CLINICAL STUDY PROTOCOL

Protocol Title:	Phase 1b/2, Multicenter, Open-label Study of Oprozomib and Dexamethasone in Patients With Relapsed and/or Refractory Multiple Myeloma
Protocol No.:	2012-001
Name of the Investigational Product:	Oprozomib Tablets and Oprozomib Extended Release (ER) Tablets
Indication:	Relapsed and/or Refractory Multiple Myeloma
IND Number:	117,851
NCT Number	**NCT01832727**
Development Phase:	Phase 1b/2
Sponsor:	Onyx Therapeutics **One Amgen Center Drive** **Thousand Oaks, CA 91320 USA** **(805) 447-1000**
Study Medical Monitor:	[redacted], **MD** **Medical Director, Clinical Development** **1120 Veterans Blvd** **South San Francisco, CA 94080 USA** **Phone:** [redacted] **Email:** [redacted]
Investigator(s):	
Date of Original Protocol:	14 December 2012
Amendment 1 Date:	18 March 2013
Amendment 2 Date:	25 June 2013
Amendment 3 Date:	26 June 2014
Amendment 4 Date	**08 February 2018**

Confidentiality Statement

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Compliance Statement

This study will be conducted in accordance with Protocol 2012-001, the relevant Onyx Therapeutic policies and procedures, the International **Council for** Harmonisation (ICH), Good Clinical Practice (GCP) guidelines, and the applicable country and regional regulatory requirements.

PROTOCOL ACCEPTANCE PAGE

Issue/Date: Protocol Number 2012-001 / Amendment 4 / 08 February 2018

I have read this protocol for Study Number 2012-001, entitled:

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

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

Investigator Name (print)

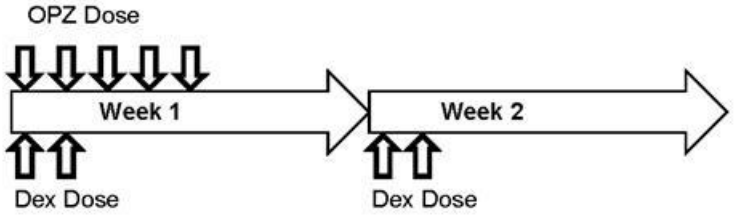
Investigator Signature Date

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 **Council for** Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) and country and regional (local) requirements while conducting this clinical investigation. Once signed, the original of this form should be detached from the protocol and returned to Onyx or its designee (please retain a copy for your files).

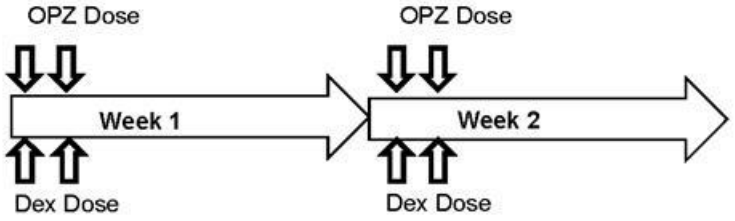
PROTOCOL SYNOPSIS

Name of sponsor/company:	Onyx Therapeutics
Name of finished product:	Oprozomib Tablets and Oprozomib Extended Release (ER) Tablets
Name of active ingredient:	Oprozomib
Title of study and protocol number:	2012-001: Phase 1b/2, Multicenter, Open-label Study of Oprozomib and Dexamethasone in Patients with Relapsed and/or Refractory Multiple Myeloma
Phase of development:	Phase 1b/2
Study objectives:	**Primary Objectives** Phase 1b • To determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of oprozomib (OPZ) given orally, once daily, on 2 different schedules: 5 consecutive days every 14 days (bimonthly; 5/14) or 2 consecutive days every 7 days (weekly; 2/7) for a 14-day treatment cycle, both schedules given in combination with dexamethasone • To evaluate safety and tolerability Phase 2 • To estimate the overall response rate (ORR), defined as the proportion of subjects with the best overall response of stringent complete response (sCR), complete response (CR), near complete response (nCR), very good partial response (VGPR), and partial response (PR) as defined by the International Myeloma Working Group-Uniform Response Criteria (IMWG-URC) and modified European Group for Blood and Marrow Transplantation (EBMT) criteria • To evaluate safety and tolerability **Secondary Objectives** • To evaluate pharmacokinetics (PK) of Oprozomib Tablets and Oprozomib ER Tablets • To estimate clinical benefit rate (CBR), defined as ORR plus minimal response (MR), as defined by the EBMT criteria • To estimate the duration of response (DOR) • To estimate progression-free survival (PFS) • To estimate time to progression (TTP) **Exploratory Objectives:** • To evaluate pharmacodynamics (PDn) and proteomic biomarkers • To evaluate genomic biomarkers that may predict for response and resistance following treatment with proteasome inhibitors
Study design:	This study is an open-label, Phase 1b/2, multicenter study in which subjects will receive oprozomib administered orally once daily in combination with 20 mg of dexamethasone, as follows: • Days 1–5 of a 14-day cycle in combination with dexamethasone on Days 1, 2, 8, and 9; or • Days 1, 2, 8, and 9 of a 14-day cycle in combination with dexamethasone on Days 1, 2, 8, and 9. Treatment will be administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

Oprozomib for 5 consecutive days bimonthly plus dexamethasone



Oprozomib for 2 consecutive days weekly plus dexamethasone



OPZ = oprozomib; Dex = dexamethasone

Phase 1b: The Phase 1b portion of the study will determine the MTD, safety, PK/PDn, and recommended Phase 2 dose (RP2D) of oprozomib administered orally once daily in combination with dexamethasone, in subjects with relapsed and/or refractory multiple myeloma, using a 3 + 3 dose-escalation scheme with or without step-up dosing. A dose-escalation plan is being followed in Phase 1b to determine the recommended Phase 2 dose for each treatment schedule. The MTD is defined as the highest dose level at which fewer than 33% of subjects have dose-limiting toxicity (DLