non-Hematologic Toxicity	Assessed as oprozomib-related and ≥ Grade 3	Hold oprozomib dose until toxicity resolves to ≤ Grade 1 or baseline; restart at 1 dose decrement	Full dose	Full dose	
	Other Non-Hematologic Toxicity	Assessed as lenalidomide-related and	Full dose	Hold lenalidomide dose until toxicity resolves to ≤ Grade	No Applicable	

Section Number	Changed from	Changed to	Rationale
	≥ Grade 3	**1 or baseline; restart at 1 dose decrement**	
	Abbreviations: 5-HT$_3$ = 5-hydroxytryptamine type-3; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CrCl = creatinine clearance; eCRF = electronic case report form; LDH = lactate dehydrogenase; LFTs = liver function tests; TLS = tumor lysis syndrome **[a] The maximum allowed dose interruption is 4 weeks.** **[b] If AST, or ALT is ≥ 3 × ULN, the "evaluation of treatment emergent liver abnormalities" eCRF should be completed.**		
9.4 Dose Delays	Dosing delays are not permitted in Cycle 1. If the initiation of Cycle 2 or later must be adjusted for reasons unrelated to toxicity (e.g., holidays or subject requests), the cycle should be started no later than 7 days after the originally scheduled next cycle. If a dose delay for toxicity is > 28 days, then the subject will be permanently discontinued from study treatment. Schedule adjustments can only be made at the beginning of each cycle and cannot be made mid-cycle.	Dosing delays are not permitted in Cycle 1. If the initiation of Cycle 2 or later must be adjusted for reasons unrelated to toxicity (e.g., holidays or subject requests), the cycle should be started no later than 7 days after the originally scheduled next cycle. ~~If a dose delay for toxicity is > 28 days, then the subject will be permanently discontinued from study treatment.~~ Schedule adjustments can only be made at the beginning of each cycle and cannot be made mid-cycle.	Deleted text for clarity and consistency around patient discontinuations.
9.6 Missed Doses	Subjects in the Phase 1b portion of the study may not miss more than 1 planned dose of oprozomib, 2 planned doses of lenalidomide, or 1 planned dose of dexamethasone in Cycle 1. A missed dose occurs when the subject does not take the dose on the planned calendar day, and the dose will not be made up. If a subject misses more than 28 consecutive days after completing Cycle 1 for reasons other than a hematopoietic stem cell harvest, the subject will be permanently discontinued from study treatment.	Subjects in the Phase 1b portion of the study may not miss ~~more than 1~~ **any of the** planned dose**s** of ~~oprozomib or~~ **cyclophosphamide,** or more than ~~2~~ **4** planned doses of lenalidomide, or ~~1~~ **2** planned dose**s of oprozomib or** dexamethasone in Cycle 1 **(See Section 4.2 for details of replacing subjects who miss more doses than allowed).** A missed dose occurs when the subject does not take the dose on the planned calendar day, and the dose will not be made up. If a subject misses more than 28 consecutive days after completing Cycle 1 for reasons other than a hematopoietic stem cell harvest, the subject will ~~be~~ permanently discontinue~~d~~ from	Updated text to reflect the addition of the OCyd treatment regimen, and to provide additional clarification on missed doses of study drug.

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		study treatment **(See Section 9.3 for interrupted oprozomib dosing > 4 weeks).**	
9.7 Safety Guidance for Investigators	See Section 9.3 for information and recommendations for dose adjustments required for specific hematologic and nonhematologic toxicities.	See Section 9.3 for information and recommendations for dose adjustments guidelines required for specific hematologic and nonhematologic toxicities. **Cases of tumor lysis syndrome have been observed with proteasome inhibitors. It is recommended that all subjects orally hydrate the day before, and days of oprozomib dosing. Additionally, allopurinol prophylaxis is recommended for renally impaired subjects and those with a high tumor burden. For specific recommendations, see Section 9.8.1.**	Added text regarding TLS in this section and a cross-reference to Section 9.8.1, Required Concomitant Medications.
9.7.2 Cyclophosphamide		**9.7.2 CYCLOPHOSPHAMIDE** **See cyclophosphamide prescribing information for additional details (Cyclophosphamide Prescribing Information 2011; Appendix H)**	Added text to reflect the addition of cyclophosphamide (in the OCyd treatment regimen).
9.8.1 Required Conconmitant Medications	*The following subsection was added:* **9.8.1 REQUIRED CONCOMITANT MEDICATIONS** **Outside of antimyeloma regimens and the TLS measures noted below, there are no required concomitant medications. However, supportive medications for nausea, vomiting and diarrhea are strongly recommended; details are provided in Section 9.8.2.** **9.8.1.1 Tumor Lysis Syndrom** **For subjects at risk for TLS (Sezer 2006), the following are required:** **Monitoring and Prophylaxis Guidelines: Oral hydration of 1.5–2 liters per 24 hours should be instituted in all subjects 24–48 hours prior to initiation of therapy in every cycle, and continued throughout days of dosing. Premedication with allopurinol or other approved uric acid lowering agents is highly recommended for subjects with high tumor burden (i.e., for multiple myeloma: Durie-Salmon or ISS Stage II/III or rapidly increasing M protein or light chains) or compromised renal function (CrCl <**		Added text to provide specific guidance for prophylaxis and treatment of tumor lysis syndrome.

Section Number	Changed from	Changed to	Rationale
	50 cc/min). These subjects may be at elevated risk for TLS and should be closely monitored. Uric acid levels should be normalized prior to initiation of treatment, if appropriate. **Subjects with laboratory abnormalities prior to dosing that are consistent with lysis of tumor cells should not receive the scheduled dose prior to institution of the aforementioned preventative measures.** **<u>TLS Laboratory Abnormalities</u>: Subjects with laboratory abnormalities prior to dosing that are consistent with lysis of tumor cells (e.g., as defined by increases of 3 of the four categories) [1] a 2 fold increase of lactate dehydrogenase (LDH) above the ULN] [2] increases in serum creatinine, uric acid, or phosphorus > 50% over baseline, [3] potassium > 30% above the ULN; or [4] decreases from baseline of calcium > 20% in the absence of concomitant bisphosphonate therapy) (Sezer 2006) should not receive the scheduled dose prior to institution of the aforementioned preventative measures.** **<u>Treatment Guidelines</u>: If TLS occurs, cardiac rhythm, fluid and serial laboratory monitoring should be instituted. Correction of electrolyte abnormalities, monitoring of renal function and fluid balance, administration of therapeutic and supportive care, including dialysis, should be done as clinically indicated. In the setting of TLS, oprozomib treatment will be interrupted until resolution of all clinical and laboratory abnormalities consistent with TLS. Once TLS has resolved, subject can resume treatment at the initial dose level.** **All cases of TLS must be reported to Onyx Therapeutics, Inc. as an SAE as outlined in the protocol.**		
9.8.2 Optional and Allowed Concomitant Medications	At least 24 hours prior to Cycle 1 Day 1 and for the duration of the study, the following medications are strongly recommended per published guidelines and institutional standards of care (Palumbo 2011): • A proton pump inhibitor, such as omeprazole or lansoprazole while taking dexamethasone • Herpes zoster prophylaxis, with acyclovir, valacyclovir, or equivalent antiviral while taking oprozomib • Thrombo-prophylaxis with aspirin (or other anticoagulant or antiplatelet	At least 24 hours prior to Cycle 1 Day 1 and for the duration of the study, the following medications are strongly recommended per published guidelines and institutional standards of care (Palumbo 2011): • A proton pump inhibitor, such as omeprazole or lansoprazole while taking dexamethasone • Herpes zoster prophylaxis, with acyclovir, valacyclovir, or equivalent antiviral while taking oprozomib • Thrombo-prophylaxis with aspirin (or	Added text to provide specific guidance for antinausea and antiemetics, and antidiarrheals.

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	medication such as clopidogrel bisulfate, low-molecular-weight heparin, or warfarin) while taking lenalidomide is also strongly recommended (refer to the Revlimid Prescribing Information 2012 for more information). Subjects may be premedicated with a 5-HT_3 inhibitor, such as ondansetron or granisetron, before administration of the first dose of oprozomib each day.	other anticoagulant or antiplatelet medication such as clopidogrel bisulfate, low-molecular-weight heparin, or warfarin) while taking lenalidomide is also strongly recommended (refer to the Revlimid Prescribing Information 2012, Appendix G for more information). **9.8.2.1 Antinausea and Antiemetics** **It is strongly recommended that subjects be premedicated with a 5 HT_3 inhibitor, such as ondansetron or granisetron, at the first onset of nausea and/or vomiting prior to oprozomib dosing each day and throughout the day as needed to prevent nausea and vomiting. If nausea/vomiting at any grade persists, aprepitant, is recommended if needed. Additional antiemetics may be used if needed.** **9.8.2.2 Antidiarrheals** **Grade 1 diarrheas is defined as an increase over baseline of < 4 stools per day or mild increase in ostomy output compared with baseline. For subjects developing any grade of diarrhea, Imodium is strongly recommended at the first onset of symptoms. For subjects with persistent diarrhea despite the use of Imodium, the addition of Lomotil is strongly recommended. Other antidiarrheal agents may be used if necessary; a work-up for other etiologies is suggested if diarrhea continues despite the prior 2 agents.** ~~Subjects may be premedicated with a 5-HT_3 inhibitor, such as ondansetron or granisetron, before administration of the~~	

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		~~first dose of oprozomib each day.~~	
9.8.3 Excluded Concomitant Medications	Concurrent therapy with an approved or investigative anticancer therapeutic is not allowed. During the study, glucocorticoid therapy (in addition to dexamethasone) is only permitted at the discretion of the treating physician after consultation with the Onyx study medical monitor to treat a concurrent medical condition (e.g., asthma, inflammatory bowel disease, or as an antiemetic, etc.).	Concurrent therapy with an approved or investigative anticancer therapeutic is not allowed. During the study, **concurrent** glucocorticoid therapy (in addition to dexamethasone) is only permitted **to treat a concurrent medical condition (e.g., asthma, inflammatory bowel disease, or as an antiemetic, etc.)** ~~at the discretion of the treating physician~~ after consultation with the Onyx study medical monitor~~ to treat a concurrent medical condition (e.g., asthma, inflammatory bowel disease, or as an antiemetic, etc.).~~	Revised text to provide clarification regarding concurrent glucocorticoid therapy.
10.3 Disease Response Assessments	The schedule of disease assessments for subjects treated is provided in Appendix A. Disease response will be assessed by the investigator. Beginning with Cycle 1, assessments are to be completed at the end of every 4 week cycle for the first year of study participation, at the end of every other cycle for the second year of study treatment, and every 12 weeks thereafter. Response assessment will be according to the International Myeloma Working Group – Uniform Response Criteria (IMWG-URC) (Appendix E). All subjects will be followed until confirmed disease progression, unacceptable toxicity, withdrawal of consent, whichever occurs first.	The schedule of disease assessments ~~for subjects treated~~ is provided in Appendix A. Disease response will be assessed by the investigator. ~~Beginning with Cycle 1, assessments are to be completed at the end of every 4 week cycle for the first year of study participation, at the end of every other cycle for the second year of study treatment, and every 12 weeks thereafter.~~ **Disease response assessments will be performed at the end of every 4-week cycle for 24 cycles of ORd or OCyd treatment, and will continue every 8 weeks thereafter, until confirmed PD (See Figure 1, Figure 2, and Figure 3, for details on the duration of cyclophosphamide dosing).** Response assessment will be according to the International Myeloma Working Group – Uniform Response Criteria (IMWG-URC) (Appendix E).	Revised and added text to provide clarification regarding disease assessments and to reflect the addition of the OCyd treatment regimen.
10.6 Assessments at End of Study	Early discontinuation and End of Study	**For subjects who discontinue treatment**	Revised text to provide

Section Number	Changed from	Changed to	Rationale
Treatment or Early Discontinuation	Assessments must be performed within 30 days following the subject's last administration of study drug and prior to initiation of any other treatment. For subjects who discontinue treatment for reasons other than progression in either study phase, disease assessments will be performed at the end of every 4 weeks for the first year of study treatment, at the end of every other cycle for the second year of treatment, and every 12 weeks thereafter. The same methods of disease assessment must be used throughout the study. If disease assessments show disease progression, assessments do not need to be repeated with End of Study Assessments.	**before PD occurs (such as for an AE, noncompliance, etc.), disease response assessments will be performed every 4 weeks during the first 24 months of the study and every 8 weeks thereafter, until confirmed PD.** ~~Early discontinuation and End of Study Assessments must be performed within 30 days following the subject's last administration of study drug and prior to initiation of any other treatment.~~ ~~For subjects who discontinue treatment for reasons other than progression in either study phase, disease assessments will be performed at the end of every 4 weeks for the first year of study treatment, at the end of every other cycle for the second year of treatment, and every 12 weeks thereafter. The same methods of disease assessment must be used throughout the study. If disease assessments show disease progression, assessments do not need to be repeated with End of Study Assessments.~~	clarification regarding disease assessments for subjects who discontinue treatment before PD occurs.
11.1 Study Treatment Discontinuation	Subjects who discontinue from all study treatments (i.e., oprozomib, lenalidomide, and dexamethasone) will be monitored for AEs for 30 days after the last dose of study treatment. Patients may discontinue study treatment for the following reasons: • Disease progression • Unacceptable toxicity • Noncompliance with study procedures • Treatment with prohibited concomitant medications • Intercurrent illness that interferes with	Subjects ~~who discontinue from all study treatments (i.e., oprozomib, lenalidomide, and dexamethasone)~~ will be monitored for AEs for 30 days after the last dose of study treatment **(i.e., oprozomib, lenalidomide/cyclophosphamide or dexamethasone).** Subjects may discontinue study treatment for the following reasons: • Disease progression • Unacceptable toxicity • Noncompliance with study procedures	Revised text to reflect the addition of the OCyd treatment regimen and for clarification.

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	study assessments • Female subject who becomes pregnant, in which case treatment must be immediately discontinued Onyx Therapeutics, Inc., or designee must be notified within 24 hours if a subject is discontinued from study treatment. If the reason for discontinuation is the occurrence of an AE, the subject will be followed by the investigator until such event(s) resolve, stabilize, and according to the investigator's judgment, there is no need for further follow-up. Subjects who discontinue study treatment for reasons other than disease progression or death may continue on study until disease progression or death. The reason for discontinuation from study treatment will be documented on the eCRF. Additional subjects may be enrolled to account for subjects who have not had adequate safety or efficacy evaluations.	• Treatment with prohibited concomitant medications**; details provided in Section 9.8.3** • Intercurrent illness that interferes with study assessments • Female subject who becomes pregnant, in which case treatment must be immediately discontinued Onyx Therapeutics, Inc., or designee must be notified within 24 hours if a subject ~~is discontinued~~ **discontinues** ~~from~~ **all** study treatment. If the reason for discontinuation is the occurrence of an AE, the subject will be followed by the investigator until such event(s) resolve, stabilize, and according to the investigator's judgment, there is no need for further follow-up. Subjects who discontinue study treatment for reasons other than disease progression ~~or death~~ may continue on study until disease progression or death. The reason for discontinuation from study treatment will be documented on the eCRF. **In the Phase 1b portion of the study,** additional subjects may be enrolled to account for subjects who have not had adequate safety ~~or efficacy~~ evaluations.	
13.1 Study Endpoints	13.1.1 Primary Endpoints The primary endpoints for the Phase 1b portion of this study are: • Incidence, nature, and severity of AEs and SAEs graded according to NCI-CTCAE, version 4.03 • The MTD of oprozomib given orally on a	13.1.1 Primary Endpoints The primary **safety** endpoint**s** for the Phase 1b **and Phase 2 portions** of this study are: • Incidence, nature, and severity of AEs, ~~and~~ SAEs, **and DLTs (Phase 1b only) of oprozomib, given in combination with dexamethasone, and either**	Updated text to reflect the addition of the OCyd treatment regimen, and to provide clarification on the study endpoints.

Section Number	Changed from	Changed to	Rationale
	5 consecutive days, bimonthly schedule in combination with lenalidomide and dexamethasone The primary endpoints for the Phase 2 portion of this study are: • Overall response, defined as a best overall response of sCR, CR, VGPR, or PR according to the IMWG-URC (see Appendix E). • Complete response, defined as a best overall response of either sCR or CR 13.1.2 Secondary Endpoints The secondary endpoints of this study are: • Incidence, nature, and severity of AEs and SAEs graded according to NCI-CTCAE (version 4.03), changes in laboratory parameters, ECGs, and vital signs. • Population-based PK parameters including, but not limited to, clearance and volume of distribution will be determined • Duration of response, defined as the time from evidence of PR or better to confirmation of disease progression or death due to any cause • PFS, defined as duration from the start of treatment to disease progression or death (due to any cause), whichever comes first 13.1.3 Exploratory Endpoints The exploratory endpoints of this study are: • Pharmacodynamic analyses of proteasome inhibition will be determined • Analyses to potentially identify genetic and gene expression biomarkers will be	**lenalidomide or cyclophosphamide, as well as changes from baseline in selected laboratory analytes, vital signs, and ECG findings** ~~graded according to NCI-CTCAE, version 4.03~~ The primary **efficacy** endpoints **for** the Phase 2 portion of this study are: • Overall response, defined as a best overall response of sCR, CR, VGPR, or PR according to the IMWG-URC (see Appendix E). • Complete response, defined as a best overall response of either sCR or CR 13.1.2 Secondary Endpoints The secondary endpoints of this study are: ~~• Incidence, nature, and severity of AEs and SAEs graded according to NCI-CTCAE (version 4.03), changes in laboratory parameters, ECGs, and vital signs.~~ • Population-based PK parameters including, but not limited to, clearance and volume of distribution will be determined • Duration of response, defined as the time from **first** evidence of PR or better to confirmation of disease progression or death due to any cause • PFS, defined ~~as duration~~ **the time** from the start of treatment to disease progression or death (due to any cause), whichever comes first 13.1.3 Exploratory Endpoints The exploratory endpoints of this study are: • Pharmacodynamic analyses of	

Section Number	Changed from	Changed to	Rationale
	conducted	proteasome inhibition will be determined • Analyses to potentially identify genetic and gene expression biomarkers will be conducted	
13.2 Analysis of Study Conduct	Enrollment, major protocol violations, and discontinuations from the study will be summarized by the assigned dose cohort and for all subjects. Demographic and baseline characteristics, such as age, sex, race, weight, number of prior therapies, and baseline ECOG performance status, will be summarized using means, standard deviations, medians, and ranges for continuous variables, and proportions for categorical variables. All summaries will be presented by the assigned dose cohort and for all subjects. Study drug administration data will be listed by dose cohort, and any dose modifications will be flagged. Means and standard deviations will be used to summarize the total dose for each component of study drug received. All summaries will be presented by the assigned dose cohort and for all subjects.	Enrollment, major protocol violations, and discontinuations from the study will be summarized **for each combination regimen** by the assigned dose cohort, **the combined MTD dose level**, and for all subjects. Demographic and baseline characteristics, such as age, sex, race, weight, number of prior therapies, and baseline ECOG performance status, will be summarized using means, standard deviations, medians, and ranges for continuous variables, and proportions for categorical variables. All summaries will be presented **for each combination regimen** by the assigned dose cohort, **the combined MTD dose level,** and for all subjects. ~~Study drug administration data will be listed by arm and dose cohort, and any dose modifications will be flagged. Means and standard deviations will be used to summarize the total dose for each component of study drug received. All summaries will be presented for each arm by the assigned dose cohort and for all subjects.~~	Added text to reflect the addition of the OCyd treatment regimen, and for clarification of summaries to be presented. Text describing study drug administration data listings was moved to Section 13.6.2, Safety Analyses.

Section Number	Changed from	Changed to	Rationale
13.5.1 Efficacy Analyses	~~All subjects who receive any amount of oprozomib, lenalidomide, or dexamethasone will be included in the efficacy analyses.~~ Response assessment data, PFS, and DOR will be **summarized and** listed for all subjects by **combination regimen, the combined MTD dose level, and** dose cohort level. **Further details on efficacy analysis populations are provided in Section 13. Definitions of study endpoints are provided in Section 13.1.** ~~Overall response rate will be estimated as the proportion of subjects achieving a best overall response of sCR, CR, VGPR, or PR according to the IMWG URC (see Appendix E).~~ ~~Complete response rate will be estimated as the proportion of subjects achieving a best overall response of sCR or CR.~~ The ~~approximate~~ lower 1-sided **exact Clopper-Pearson** 90% confidence intervals ~~based upon the normal approximation~~ will be calculated for both the ORR and CRR. In addition, exact Clopper Pearson 95% confidence intervals will be calculated for estimated ORR and CRR. ~~Among subjects who respond, DOR will be defined as the time from the first evidence of confirmed PR or better to confirmation of disease progression or death due to any cause (see Table 13 for more information).~~ ~~Progression-free survival is defined as the time from the first day of study treatment (Cycle 1 Day 1) to the earlier of disease progression or deaths due to any cause.~~ Summary statistics for DOR and PFS will be calculated using the Kaplan-Meier method. **For purposes of calculating PFS, the start date for PD is the date at which progression is first observed. For such subjects, the primary analysis of PFS and DOR will be right-censored according to the conventions described in Table 13.**		Added text to define the response evaluable population. Redundant text was deleted and cross-references were added to Sections 13 and 13.1. Text describing censoring for primary analysis of PFS and DOR was moved to this section from Section 13.7, Handling of Missing Data.

<table>
<tr><th>Section Number</th><th>Changed from</th><th>Changed to</th><th>Rationale</th></tr>
<tr><td></td><td colspan="2">Table 13: Date of Progression or Censoring for Progression-free Survival and Duration of Response
<table>
<tr><th>Situation</th><th>Date of Progression or Censoring</th><th>Outcome</th></tr>
<tr><td>No baseline disease assessments</td><td>Date of first study drug</td><td>Censored</td></tr>
<tr><td>New anticancer treatment started before documentation of PD or death[a]</td><td>Date of last disease assessment prior to start of a new anticancer treatment</td><td>Censored</td></tr>
<tr><td>Death or PD immediately after more than 1 consecutively missed disease assessment visits</td><td>Date of last disease assessment visit without documentation of PD that is before the first missed visit</td><td>Censored</td></tr>
<tr><td>Alive and without PD documentation</td><td>Date of last disease assessment</td><td>Censored</td></tr>
<tr><td>Death[a] or PD between planned disease assessments</td><td>Date of death or first disease assessment showing PD, whichever occurs first</td><td>Progressed</td></tr>
<tr><td>Death[a] before first disease assessment</td><td>Date of death[a]</td><td>Progressed</td></tr>
</table>
DOR = duration of response; PD = progressive disease; PFS = progression-free survival.
[a] For DOR, death must be due to disease progression, otherwise, both outcomes will be censored at the date of last disease assessment. For PFS, death due to any cause is counted as an event.
The follow-up time for PFS will be summarized by reverse Kaplan-Meier method (Schemper 1996).</td><td></td></tr>
<tr><td>13.5.2 Safety Analyses</td><td>All subjects who receive any amount of oprozomib, lenalidomide, or dexamethasone will be included in the safety analyses.
Safety will be assessed through summaries of DLTs, AEs, and changes in laboratory test results, ECGs, vital signs, and oprozomib exposure by dose cohort and for all subjects.
All collected AE data will be listed by study site, dose cohort, subject number, and study day.</td><td>All subjects who receive any amount of oprozomib, and dexamethasone, lenalidomide, or cyclophosphamide will be included in the safety analyses.
Safety and tolerability will be assessed through summaries of study drug administration, DLTs (Phase 1b only), AEs, and changes in selected laboratory ~~test results~~ analytes, ECGs, and vital signs, ~~and oprozomib exposure~~ by dose cohort, the combined MTD dose level, and for all</td><td>Revised text to reflect the addition of the OCyd treatment regimen and for clarification of summaries to be presented. Text describing study drug administration data listings was moved here from Section 13.2, Analysis of Study Conduct.</td></tr>
</table>

Section Number	Changed from	Changed to	Rationale
		subjects. **Study drug administration data will be listed by combination regimen and dose cohort, and any dose modifications will be flagged. Means and standard deviations will be used to summarize the total dose for each component of study drug received. All summaries will be presented for each combination regimen by the assigned dose cohort, the combined MTD dose level, and for all subjects.** All ~~collected~~ AE data will be listed by study site, **treatment regimen,** dose cohort, subject number, and study day.	
13.5.3 Pharmacokinetic Analyses	The NONMEM statistical software program (Pharsight, Sunnyvale, CA) will be used to fit a nonlinear, mixed effects model to estimate PK parameters (clearance and volume of distribution), the inter- and intra-patient variability and the population variability in the parameter estimates.	**A population PK software program** ~~The NONMEM statistical software program (Pharsight, Sunnyvale, CA)~~ will be used to fit a nonlinear, mixed effects model to estimate PK parameters (clearance and volume of distribution), the inter- and intra-patient variability and the population variability in the parameter estimates.	Text was revised as the PK software and vendor are to be determined.
13.6 Handling of Missing Data	~~Subjects with no post baseline response assessments will be classified as nonresponders in the estimation of ORR or CRR.~~ ~~For purposes of calculating PFS, the start date for PD is the date at which progression is first observed. The duration of PFS will be right-censored for subjects who meet any one of the following conditions: 1) no baseline disease assessments; 2) begin a new anticancer therapy prior to documentation of disease progression or death due to any cause; 3) disease progression or death immediately after more than 1 consecutively missed disease assessment visit; or 4) are alive without documentation of disease progression prior to the data cutoff date. The same conventions hold for DOR. For such subjects, the primary analysis of PFS and DOR will be right-censored according to the conventions described in Table 13.~~ ~~Table 13: Date of Progression or Censoring for Progression-free Survival and Duration of~~		Deleted redundant text describing nonresponders; cross-reference to definition of response evaluable population in Section 13 was added.

<table>
<tr><th>Section Number</th><th>Changed from</th><th>Changed to</th><th>Rationale</th></tr>
<tr><td></td><td>~~Response~~
<table><tr><th>~~Situation~~</th><th>~~Date of Progression or Censoring~~</th><th>~~Outcome~~</th></tr><tr><td>~~No baseline disease assessments~~</td><td>~~Date of first study drug~~</td><td>~~Censored~~</td></tr><tr><td>~~New anticancer treatment started before documentation of PD or death[a]~~</td><td>~~Date of last disease assessment prior to start of a new anticancer treatment~~</td><td>~~Censored~~</td></tr><tr><td>~~Death or PD immediately after more than 1 consecutively missed disease assessment visits~~</td><td>~~Date of last disease assessment visit without documentation of PD that is before the first missed visit~~</td><td>~~Censored~~</td></tr><tr><td>~~Alive and without PD documentation~~</td><td>~~Date of last disease assessment~~</td><td>~~Censored~~</td></tr><tr><td>~~Death[a] or PD between planned disease assessments~~</td><td>~~Date of death or first disease assessment showing PD, whichever occurs first~~</td><td>~~Progressed~~</td></tr><tr><td>~~Death[a] before first disease assessment~~</td><td>~~Date of death[a]~~</td><td>~~Progressed~~</td></tr></table>~~DOR = duration of response; PD = progressive disease; PFS = progression-free survival.~~
~~[a] For DOR, death must be due to disease progression, otherwise, both outcomes will be censored at the date of last disease assessment. For PFS, death due to any cause is counted as an event.~~
Missing data for partial dates on AEs or concomitant medication may be imputed according to prespecified, conservative imputation rules. Censoring rules for PFS and DOR and details about the handling of missing data are described in Section 13.5.1.
Details on the response evaluable population are provided in Section 13.</td><td></td></tr>
<tr><td>14 References</td><td>**Cyclophosphamide [package insert]. Deerfield, IL: Baxter Healthcare Corporation; April 2011.**
Demo SD, Kirk CJ, Aujay MA, et al. Anti-tumor activity of PR-171, a novel irreversible inhibitor of the proteasome. Cancer Res. 2007;67:6383-6391.
Dispenzieri A, Rajkumar SV, Gertz MA, et al. Treatment of newly diagnosed multiple myeloma based on Mayo Stratification of Myeloma and Risk-adapted Therapy (mSMART): consensus statement. Mayo Clin Proc. 2007 Mar;82(3):323-41.
Kaufman JL, Siegel D, Vij R, et al. Clinical profile of once-daily, modified-release oprozomib tablets in patients with hematologic malignancies: results of a phase 1b/2 trial. Presented at the European Hematological Association (EHA) Meeting; June 13–16, 2013; Stockholm, Sweden. Abstract P233.</td><td>Added references to provide background on cyclophosphamide (reflecting the addition of the OCyd treatment regimen). Updated reference for median OS estimates for patients with multiple myeloma (Mikhael 2013). Added reference for guidance on TLS laboratory abnormalities (Sezer 2006).</td></tr>
</table>

Section Number	Changed from	Changed to	Rationale
	Kropff M, Bisping G, Schuck E, et al.; Deutsche Studiengruppe Multiples Myelom. Bortezomib in combination with intermediate-dose dexamethasone and continuous low-dose oral cyclophosphamide for relapsed multiple myeloma. Br J Haematol. 2007 Aug;138(3): 330–7. **Korde N, Zingone A, Kwok M, et al. Phase II Clinical and Correlative Study of Carfilzomib, Lenalidomide, and Dexamethasone (CRd) in Newly Diagnosed Multiple Myeloma (MM) Patients. Blood (ASH Annual Meeting Abstracts) 2012 120: Abstract 732.** **Kropff M, Liebisch P, Knop S, et al.; Deutsche Studiengruppe Multiples Myelom, DSMM. DSMM XI study: dose definition for intravenous cyclophosphamide in combination with bortezomib/dexamethasone for remission induction in patients with newly diagnosed myeloma. Ann Hematol. 2009;88(11):1125–30.** **Kummar S, Gutierrez M, Doroshow JH, Murgo, AJ. Drug development in oncology: classical cytotoxics and molecularly targeted agents. Br J Clin Pharm. 2006;62:15–26.** **Mikhael JR, Reeder CB, Libby EN III, et al. Results from the phase II dose expansion of cyclophosphamide, carfilzomib, thalidomide and dexamethasone (CYCLONE) in patients with newly diagnosed multiple myeloma. ASH 2012, abstr 445.** **Mikhael JR, Dingli D, Roy V, et al. Management of newly diagnosed symptomatic multiple myeloma: updated mayo stratification of myeloma and risk adapted therapy (msmart) consensus guidelines 2013. Mayo Clin Proc. n April 2013;88(4):360 376.** **Morgan GJ, Davies FE, Gregory WM, et al. Cyclophosphamide, thalidomide, and dexamethasone (CTD) as initial therapy for patients with multiple myeloma unsuitable for autologous transplantation. Blood. 2011 Aug 4;118(5):1231-8.** **Palumbo A, Bringhen S, Villani O, et al. Carfilzomib, cyclophosphamide and dexamethasone (CCd) for newly diagnosed multiple myeloma (MM) patients. ASH 2012; abstr 730** **Reece DE, Rodriguez GP, Chen C, et al. Phase I-II trial of bortezomib plus oral cyclophosphamide and prednisone in relapsed and refractory multiple myeloma. J Clin Oncol. 2008 Oct 10;26(29):4777–83.** **Reeder CB, Reece DE, Kukreti V, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. Leukemia. 2009;23(7):1337–41.** **Reeder CB, Reece DE, Kukreti V, et al. Once- versus twice-weekly bortezomib induction therapy with CyBorD in newly diagnosed multiple myeloma. Blood. 2010;115(16):3416–7.** **Sezer O, Vesole DH, Singhal S, et al. Bortezomib-Induced Tumor Lysis Syndrome in Multiple Myeloma. Clinical Lymphoma and Myeloma. Vol. 7, No. 3, 233-235, 2006.**		Added reference for the definition of MTD (Kummar 2006).

Section Number	Changed from	Changed to	Rationale
	Volpe DA, Warren MK. Myeloid clonogenic assays for comparison of the in vitro toxicity of alkylating agents. Toxicol In Vitro. 2003 Jun;17(3):271-7.		
14 References	Jagannath S, Richardson RG, Barlogie B, et al. Bortezomib in combination with dexamethasone for the treatment of patients with relapsed and/or refractory multiple myeloma with less than optimal response to bortezomib alone. Haematologica. 2006;91(7): 929–34.	~~Jagannath S, Richardson RG, Barlogie B, et al. Bortezomib in combination with dexamethasone for the treatment of patients with relapsed and/or refractory multiple myeloma with less than optimal response to bortezomib alone. Haematologica. 2006;91(7): 929–34.~~	Removed reference as it is no longer relevant in the revised section.
14 References	Jawed I, Lee CM, Tward JD, et al. Survival outcomes for multiple myeloma over three decades: A Surveillance, Epidemiology, and End Results (SEER) analysis. J Clin Oncol. 2007;25 (No. 18S June 20 Supplement): Abstract 8019.	~~Jawed I, Lee CM, Tward JD, et al. Survival outcomes for multiple myeloma over three decades: A Surveillance, Epidemiology, and End Results (SEER) analysis. J Clin Oncol. 2007;25 (No. 18S June 20 Supplement): Abstract 8019.~~	Removed reference as an updated reference was added (Mikhael 2013).
Appendix B Eastern Cooperative Oncology Group (ECOG) Performance Scale	**Grade** / **Description** **0** ~~Normal activity.~~ **F**ully active, able to carry on all predisease performance without restriction. **1** ~~Symptoms, but fully ambulatory.~~ **R**estricted in physically strenuous but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). **2** Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. **3** Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. **4** Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. **5** Death		Added the ECOG source information in the table footnote; revised text to match the source information.
Appendix H Cyclophosphamide Prescribing Information 2011		**Cyclophosphamide Prescribing Information 2011**	Added cyclophosphamide prescribing information as an appendix, reflecting the addition of the OCyd

Section Number	Changed from	Changed to	Rationale
			treatment regimen.
Appendix J Revlimid REMS Guide		**http://www.revlimidrems.com/pdf/REV_Prescriber_Guide.pdf**	Added Revlimid REMS Guide as an appendix to provide guidance for females and males of reproductive potential. This change was applied to both treatment regimens to minimize the risk for confusion around the guidance.
Other	Administrative updates, editorial changes, and style and formatting revisions have been made to improve clarity and consistency throughout the document.		

Changes in Appendix A of Amendment 1: Strikethrough indicates text that was deleted and bold indicates text that was added. The changes in Appendix A were made to reflect the addition of the OCyd treatment regimen, and to provide additional clarification regarding the study assessments.

APPENDIX A: SCHEDULE OF STUDY ASSESSMENTS

Visit	Screening	Cycle 1										Cycle 2–24				Cycle 25+		~~EOS/ Early Discon.~~ **End of Study Treatment**[b]
	Day -14 to -1	Day 1	Day 2	Day 3, 4	Day 5	Day 6, 7	Day 8 ± 1	Day 9–14	Day 15 ± 1	Day 16–21	Day 22–28	Day 1	Day 2–14	Day 15 ± 1	Day 22–28	Day 1	Day 22–28[a]	
Written Informed Consent	X																	
Inclusion/Exclusion Criteria	X																	
Medical History	X																	
Previous Treatment History	X																	
Physical Examination[c]	X	X					X		X		X	X		X		X		X
Height	X																	
Weight	X	X										X						X
Neurological Assessment (BPNS and CTCAE Grading)[d]	X											X[d]						X
Vital Signs	X	X[e]	X[e]		X[e]		X		X[e]		X	X[f]		X[f]				X
12–lead ECG (Local)	X	X[g]										X[g]						X
Urinalysis[h]	X																	X
Serum Chemistry[j]	X	X			X		X		X		X	X[j]		X		X[j]		X
CBC with Diff and Platelets[k]	X	X			X		X		X		X	X[j]		X		X[j]		X
Coagulation Tests[l]	X	X										X[j]				X[j]		
Pregnancy Test[m]	X	X					X		X		X	X		X				X
SPEP/UPEP/Immunofixation[n]	X										X				X		X	X
β2 Microglobulin	X																	
SFLC assay and ratio[o]	X										X				X		X	X
Skeletal Survey[p]	X										X				X		X	X
Plasmacytoma Evaluation[q]	X										X				X		X	X
Bone Marrow Aspirate and FISH Analyses[r]	X																	X[s]

APPENDIX A: SCHEDULE OF STUDY ASSESSMENTS (CONT'D)

Visit	Cycle 1											Cycle 2–24				Cycle 25+		End of Study Treatment[b]
	Day -14 to -1	Day 1	Day 2	Day 3, 4	Day 5	Day 6, 7	Day 8 ± 1	Day 9-14	Day 15 ± 1	Day 16–21	Day 22–28	Day 1[a]	Day 2–14	Day 15 ± 1	Day 22-28	Day 1	Day 22–28[a]	
Optional – Genomic Biomarker Assessment: Blood[s]	X																	~~X~~
Optional – Genomic Biomarker Assessment: Saliva[s]	X																	
Blood for PK[t]		X										X						
Blood for PDn Assay[u]		X	X									X						
~~Oprozomib Dosing~~		~~X~~	~~X~~	~~X~~	~~X~~				~~X~~	~~X~~		~~X~~	~~X~~	~~X~~		~~X~~		
~~Dexamethasone Dosing~~		~~X~~	~~X~~				~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~			
~~Lenalidomide Dosing~~		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~		~~X~~	~~X~~	~~X~~				
Treatment Regimen 1 (ORd) Dosing[v]: **Oprozomib**		**X**	**X**	**X**	**X**				**X**	**X**		**X**	**X**	**X**		**X**		
Lenalidomide		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**				
Dexamethasone		**X**	**X**				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			
Treatment Regimen 2 (OCyd) Dosing[w]: **Oprozomib**		**X**	**X**	**X**	**X**				**X**	**X**		**X**	**X**	**X**		**X**		
Cyclophosphamide		**X**					**X**		**X**			**X**	**X**	**X**				
Dexamethasone		**X**	**X**				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			
AEs and Con Meds[x]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cycle 1 Follow-up Telephone Call to Subject				X[y]														

AE, = adverse event; **ALT = alanine aminotransferase; AST = aspartate aminotransferase**; BPNS = Brief Peripheral Neuropathy Screen; **CBC = complete blood count; CR = complete response; CrCl = creatinine clearance; CRF = case report form; CT = computed tomography;** CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; **eCRF = electronic case report form;** ~~EOS = End of Study;~~ **FCBP = females of child-bearing potential;** FISH = fluorescent in-situ hybridization; **MRI = magnetic resonance imaging; OCyd = oprozomib, cyclophosphamide, and dexamethasone; ORd = oprozomib, lenalidomide, and dexamethasone; PD = progressive disease;** PDn = pharmacodynamics; **PET = positron emission tomography;** PK = pharmacokinetics; **SFLC = serum free light chain;** SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

[a] ~~Disease response assessments will occur every cycle for the first year (Cycles 1–12), every other cycle for the second year (Cycles 13–24) and every 12 weeks (3 cycles) starting with Cycle 27 (e.g., Cycle 27, Cycle 30, Cycle 33, etc.). Test results must be available before starting the next 28–day cycle of oprozomib.~~
Following completion of 8 cycles of ORd or OCyd treatment, disease response assessments will continue every 8 weeks until confirmed PD. For subjects who discontinue treatment before PD occurs (such as for an AE, noncompliance, etc.), disease response assessments will be performed every4 weeks during the first 24 months of the study and every 8 weeks thereafter, until confirmed PD or the start of alternative, non-protocol antimyeloma therapy.

[b] **All End of Study Treatment/Early Discontinuation Assessments must be performed within 30 days following the subject's last administration of study drug and prior to initiation of any other treatment. The same methods of disease assessment must be used throughout the study.** ~~For subjects who discontinue treatment for reasons other than progression, disease assessments must be performed every 8 weeks (or 12 weeks if patient at cycle > 24) or until a new multiple myeloma therapy is started or disease progresses.~~ **If disease assessments show disease progression, assessments do not need to be repeated with End of Study Treatment Assessments.**

[c] Complete physical exams will be performed during Screening and at the End of Study Treatment visit. All other physical exams will be limited physical exams. A complete physical examination will include examination of the skin, head and neck, chest (heart and lungs), abdomen, extremities, and a brief neurological exam including an assessment for peripheral neuropathy. Rectal and pelvic examinations are optional. Eastern Cooperative Oncology Group performance status (assessed at the time of the physical exam) will be ~~conducted~~ **collected during a complete physical exam.** A limited physical examination will include an examination of the chest (heart and lungs)~~,~~ **and** abdomen, with additional examinations as clinically indicated or directed by AEs.

[d] Neurological assessments (BPNS, and if applicable, record adverse events with CTCAE grading) will be performed at Screening and on Day 1 for Cycles 2–24.

[e] Measure ~~within 1 hour prior to~~ **on day of dosing, prior to the administration of** oprozomib dose and at 30 minutes, 1 hour, and 2 hours after each oprozomib dose (Cycle 1 Days 1, 2, 5, ~~8,~~ and 15). At the investigator's medical discretion, vital signs monitoring may be extended beyond the time periods specified above

[f] Cycles 2 and higher, vital signs are required ~~within 1 hour~~ **on the day of dosing,** prior to **the administration of** oprozomib **dose.**

[g] Perform ECG ~~within 1 hour predose and~~ 2 hours postdose of oprozomib (see Laboratory Manual) for Cycles 1, 2, 3, 4, 6, 8, 12, 18, 24 and then every 6 months (Cycle 30, 36, etc.).

[h] Subjects with urine positive for protein (> than trace) will need to collect a 24–hour urine sample for creatinine and protein.

[i] Full chemistry panel (sodium, potassium, calcium, alkaline phosphatase, blood urea nitrogen, uric acid, lactate dehydrogenase, creatinine, chloride, bicarbonate, glucose, total protein, albumin, total bilirubin, ALT, AST, phosphorous, and magnesium) to be done within 4 hours prior to dosing. Calculate **or measure** CrCl. Screening results may be used for Cycle 1 Day 1 if obtained within 72 hours of Cycle 1 Day 1.

[j] Day 1 labs can be drawn up to 3 days prior to Day 1.

[k] Complete blood count (CBC) with differential includes the following: hemoglobin, hematocrit, white blood cell count with complete manual or automated differential (total neutrophils, lymphocytes, monocytes, eosinophils, basophils; reported as absolute counts), red blood cell count, and platelet count.

[l] Coagulation tests include the following: prothrombin time, activated partial thromboplastin time, and international normalized ratio.

[m] **For both treatment regimens (ORd and OCyd):** Screening pregnancy testing for females of childbearing potential (FCBP) must have a sensitivity of at least 25 mIU/mL with TWO medically supervised tests performed before lenalidomide **or cyclophosphamide** dosing starts. One test must be obtained within 10–14 days and one test within 24 hours prior to the start of lenalidomide **or cyclophosphamide** on Cycle 1 Day 1. A medically supervised negative serum pregnancy test will be done within 1 day prior to each cycle of lenalidomide **or cyclophosphamide** dosing, **on Day 8, Day 15, and between Days 22–28 of Cycle 1; on Day 15 for Cycles 2 and higher; and at the End of Study Treatment visit,** in FCBP ~~potential~~ only. Pregnancy tests will be repeated on Day 15 of each Cycle 2 and beyond if menses are irregular or not present in FCBP.

[n] ~~Results for both SPEP and UPEP done during screening must be available before starting study drug treatment. When the subject is on study drug, the disease response assessments will be performed at the end of each cycle for the first year (Cycles 1–12), every other cycle for year 2 (Cycle 13–24) and every 3 cycles for year 3 (Cycle 27, Cycle 30, Cycle 33, etc.). If the subject comes off study then disease response assessments will be performed every 4 weeks during the first year of treatment, every 8 weeks during the second year and every 12 weeks thereafter. Obtain blood for serum electrophoresis (SPEP), serum immunofixation, serum immunoglobulin levels, and serum FLCs and 24–hour urine sample for urine protein electrophoresis (UPEP) and urine immunofixation. NOTE: UPEP (on a 24–hour collection) is required; no substitute method is acceptable. Subjects with negative serum and urine M–proteins are required to complete FLC at each time point.~~

SPEP and UPEP (24-hour assessment, no substitute method is acceptable) is required for all subjects at Screening. Thereafter, SPEP is to be done at each assessment for all subjects. UPEP with 24-hour urine collection is required at each assessment only if screening UPEP shows measurable paraprotein in the urine. If screening UPEP is negative, spot urine is required at each assessment. If positive for paraprotein, a 24 hour urine collection with UPEP must be done at the next assessment and at each subsequent assessment unless the UPEP shows the absence of paraprotein. Immunofixation is required at next assessment only if SPEP or UPEP results are zero/undetectable.

[o] **Serum free light chain: Only in subjects without measurable serum and urine M-protein levels (serum M-protein < 0.5 g/dL or urine M-protein < 200 mg/24 hours) at Screening will SFLC assays be used to determine eligibility and response.**

[p] ~~Skeletal survey does not need to be repeated if previously done within 30 days of consent. If a skeletal survey was previously done greater than 30 days before consent, it may be acceptable with study medical monitor approval. If present at Baseline, bone lesion (s) must be monitored throughout the study per IMWG response criteria.~~

Skeletal survey will include lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. **The skeletal survey will be conducted at Screening and will be repeated if worsening clinical symptoms suggest PD, or as clinically indicated.**

[q] ~~Subjects are required to have a plasmacytoma evaluation at Screening and End of Study. If present at Baseline, the plasmacytoma(s) must be monitored throughout the study per IMWG response criteria.~~

Extramedullary plasmacytoma evaluation will be conducted at Screening only if a lesion is suspected clinically. Only measurable plasmacytomas will be followed for response and progression. Measurable lesions must have a longest diameter of at least 1 cm and the product of cross diameter is at least 1 cm2. Plasmacytomas of lessor size are considered non measurable. If an extramedullary plasmacytoma is detected, evaluation will be repeated during treatment as clinically indicated, or to confirm a response of PR or better, or to confirm PD. The same technique (which may include clinical evaluation by palpation, ultrasound, x-ray, CT scan, MRI, or PET) should be employed for each measurement of plasmacytoma dimensions as clinically appropriate (refer to Appendix D). Bi-dimensional lesion measurements must be performed and recorded in the designated eCRF.

[r] ~~Bone marrow aspirate or biopsy – quantitate percent myeloma cell involvement. Obtain bone marrow sample for fluorescent in situ hybridization (FISH) studies. Repeat bone marrow aspirate when appropriate to confirm achievement of sCR or CR.~~

Bone marrow aspiration and biopsy are required for all subjects at Screening to quantify percent plasma cell involvement and for FISH. FISH will be performed at a central laboratory. Thereafter, an additional bone marrow aspiration is required to confirm a CR; a biopsy is required if bone marrow aspiration cannot be performed.

[s] Optional genomic biomarker samples: For subjects who consent to participate, bone marrow aspirate (obtained from the bone marrow aspirate for FISH analysis; no new sample is required), blood, and saliva samples will be collected at baseline. Bone marrow aspirate will also be collected at the ~~time of progression~~ **End of Study Treatment** visit (may be at time of treatment discontinuation or during long term follow-up) for isolation of CD138+ cells; bone marrow will be collected

only from subjects consenting to genomic biomarker analyses ~~and who achieve less than a CR; bone marrow will be collected at the time of PD or End of Treatment.~~

[t] Blood for PK for subjects will occur at two postdose time points on Cycle 1 Day 1, one predose and 2 postdose time points on Cycle 3 Day 1 and Cycle 5 Day 1. Sampling times and volumes are provided in the Laboratory Manual.

[u] Blood for ~~PDn analyses~~ **measurement of proteasome activity in whole blood and PBMCs** will only be collected in Phase 1b. Samples will be collected predose, ~~and~~ **at** 2 postdose time points on Day 1 of Cycles 1 and 2**,** and predose on Cycle 1 Day 2. Sampling times and volumes are provided in the Laboratory Manual.

[v] **Treatment Regimen 1 (ORd):** Oprozomib treatment will be administered on Days 1–5 and 15–19 during 28-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason. Subjects will receive 20 mg of dexamethasone on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day treatment cycle up to Cycle 24. After Cycle 1, the dexamethasone dose may be decreased to 10 mg/day in subjects > 75 years of age, at the discretion of the investigator. On days when both oprozomib and dexamethasone are administered ~~concurrently~~ (i.e., on Days 1, 2, 15, and 16 of each cycle), dexamethasone should be taken at least 30 minutes prior to oprozomib. **Except for PK collection days,** lenalidomide will be administered **orally at a dose of 25 mg, with or without food at investigator and subject discretion, on** Days 1–21 of each 28 day cycle up to Cycle 24. **Subjects may take lenalidomide following oprozomib administration, however it is recommended that they take lenalidomide at approximately the same time each day~~Oprozomib and lenalidomide should be taken concurrently, i.e., within 5 minutes of each other.~~ On days when oprozomib is not administered, subjects should take lenalidomide at approximately the same time of the day for consistency.**

[w] **Treatment Regimen 2 (OCyd): Oprozomib treatment will be administered on Days 1–5 and 15–19 during 28-day cycles for up to 8 cycles or until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason. Subjects will receive 20 mg of dexamethasone on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day treatment cycle up to Cycle 8. After Cycle 1, the dexamethasone dose may be decreased to 10 mg/day in subjects > 75 years of age, at the discretion of the investigator. On days when both oprozomib and dexamethasone are administered (i.e., on Days 1, 2, 15, and 16 of each cycle), dexamethasone should be taken at least 30 minutes prior to oprozomib. Except for PK collection days, cyclophosphamide will be administered orally at 300 mg/m^2 (up to a maximum of 600 mg), with or without food at investigator and subject discretion, on Days 1, 8, and 15 of each cycle for a total of 8 cycles. Subjects may take cyclophosphamide following oprozomib administration at, however it is recommended that they take cyclophosphamide concurrently with oprozomib at approximately the same time each day. On days when oprozomib is not administered, subjects should or must take cyclophosphamide at approximately the same time of the day for consistency.**

[x] Record all AEs from time of consent through 30 days after the last dose of study drug. Start to record concomitant medications from 30 days prior to Day 1 until 30 days after the last dose of study drug. If there is any change in the subject's concomitant medications during the study, it must be recorded on the CRF.

[y] For subjects in the Phase 1b portion: The study nurse (or designee) will call the subject on Cycle 1 Days 3 and 4, approximately 6–10 hours after the expected study drug dosing time to follow up on dosing compliance and to collect start, stop, and duration times as well as severity of any AEs, if applicable.

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Title: Vice President, Global Regulatory Affairs
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Meaning: I have reviewed and approved this document.
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UserName: [redacted]
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Date: Wednesday, 18 September 2013, 07:42 PM Pacific Daylight Time
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==========

APPENDIX L SUMMARY OF CHANGES IN PROTOCOL OPZ003 AMENDMENT 2

The main changes in Clinical Study OPZ003 Amendment 2 are listed below:

Study Design

1. The current dose of oprozomib on the 5/14 schedule is 150 mg. The study was initiated at 210 mg and the dose was reduced to 150 mg after DLTs were reported in the 210 and 180 mg cohorts. The protocol has been updated through out to reflect these events. The 150 mg dose is 3 full dose levels below the single-agent MTD.
2. The dosing schedule was changed from 5/14 to 2/7 for subsequent cohorts in the ORd arm and for all subjects in the OCyd arm to provide an increased margin of safety for subjects participating in this study. The initial dose of oprozomib for the OCyd and ORd arms on the 2/7 schedule is 210 mg. It is 3 full dose levels below the single agent MTD on the 2/7 schedule.
3. Introduced the new Oprozomib Extended Release (ER) Tablet and the strengths to be used in this study.

Exclusion Criteria

4. Added language excluding patients undergoing or expected to require plasmapheresis during the screening process or any time during the study.
5. Added exclusion criterion for patients with prior clinically significant bleed in the 6 months prior to first dose of study treatment.

Dose Modification Guidelines/Safety Guidance for the Investigator

6. Additional safety guidance regarding Grade 3 or 4 GI hemorrhages.
7. Added guidance for subjects receiving anti-hypertensive therapy about the risk for hypotension.

Laboratory Evaluations for Safety

8. Platelet function assessment to understand impact of oprozomib, if any, on platelet adherence, activation, aggregation and interaction with clotting factors.

Administrative updates, editorial changes, and style and formatting revisions have been made to improve clarity and consistency throughout the document. Significant changes are described in the table below. Detailed, changed text is displayed for **first major** occurrence only. Changes in sections of the protocol body were also made in the protocol synopsis and elsewhere in the document, as applicable. Deletions of text are presented in strikethrough format. Added text is presented in bold format.

Section Number	Changed from	Changed to	Rationale
Cover Page Signature Page Protocol Acceptance Page	*New text added*	Amendment 2 and 15 October 2014	Updated for new amendment
Compliance, confidentiality, and approval statements	This document is signed with electronic signatures at Onyx Therapeutics~~, Inc.~~ (a wholly owned subsidiary of Onyx Pharmaceuticals~~, Inc.~~). Electronic signatures made by our employees, agents, or representatives, located anywhere in the world, are the legally binding equivalent of traditional handwritten signatures.	This document is signed with electronic signatures at Onyx Therapeutics) a wholly owned subsidiary of Onyx Pharmaceuticals) **an Amgen subsidiary**. Electronic signatures made by our employees, agents, or representatives, located anywhere in the world, are the legally binding equivalent of traditional handwritten signatures.	Updated compliance and approval statements where Onyx Therapeutics and Onyx Pharmaceuticals are listed to be consistent with current company name and study sponsorship
Global: in all sections listing Inc.		*Deleted: Inc.*	Removed all references to "Inc." to be consistent with current company name and study sponsorship
Cover Page		*Added text* Amendment 2 or "2"	Updated for new amendment
Signature Page	*Superseded:* List of approvers	*Updated:* List of approvers	Updated list of approvers
Synopsis Study Objectives Secondary Objective Section 3.2 Study Objectives Synopsis Study Design Pharmacokinetics Section 13.6.3 Pharmacokinetic Analysis	**Secondary Objectives** • To evaluate population pharmacokinetic (PK) parameter estimates of oprozomib and the variability in these estimates.	**Secondary Objectives** • To evaluate population pharmacokinetic (PK) parameter estimates of oprozomib **and, may include its metabolite(s),** and the variability in these estimates.	Added option to perform these analyses if necessary

Section Number	Changed from	Changed to	Rationale
Synopsis Study Design Treatment regimen Section 4 Study Design Updated the study schema to add the 2/7 schedule and added an additional study scheme for 2/7 schedule Added a dose administration figure for the 2/7 schedule Section 9 Dosage and Treatment Administration Added Appendix B Schedule of Assessments for the 2/7 Schedule	In one combination regimen, ORd~~, subjects will receive Oprozomib Tablets (hereafter referred to as oprozomib)~~ administered orally, once daily on Days 1-5 and on Days 15-19 in combination with lenalidomide at a dose of 25 mg on Days 1 through 21, and dexamethasone at a dose of 20 mg on Days 1, 2, 8, 9, 15, 16, 22, and 23 of 28-day cycles (see dose administration schema below). In the second combination regimen (OCyd), subjects will receive oprozomib administered ~~orally, once daily on Days 1–5 and on Days 15–19 in~~ combination with oral cyclophosphamide at a dose of 300 mg/m^2 on Days 1, 8, and 15, and dexamethasone at a dose of 20 mg on Days 1, 2, 8, 9, 15, 16, 22, and 23 of 28-day cycles (See dose administration schema below). Dexamethasone will be administered at a dose of 20 mg/day, as described above, through the first cycle, after which the dose may be decreased to 10 mg/day in subjects > 75 years of age, at the discretion of the investigator.	The **ORd** combination regimen treatment cycles are 28 days in duration. **Subjects enrolled under the original protocol and Amendment 1** will receive oprozomib once daily on Days 1 through 5 and Days 15 through 19 **(referred to as the 5/14 schedule). Subjects enrolled under Amendment 2 will receive oprozomib once daily on 2 consecutive days every 7 days; specifically on Days 1, 2, 8, 9, 15, 16, 22, and 23 (referred to as the 2/7 schedule).** All subjects on the ORd arm will receive lenalidomide at a dose of 25 mg will be given on Days 1 through 21 and dexamethasone at a dose of 20 mg will be given on Days 1, 2, 8, 9, 15, 16, 22, and 23 of every 28-day cycle (see dose administration schemas below). The **OCyd regimen treatment cycles are 28 days in duration. One (1) oprozomib dosing schedule (2/7) will be assessed during dose escalation. All study subjects will receive oprozomib administered orally, once daily on 2 consecutive days every 7 days; specifically on Days 1, 2, 8, 9, 15, 16, 23, and 22 (referred to as the 2/7 schedule)** in combination with oral cyclophosphamide at a dose of 300 mg/m^2 on Days 1, 8, and 15, and dexamethasone at a dose of 20 mg on Days 1, 2, 8, 9, 15, 16, 22, and 23 of 28-day cycles. (See dose administration schema below.) Dexamethasone will be administered at a dose of 20 mg/day, as described above, through the first cycle, after which the dose may be decreased to 10 mg/day in subjects > 75 years of age, at the discretion of the investigator.	The dosing schedule was changed from 5/14 to 2/7 for subsequent cohorts in the ORd arm and for all subjects in the OCyd arm to provide an increased margin of safety for subjects participating in this study.

Section Number	Changed from	Changed to	Rationale
Synopsis Study Design Phase 1b Section 2.5 Dose Rationale Section 4 Study Design Section 4.2 Dose Escalation Plan Modified Tables 3 and 4 and added Table 5 Added Appendix B Schedule of Assessments for the 2/7 Schedule	Phase 1b The initial cohort for each combination regimen will be ~~entered at a dose level of 210 mg/day oprozomib.~~ The dose of oprozomib for subsequent cohorts will be escalated in 30-mg increments until the MTD is established. ~~In the Phase 1b portion of the study, dose cohorts will be enrolled sequentially, alternating between the ORd and OCyd treatment regimens across sites.~~ There will not be a predefined maximum dose to be studied. Subjects will be evaluated for DLTs according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03. In the event that the initial cohorts at the 210 mg dose are found to exceed the MTD, dosing will proceed at 180 mg or a lower dose as agreed to by the Cohort Safety Review Committee (CSRC), comprised of the Onyx study medical monitor, Onyx safety representative, and the active investigators. Intrasubject dose escalation to the MTD or recommended Phase 2 dose may be permitted once that dose has been determined and after a discussion has occurred between the treating physician and Onyx study medical monitor.	Phase 1b The initial cohort **dose levels** for each combination regimen **is as follows:** • **Original Protocol and Amenment 1 - ORd (5/14 schedule): 210 mg/day of oprozomib (current 5/14 cohort dose level is 150 mg/day of oprozomib) There have been 2 dose de-escalations in the ORd 5/14 arm in response to dose limiting toxicities (DLTs) occurring at the 210 mg and the 180 mg cohort level.** • **Amendment 2 - ORd (2/7 schedule): 210 mg/day of oprozomib** • **Amendment 2 - OCyd (2/7 schedule): 210 mg/day of oprozomib** The dose of oprozomib for cohorts will be escalated **or de-escalated** in 30-mg increments until the MTD is established**. Subjects on the 5/14 schedule will not have their oprozomib dose escalated above 150 mg/day.** There will not be a predefined maximum dose to be studied. Subjects will be evaluated for DLTs according to the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. **In the event that the ORd cohort at the 210 mg dose (2/7 schedule)** is found to exceed the MTD, dosing will proceed at 180 mg or a lower dose as agreed to by the Cohort Safety Review Committee (CSRC), comprised of the Onyx study medical monitor, Onyx safety representative, and the active investigators. **In the event that the initial OCyd cohorts at the 210 mg dose (2/7 schedule) are found to**	The dosing schedule was changed from 5/14 to 2/7 for subsequent cohorts in the ORd arm and for all subjects in the OCyd arm to provide an increased margin of safety for subjects participating in this study Dose de-escalation language has been added.

Section Number	Changed from	Changed to	Rationale
		exceed the MTD, dosing will proceed at 180 mg or a lower dose as agreed to by the CSRC. Intrasubject dose escalation to the MTD or recommended Phase 2 dose **(RP2D)** may be permitted once that dose has been determined and after a discussion has occurred between the treating physician and Onyx study medical monitor.	
Synopsis Study Design Dose-Limiting Toxicities Section 9.1.3 Definition of Dose-Limiting Toxicity Table 13: Dose Modification Guidelines for Oprozomib-, Lenalidomide-, and Cyclophosphamide-Related Nonhematologic Toxicities Post-Cycle 1 (*added last row and related footnote*)	Hematologic DLT: • Grade 4 neutropenia: Absolute neutrophil count (ANC) < 0.5×10^9/L lasting ≥ 7 days, despite myeloid growth factor support • Febrile neutropenia: Any single temperature ≥ 38.3°C or a sustained temperature of ≥ 38.0°C for over 1 hour with Grade ≥ 3 neutropenia (ANC < 1.0×10^9/L) • Grade 4 thrombocytopenia lasting ≥ 7 days ~~or Grade 3 thrombocytopenia with bleeding or requiring platelet transfusion~~ • Note: Grade 4 anemia will not be considered a DLT.	Hematologic DLT: • Grade 4 neutropenia: Absolute neutrophil count (ANC) < 0.5×10^9/L lasting ≥ 7 days, despite myeloid growth factor support • Febrile neutropenia: Any single temperature ≥ 38.3°C or a sustained temperature of ≥ 38.0°C for over 1 hour with ≥ Grade 3 neutropenia (ANC < 1.0×10^9/L) • Grade 4 thrombocytopenia lasting ≥ 7 days or • **Grade 4 thrombocytopenia lasting < 7 days with ≥ Grade 2 clinically significant bleeding or < 10,000 platelets requiring platelet transfusion, or** • **Grade ≥ 3 thrombocytopenia with clinically significant bleeding or requiring platelet transfusion.** Note: Grade 4 anemia will not be considered a DLT, **but should be treated with supportive measures in accordance with institutional guidelines.**	Additional guidance to investigators to mitigate Grade 3 or 4 GI hemorrhage

Section Number	Changed from	Changed to	Rationale
Synopsis Study Design Subject Replacement	**Subject Replacement** **Phase 1b:** In the Phase 1b portion of the study, subjects must meet the following criteria to be considered evaluable for MTD determination during the 4-week DLT evaluation period: • A minimum of 8 of 10 planned doses of oprozomib must be received • A minimum of 6 of 8 planned doses of dexamethasone must be received • All 3 planned doses of cyclophosphamide must be received (OCyd combination regimen only) • A minimum of 17 of 21 planned doses of lenalidomide must be received (ORd combination regimen only) • Subjects not meeting all of the above criteria or assessed as unevaluable will be replaced. Subjects who do not meet the criteria above because of a DLT will be considered DLT-evaluable.	**Subject Replacement** **Phase 1b:** In the Phase 1b portion of the study, subjects must meet the following criteria to be considered evaluable for MTD determination during the 4-week DLT evaluation period: • A minimum of 8 of 10 planned doses of oprozomib must be received **for the 5/14 dosing schedule** • **A minimum of 7 of 8 planned doses of oprozomib must be received for the 2/7 dosing schedule** • A minimum of 6 of 8 planned doses of dexamethasone must be received • All 3 planned doses of cyclophosphamide must be received (OCyd combination regimen only) • A minimum of 17 of 21 planned doses of lenalidomide must be received (ORd combination regimen only) • Subjects not meeting all of the above criteria or assessed as unevaluable will be replaced. Subjects who do not meet the criteria above because of a DLT will be considered DLT-evaluable.	Updated to include subject replacement information for both dosing schedules

Section Number	Changed from	Changed to	Rationale
Synopsis Study Design Phase 2 Section 4 Study Design Section 4.2 Dose-Escalation Plan Modified Tables 3 and 4, and added Table 5	Phase 2 The Phase 2 portion of the study will include up to 35 additional subjects in each of the ~~two~~ combination regimens, with the same eligibility criteria as those in Phase 1b. Phase 2 subjects will be treated at the ~~recommended Phase 2 dose~~ and schedule of oprozomib identified during the Phase 1b portion of the study in order to better characterize the safety and tolerability, antimyeloma activity, and PK. The ~~recommended Phase 2~~ dose may or may not be the same as the MTD, and will be assessed on the basis of the totality of safety and PK/PDn data. ~~In the Phase 2 portion of the study, subjects will be enrolled alternately between OCyd and ORd treatment regimens at each study site.~~	**Phase 2** The Phase 2 portion of the study will include up to 35 additional subjects in each of the 2 combination regimens, with the same eligibility criteria as those in Phase 1b. Phase 2 subjects will be treated at the **RP2D** dose and schedule of oprozomib identified during the Phase 1b portion of the study in order to better characterize the safety and tolerability, antimyeloma activity, and PK. The **RP2D** may or may not be the same as the MTD, and will be assessed on the basis of the totality of safety and PK/PDn data. **Subjects enrolled under Amendment 2 will receive Oprozomib Extended Release (ER) Tablets**	Introduce the new Oprozomib Extended Release (ER) Tablet. Removed last sentence to allow flexibility for enrollment and avoid possible protocol deviations.
Synopsis Study Design Genomics Criteria for evaluation Other Genomics Section 10.5 Genomic Evaluations Appendix A and B: Schedule of Study Assessments and related footnotes	Genomics: Analysis of genetic ~~and~~ gene expression, biomarkers that may predict for response and resistance following treatment with proteasome inhibitors will be performed on all subjects who consent to optional genomic biomarker analysis. These analysis will be performed on a ~~baseline~~ bone marrow aspirate (the remaining portion of the bone marrow aspirate sample ~~obtained at baseline will be used, no additional samples are required~~) of blood, and saliva. Additional bone marrow samples for biomarkers may be collected at the End of Study Treatment visit from all subjects who consent. End of Study Treatment is defined as the end of protocol-defined therapy**.** Whole genome sequencing (WGS), whole exome sequencing (WES), and/or whole transcriptome sequencing will be conducted on isolated tumor ($CD138^{+}$) cells from bone marrow samples taken at baseline and disease progression. In addition, WGS or WES will be performed on a normal tissue sample (e.g., saliva or $CD3^{+}$ T–cells	Genomics: Analysis of genetic, gene expression **and cell surface** biomarkers that may predict for response and resistance following treatment with proteasome inhibitors will be performed on all subjects who consent to optional genomic biomarker analysis. These analyses will be performed on a bone marrow aspirate **collected at Baseline, prior to Cycle 1 Day 1 (C1D1), and a sample of blood and/or saliva will be collected at Baseline, prior to dosing on C1D1. The bone marrow aspirate used for genomics is the remaining portion of bone marrow sample left after the amount required for disease assessment using FISH is performed. No additional bone marrow sample is required at Baseline.** Additional bone marrow samples for biomarkers may be collected at the End of Study Treatment visit from all subjects who consent. End of Study Treatment is defined as **at disease progression or at** the end of protocol-defined	Updated text to what is currently planned for genomic biomarker analysis.

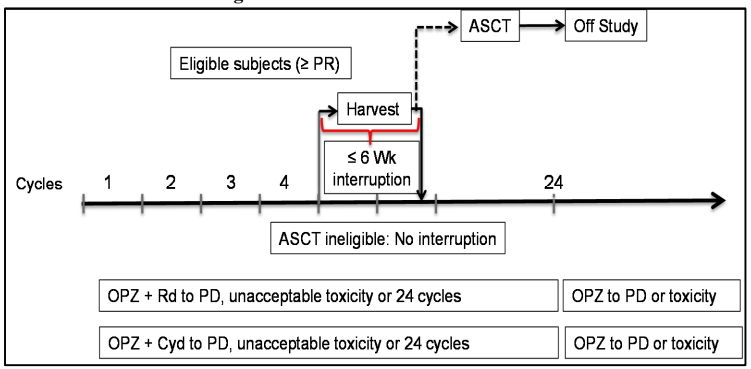
Section Number	Changed from	Changed to	Rationale
	isolated from PBMCs) to determine the presence of somatic mutations in tumor cell samples. Data will be analyzed to characterize whether drug response is related to alterations in genes regulated by or involved ~~in activation of nuclear factor kappa light chain enhancer of activated B cell (NF-κB) transcription factors as well as genes involved in immunoglobulin production and plasma cell protein homeostasis.~~ These data will also be used to derive hypotheses about mechanisms of drug response, resistance, and safety.	therapy **if end of treatment is due to progressive disease (PD)**. Whole genome sequencing (WGS), whole exome sequencing (WES), whole transcriptome sequencing (RNA-Seq), and/or other forms of nucleic acid and protein quantification will be conducted on isolated tumor ($CD138^{+}$) cells from bone marrow samples taken at **Baseline** and disease progression. In addition, WGS or WES will be performed on a normal tissue sample (e.g., saliva or $CD3^{+}$ T-cells isolated from PBMCs) to distinguish germline mutations from somatic mutations in tumor cell samples. Data will be analyzed to characterize whether drug response is related to alterations in genes regulated by or involved **in immunoglobulin production and protein homeostasis, i.e., IGH, as well as in genes regulated by or involved** in the activation of nuclear factor kappa light chain enhancer of activated B cell (NF-Kappa B) transcription factors. Immunoglobulin levels in tumor cells **will be quantified by qPCR, or immunocytochemistry** and/or other protein or gene expression quantification methods. These data will also be used to derive hypotheses about mechanisms of drug response, resistance, and safety.	
Synopsis Planned number of subjects Section 5 Number of Subjects	Total enrollment of up to ~~118~~ evaluable subjects is planned for this study, including up to approximately ~~48~~ evaluable subjects for the Phase 1b portion of the study (24 ~~for each combination regimen~~ and ~~schedule for~~ ORd and OCyd ~~respectively~~) and 70 subjects for the Phase 2 portion of the study (35 subjects for each combination regimen).	Total enrollment of up to **approximately 134** evaluable subjects is planned for this study, including up to approximately **64** evaluable subjects for the Phase 1b portion of the study (**40 and** 24 for ORd and OCyd, respectively) and **approximately** 70 subjects for the Phase 2 portion of the study (35 subjects for each combination regimen).	Added additional subjects due to added dose schedule (2/7)

Section Number	Changed from	Changed to	Rationale
Synopsis Sample size justification Section 4.5.1 Phase 1b	The estimated sample size for the dose-escalation portion of the study of up to 24 subjects for each combination regimen is based upon standard 3 + 3 dose-escalation rules and the expectation that 2–6 dosing cohorts of 3–6 subjects per cohort will be required to establish the MTD for each treatment regimen. Enrollment of 35 additional subjects in each combination regimen during the Phase 2 portion of the study is based upon the goal of ruling out an ORR < 85% and a CRR < 50% based upon the approximate lower 1-sided 90% confidence interval for each parameter. This sample size is based upon a simulation of a multinomial outcome of CR, PR, or PD for various cohort sizes. With 35 subjects per combination regimen, and an assumed true ORR and true CRR of 95% and 75%, respectively, the probability of ruling out an ORR < 85% and a CRR < 50% with 90% confidence is approximately 88%, from the simulation described above. The same assumptions for ORR and CRR are used in determining the sample size for each combination regimen.	The estimated sample size for the dose-escalation portion of the study of **up to 40 subjects for the ORd combination regimen and** up to 24 subjects for the **OCyd** combination regimen is based upon standard 3 + 3 dose-escalation rules and the expectation that 2–6 dosing cohorts of 3–6 subjects per cohort will be required to establish the MTD for each treatment regimen. Enrollment of 35 additional subjects in each combination regimen during the Phase 2 portion of the study is based upon the goal of ruling out an ORR < 85% and a CRR < 50% based upon the approximate lower 1-sided 90% confidence interval for each parameter. This sample size is based upon a simulation of a multinomial outcome of CR, PR, or PD for various cohort sizes. With 35 subjects per combination regimen, and an assumed true ORR and true CRR of 95% and 75%, respectively, the probability of ruling out an ORR < 85% and a CRR < 50% with 90% confidence is approximately 88%, from the simulation described above. The same assumptions for ORR and CRR are used in determining the sample size for each combination regimen.	Added additional subjects due to added dose schedule (2/7)
Synopsis Duration of study/treatment period Section 4.6 Estimated Study Duration	The total study duration is expected to be approximately ~~39~~ months based upon the assumption that approximately **15** months may be required to enroll all subjects (approximately ~~9~~ months to enroll Phase 1b subjects and up to approximately ~~6~~ months to enroll Phase 2 subjects) and that the average time on study will be approximately 24 months.	The total study duration is expected to be approximately **59** months based upon the assumption that approximately **35** months may be required to enroll all subjects (**approximately 23 months** to enroll Phase 1b subjects and **up to approximately 12** months to enroll Phase 2 subjects) and that the average time on study will be approximately 24 months.	Updated to reflect new timetable for study
Synopsis Test product, dose, and mode of administration	Oprozomib ~~with tablet strengths of~~ 60, 90, and 120 mg to be given orally (PO).	Oprozomib **Tablets** containing 60, 90, **or** 120 mg of oprozomib **or Oprozomib ER Tablet with strengths of 120, 150, 180, 210, 240,**	Introduce the new Oprozomib Extended Release (ER) Tablet and the strengths to be used in

Section Number	Changed from	Changed to	Rationale
Study Design Section 4 Study Design 8.1.2 Packaging and Labeling Section 8.1.3 Oprozomib ER Tablet Drug Properties	Lenalidomide 25 mg to be given PO Cyclophosphamide 300 mg/m^2 (up to 600 mg) to be given PO Dexamethasone 20 mg to be given PO	**and 270 mg** to be given orally (PO). Lenalidomide 25 mg to be given PO Cyclophosphamide 300 mg/m^2 (up to 600 mg) to be given PO Dexamethasone 20 mg to be given PO **New Formulation: A new oprozomib tablet, Oprozomib Extended Release (ER) Tablet, will be introduced in the trial with Amendment 2. There are minimal changes in the tablet coating and ratio of current excipients, and no change in the ratio of active pharmaceutical ingredient to excipients. Given these minimal changes, the new Oprozomib ER Tablet is not expected to result in altered exposure or additional adverse events related to formulation.** **Subjects enrolled in the original protocol or Amendment 1 will receive Oprozomib Tablets and may receive Oprozomib Extended Release (ER) Tablets when available. Subjects enrolled under Amendment 2 will receive Oprozomib ER Tablets only.**	this study.
Synopsis Exclusion Criteria Section 5.2 Exclusion Criteria		*Added Text* **4. Plasmapheresis is not permitted at any time during the Screening period or while the subject is receiving study treatment. If a subject has started Screening procedures requiring plasmapheresis, or is anticipated to require plasmapheresis during or after the Screening period, this patient will be considered ineligible and should not be enrolled.** **6. Clinically significant GI bleed in the 6 months prior to Cycle 1 Day 1 (C1D1)**	Added plasmapheresis to excluded concomitant medications to indicate that plasmapheresis is not permitted at any time during the study. Added GI exclusion criteria because of the toxicities observed.

Section Number	Changed from	Changed to	Rationale
		first dose	
Added Section Section 2.1 Introduction		**2.1 INTRODUCTION** *New section, too long to include here*	Section added to briefly summarize the purpose of the amendments
Section 2.4.2 Oprozomib Clinical Background		*Replaced section, too long to include here*	Section 2.4.2 was replaced with updated information from the current IB.
Section 2.4.4 Cyclophosphamide Background Section 2.4.4.1 Section heading added to second paragraph		**2.4.4.1 Cyclophosphamide and Dexamethasone with Epoxyketone Proteosome Inhibitors** *Content of paragraph is the same, only heading added*	Section heading added to second paragraph for clarity

Section Number	Changed from	Changed to	Rationale
Section 2.5 Dose Rationale		*Section heading added* **2.5.1 Amendment 1** *Section added* **2.5.2 Amendment 2** **Two of the 3 subjects enrolled in the 210 mg cohort of the OPZ003 ORd arm experienced syncope, a DLT (see Section 2.4.2.4). These DLTs prompted a dose de-escalation to the 180 mg cohort. Seven subjects were enrolled at the 180 mg dose level. Two DLTs, abdominal pain with distension and hypotension were observed prompting dose de-escalation to 150 mg on the 5/14 schedule.** **The dose of oprozomib for subjects enrolled in the ORd arm will continue at 150 mg on the 5/14 schedule unless 2 or more DLTs are reported.** **Given the increased clinical experience with the 2/7 schedule in 2011-001, and the experience in Amendment 1 of this trial, the starting dose for subjects enrolling in the ORd arm under Amendment 2 will be 210 mg on the 2/7 schedule.** **The starting dose for subjects enrolled in the OCyd arm under Amendment 2 will also be 210 mg on the 2/7 schedule. No subjects were enrolled in the OCyd arm prior to Amendment 2.** **Starting with Amendment 2, an ER tablet will be administered. There are minimal changes between the ER formulation and the modified release formulation used in Amendment 1. As such, dosing with the ER formulation will occur at the same level as the modified formulation.** **Subjects enrolled in the original protocol or**	Section headings added for clarity Amendment 2 dose rationale added

Section Number	Changed from	Changed to	Rationale
		Amendment 1 will receive Oprozomib Tablets and may receive Oprozomib Extended Release (ER) Tablets when available. Subjects enrolled under Amendment 2 will receive Oprozomib ER Tablets only.	
Added Section **Section 4.1.1 Patients Electing To Have Stem Cells Collected** Appendix A and Appendix B: Schedule of Study Assessments and related footnotes		**Subjects enrolling in the OPZ 003 study must be newly diagnosed and require treatment as per the NCCN guidelines. Subjects scheduled for or planning to proceed with transplant in the front-line setting should not be enrolled. However, subjects may have their stem cells collected for future salvage transplant. The schema below (Figure 5) depicts the schedule for subjects electing to bank their stem cells.** **In the event that a subject who had not previously intended to proceed to front-line transplant elects to proceed, that subject will be discontinued from study (see Section 11.0).** **Figure 5 Schedule for Stem Cell Collection**  **ASCT = autologous stem cell transplantation; Cyd = cyclophosphamide and dexamethasone; OPZ = oprozomib; PD progressive disease; PR = partial response; Rd = lenalidomide and dexamethasone**	Added guidance for investigators if patient achieves a good objective response and investigator decides to proceed to stem cell collection.

Section Number	Changed from	Changed to	Rationale
Section 4.2 Dose-Escalation Plan Modified Tables 3 and 4, and added Table 5	In the Phase 1b portion of the study, oprozomib doses will be escalated in sequential groups of 3 subjects for each combination regimen, with expansion to up to 6 subjects if a DLT is observed in 1 of the first 3 subjects. The doses of lenalidomide, cyclophosphamide, and dexamethasone will remain fixed in all dose cohorts. Enrollment in the initial cohort (Table 3) for the ORd arm was entered at a daily dose level of 210 mg on the 5/14 schedule. Two DLTs (syncope) were observed in the first 3 subjects and the cohort dose was decreased by 1 dose level to 180 mg of oprozomib. The dosing cohort was de-escalated to 150 mg after 2 DLTs (abdominal pain and hypotension) in 6 DLT evaluable subjects were reported at the 180 mg dosing level.	In the Phase 1b portion of the study, oprozomib doses will be escalated in sequential groups of 3 subjects for each combination regimen, with expansion to up to 6 subjects if a DLT is observed in 1 of the first 3 subjects. The doses of lenalidomide, cyclophosphamide, and dexamethasone will remain fixed in all dose cohorts. Enrollment in the initial cohort (Table 3) for the ORd arm was entered at a daily dose level of 210 mg on the 5/14 schedule. Two DLTs (syncope) were observed in the first 3 subjects and the cohort dose was decreased by 1 dose level to 180 mg of oprozomib. The dosing cohort was de-escalated to 150 mg after 2 DLTs (abdominal pain and hypotension) in 6 DLT evaluable subjects were reported at the 180 mg dosing level. **With the introduction of the ER Tablet with Amendment 2, there will be no further attempt at dose escalation in the 5/14 schedule with the tablet formulation. The starting dose for subjects enrolled in the ORd and OCyd arms under Amendment 2 will be 210 mg on the 2/7 schedule (Table 4 and Table 5).**	New ER Tablet formulation dose-escaltion language added

Section Number	Changed from	Changed to	Rationale
Section 6 Subject Screening Appendix A and Appendix B: Schedule of Study Assessments and related footnotes	A signed and dated ICF will be obtained before any screening procedures are performed. Evaluations obtained as part of routine medical care and performed prior to obtaining informed consent may be used in place of the study-specific evaluations, provided they meet the time windows described in the Schedule of Assessments (Appendix A). Subjects will acknowledge and agree to the possible use of this information for the study by giving informed consent. The screening period for a particular subject commences when the subject undergoes the first study-specific screening assessment, and must be completed within 14 days.	A signed and dated ICF will be obtained before any screening procedures are performed. Evaluations obtained as part of routine medical care and performed prior to obtaining informed consent may be used in place of the study-specific evaluations, provided they meet the time windows described in the Schedule of Assessments (Appendix A **and Appendix B**). Subjects will acknowledge and agree to the possible use of this information for the study by giving informed consent. The screening period for a particular subject commences when the subject undergoes the first study-specific screening assessment, and must be completed within 14 days**. The window of assessment for bone marrow aspirate and biopsy in the Phase 1b is 8 weeks and is the only exception to the 21-day screening assessment window. In the Phase 2, the bone marrow assessments must be performed within 21 days prior to Cycle 1 Day 1 (C1D1).**	Revised for consistency and clarity

Section Number	Changed from	Changed to	Rationale
Section 7 Subject Enrollment	All subjects who sign consent will be assigned a unique study number. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The Onyx study medical monitor will review the subject's information before enrollment. Only subjects who are approved by the Onyx study medical monitor will be allowed to enroll into the study. A minimum of 24 hours during weekdays (Monday through Friday) will be required for the Onyx study medical monitor to approve a subject for enrollment, and additional time may be required when approval is sought during a weekend or holiday. Subjects are only considered enrolled when the Onyx study medical monitor approves the patient for enrollment.	All subjects who sign consent will be assigned a unique study number. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The Onyx study medical monitor will review the subject's information before enrollment. Only subjects who are approved by the Onyx study medical monitor **or designee** will be allowed to enroll into the study. A minimum of 24 hours during weekdays (Monday through Friday) will be required for the Onyx study medical monitor to approve a subject for enrollment, and additional time may be required when approval is sought during a weekend or holiday. Subjects are only considered enrolled when the Onyx study medical monitor approves the patient for enrollment. **The logistics of cohort assignment are detailed in the Cohort Management Plan.**	Added language to clarify where the cohort assignment plan is located

Section Number	Changed from	Changed to	Rationale
Section 9.1.1 Treatment Administration Appendix A and Appendix B: Schedule of Study Assessments and related footnotes	~~**Dosing instructions for days on which PK samples will not be collected (non-PK days):**~~ Subjects should take oprozomib with approximately 8 ounces of water at approximately the same time of day, with food~~or without food at their descretion~~. When oprozomib is given on the same day with other treatments, dexamethasone should be administered 30 minutes before oprozomib, lenalidomide and cyclophosphamide. Subjects may take lenalidomide or cyclophosphamide following oprozomib administration at investigator's discretion, however it is recommended that they take their study drugs at approximately the same time each day. ~~**Dosing instructions for days on which PK samples will be collected (PK days):**~~ ~~Dexamethasone should be administered at least 30 minutes before the other medications. Oprozomib and either lenalidomide or cyclophosphamide will be administered in the clinic. Oprozomib should be administered concurrently (i.e., within 5 minutes of each other) with lenalidomide or cyclophosphamide, with approximately 8 ounces of water, to subjects on an empty stomach (at least 2 hours after and 1 hour before a meal).~~	Oprozomib **ER** Tablets will be administered in single daily doses (**Table 3, Table 4, and Table 5**) in the following manner: **It is recommended that** subjects should take oprozomib with approximately 8 ounces of water at approximately the same time of day, with food. When oprozomib is given on the same day with other treatments, dexamethasone should be administered 30 minutes before oprozomib, lenalidomide and cyclophosphamide. Subjects may take lenalidomide or cyclophosphamide following oprozomib administration at investigator's discretion; however it is recommended that they take their study drugs at approximately the same time each day.	Revised for clarity and consistency
Section 9 Dosage and Treatment Administration		*Added section heading* 9.1.4 Subject Replacement	Added section heading for clarity

Section Number	Changed from	Changed to	Rationale
Section 9.6 Missed Doses	Subjects in the Phase 1b portion of the study may not miss any of the planned doses of cyclophosphamide, or more than 4 planned doses of lenalidomide, or 2 planned doses of oprozomib or dexamethasone in Cycle 1~~. (See Section 4.2 for details of replacing subjects who miss more doses than allowed.)~~ A missed dose occurs when the subject does not take the dose on the planned calendar day~~, and the~~ dose ~~will~~ not be made up. If a subject misses more than 28 consecutive days after completing Cycle 1 for reasons other than a hematopoietic stem cell harvest, the subject will permanently discontinue study treatment (See Section 9.3 for interrupted oprozomib dosing > 4 weeks).	Subjects in the Phase 1b portion of the study may not miss any of the planned doses of cyclophosphamide, or more than 4 planned doses of lenalidomide, or 2 planned doses of oprozomib **for the 5/15 schedule or 1 planned dose of oprozomib for the 2/7 schedule , or 2 planned doses of** dexamethasone in Cycle 1. **Subjects who miss more doses than allowed during Cycle 1 will not be evaluable and will be replaced.** A missed dose occurs when the subject does not take the dose on the planned calendar day. **The missed** dose **will** not be made up. If a subject misses more than 28 consecutive days after completing Cycle 1 for reasons other than a hematopoietic stem cell harvest, the subject will permanently discontinue study treatment (see Section 9.3 for interrupted oprozomib dosing > 4 weeks).	Revised for clarity and consistency

Section Number	Changed from	Changed to	Rationale
Section 9.7 Safety Guidance for Investigators	See Section 9.3 for dose adjustments guidelines required for specific hematologic and nonhematologic toxicities. Cases of tumor lysis syndrome have been observed with proteasome inhibitors. It is recommended that all subjects orally hydrate the day before, and days of oprozomib dosing. Additionally, allopurinol prophylaxis is recommended for renally impaired subjects and those with a high tumor burden. For specific recommendations, see Section 9.8.1.	Additional guidance regarding nonhematologic toxicities and dosing actions is as follows: • **Nontreatment-related events: If the toxicity resolves to ≤ Grade 1 or baseline and the toxicity is not treatment-related, oprozomib may be restarted at the same dose level.** • **Subjects who develop Grade 3 or 4 GI hemorrhage should not be rechallenged with oprozomib. Oprozomib should be permanently discontinued. Endoscopy should be strongly considered for any subject with GI hemorrhage.** • **Syncope, hypotension (including orthostatic hypotension), and dehydration have been reported for subjects treated with oprozomib. Blood pressure monitoring as detailed in Appendix A and Appendix B is required.** • Tumor lysis syndrome has been reported for subjects treated with oprozomib. Hydration and allopurinol prophylaxis is recommended for renally impaired subjects and those with a high tumor burden. For specific recommendations, see Section 9.8.1. See Section 9.3 for additional dose adjustment guidelines required for specific hematologic and nonhematologic toxicities.	Additional safety guidance added regarding Grade 3 or 4 GI hemorrhages and other toxicities

Section Number	Changed from	Changed to	Rationale
9.8.1 Required Concomitant Medications	~~Outside of antimyeloma regimens and the~~ TLS measures noted below, there are no required concomitant medications. However, supportive medications for nausea, vomiting and diarrhea are strongly recommended; details are provided in Section 9.8.2	**Required medications are:** TLS prophylaxis, **proton pump inhibitors such as omeprazole or lansoprazole, anti-thrombotic agents for those on the ORd arem, such as asprin (or other anticoagulant or antiplatelet medication such as clopidogrel bisulfate, low-molecular-weight heparin, or warfarin) while taking lenalidomide.** Supportive medications for nausea, vomiting and diarrhea are strongly recommended; details are provided in Section 9.8.2. **9.8.1.1 Acid related Medications** **Lansoprazole or another oral proton pump inhibitor is required (unless subject has intolerance or hypersensitivity) for the duration of treatment to prevent peptic disease or other GI toxicities.** **9.8.1.3 Anti-thrombotic Agents** **Antithrombitic agents are required for those on the ORd arm such as aspirin (or other anticoagulant or antiplatelet medication such as clopidogrel bisulfate, low-molecular-weight heparin, or warfarin) while taking lenalidomide is required (refer to the Revlimid Prescribing Information, Appendix H for more information).**	Added as proton pump inhibitors are now required for subjects on oprozomib Added antithrombotic agents as required to conform with Revlimid PI
Section 9.8.2 Optional and Allowed Concomitant Medications	• ~~A proton pump inhibitor, such as omeprazole or lansoprazole while taking dexamethasone~~ ~~Anti-thrombotic Agents~~ ~~Antithrombitic agents are required for those on the ORd arm such as aspirin (or other anticoagulant or antiplatelet medication such as clopidogrel bisulfate, low-molecular-weight heparin, or warfarin) while taking lenalidomide is required (refer to the Revlimid Prescribing~~	*Added references* *Added text:* • **Bisphosphonate therapy such as pamidronate or zoledronic acid for skeletal prophylaxis** **Section 9.8.2.3 Antihypertensives** **Dehydration, hypotension and syncope have been reported in subjects treated with oprozomib monotherapy and combination therapy. It is strongly recommended that**	Added additional concomitant information to prevent peptic disease that occurs with use of dexamethasone. Move anti-thrombotic agents to 9.8.1

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	~~Information 2012, Appendix H for more information).~~	**subjects utilizing anti-hypertensives have their volume status, blood pressure, and antihypertensive therapy dosing monitored closely while on protocol directed therapy. See Appendix A and Appendix B.**	
Section 10.1.1 Vital Signs Appendix A and Appendix B: Schedule of Study Assessments and related footnotes	Vital signs measurements include blood pressure, pulse rate, ~~respiration rate,~~ and temperature. At the investigator's discretion, vital signs monitoring may be extended beyond the time periods specified in the Schedules of Assessments (Appendix A).	Vital signs measurements include blood pressure, pulse rate, and temperature. **Orthostatic BP should be assessed for subjects with evidence of dehydration.** At the investigator's discretion, vital signs monitoring may be extended beyond the time periods specified in the Schedules of Assessments (Appendix A **and Appendix B**).	Added additional guidance for subjects who may experience orthostatic hypotension.
Section 10.3 Disease Response Assessments	The schedule of disease assessments is provided in Appendix A. Disease response will be assessed by the investigator. Disease response assessments will be performed at the end of every 4-week cycle for 24 cycles of ORd or OCyd treatment, and will continue every 8 weeks thereafter, until confirmed PD (See Figure 1, Figure 2, and Figure 3 for details on the duration of cyclophosphamide dosing). Response assessment will be according to the ~~International Myeloma Working Group – Uniform Response Criteria~~ (IMWG-URC) (Appendix E).	The schedule of disease assessments is provided in Appendix A **and Appendix B**. Disease response will be assessed by the investigator. Disease response assessments will be performed at the end of every 4-week cycle for 24 cycles of ORd or OCyd treatment, and will continue every 8 weeks thereafter, until confirmed PD (see Figure 1, Figure 2, and Figure 3 for details on the duration of cyclophosphamide dosing) **or the start of alternative, nonprotocol antimyeloma therapy.** Response assessment will be according to the IMWG-URC (Appendix E).	Revised for clarity and consistency.
Added Section **Section 10.3.1 Tumor Response Assessments** Appendix A and Appendix B: Schedule of Study Assessments and related footnotes		**The following confirmation assessments are required for all response categories (sCR, CR, VGPR, and PR; refer to definitions in Appendix E):** • **All response categories require 2 consecutive assessments made at any time before initiation of any new therapy** • **All response categories require no evidence of progression including new bone lesions if radiographic studies**	Added for clarity and consistency across protocols.

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		were performed • **Confirmation of CR or sCR requires bone marrow biopsy or aspirate slides (a confirmatory bone marrow sample is not required)** • **Extramedullary plasmacytoma evaluation (if present at Screening)**	
Added Section **Section 10.6 Platelet Functional Assessment** 10.2 Laboratory Evaluations for Safety *(added related sentence)* Appendix A and Appendix B: Schedule of Study Assessments and related footnotes		**Platelet function assessments will be conducted in the 10 to 20 subjects enrolled in the OCyd arm for which the platelet function tests below may be performed. Assessments of platelet adherence, activation, aggregation, and interaction with coagulation factors will be conducted utilizing the PFA-100 (N=10).** **Subjects participating in this study component:** • **May not be treated with antiplatelet agents, aspirin or nonsteroidal anti-inflammatory drugs in the 2 weeks prior to assessment.** • **Must have a screening and pretest value for platelets of ≥ 100,000/mm^3.** • **Must have hematocrit of 28%** **The PFA-100 test will be conducted according to site SOPs on C1D1 (prior to protocol mandated dosing), Cycle 1 Day 2 (C1D2), Cycle 4 Day 1 (C4D1) and 30 days after the completion of oprozomib therapy.**	Revised the limit for platelets to increase patient safety.
Moved Section from 10.7 to 11.1.1 Assessments at End of Study Treatment or Early Discontinuation	10.7 Assessments at End of Study Treatment or Early Discontinuation For subjects who discontinue treatment before PD occurs (such as for an AE, noncompliance, etc.), disease response assessments will be performed every 4 weeks during the first 24 months of the	11.1.1 Assessments at End of Study Treatment or Early Discontinuation For subjects who discontinue treatment before PD occurs (such as for an AE, noncompliance, etc.), disease response assessments will be performed every 4 weeks during the first	Moved for clarity and consistency.

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	study and every 8 weeks thereafter, until confirmed PD, or the start of alternative, nonprotocol antimyeloma therapy.	24 months of the study and every 8 weeks thereafter, until confirmed PD, or the start of alternative, nonprotocol antimyeloma therapy.	
Added Section **11.1.2 Follow-up for Subjects Who End Study Treatment Without Documented Progressive Disease** Appendix A and Appendix B: Schedule of Study Assessments and related footnotes		**Subjects who have ended study therapy without evidence of progression enter active follow up after completing their end of study treatment visit. They will be followed for progression free survival.** • **Disease response assessments will be performed every 4 weeks through 24 months post C1D1, and then every 8 weeks thereafter, until progression or initiation of new anti-myeloma therapy whichever occurs first** • **Subjects who have consented to evaluate their genomic biomarkers and end study treatment prior to progression will have a bone marrow aspirate collected for genomic analysis at the time of progression or the start of new anti-myeloma therapy, whichever comes first** **Active follow-up will continue until the subject has withdrawn consent for further participation, is lost to follow-up, has died, or the sponsor makes a decision to close the study.**	Added for clarity and consistency across protocols.
Section 12.3.2 Disease Progression	~~Disease progression will be documented in an eCRF intended to capture PD information and will be analyzed as a study endpoint.~~ Signs and symptoms related to disease progression (e.g., pathologic fracture in a subject with progressive multiple myeloma) should be reported in the appropriate case report form as an AE or as an SAE (if the event in question meets the criteria for seriousness). Verbatim terms such as "disease progression", "progressive disease", etc., should not be reported as AEs or SAEs unless the	Signs and symptoms related to disease progression (e.g., pathologic fracture in a subject with progressive multiple myeloma) should be reported in the appropriate case report form as an AE or as an SAE (if the event in question meets the criteria for seriousness). Verbatim terms such as "disease progression", "progressive disease", etc., should not be reported as AEs or SAEs unless the investigator considers the progression to be atypical **and/or** accelerated.	Revised for clarity and consistency across protocols.

Section Number	Changed from	Changed to	Rationale
	investigator considers the progression to be atypical accelerated. ~~or caused by the study drug.~~		
Added Section Section 12.4 Long-term Follow-up Appendix A and Appendix B: Schedule of Study Assessments and related footnotes		**After completion of the End of Study Treatment visit, subjects who have ended study therapy due to an AE enter long term follow up. They will be followed for progression free survival.** **Disease response assessments will be performed every 4 weeks through 24 months post C1D1, and then every 8 weeks thereafter, until progression or initiation of next therapy, whichever occurs first.** **Subjects who have consented to evaluate their genomic biomarkers and end study treatment prior to progression will have a bone marrow aspirate collected for genomic analysis at the time of progression or the start of new anti-myeloma therapy, whichever comes first.** **Long-term follow-up will continue until the subject has withdrawn consent for further participation, is lost to follow-up, has died, or the sponsor makes a decision to close the study.**	Added to clarify procedures for the post-treatment follow-up for subjects who discontinue treatment for a reason other than PD.

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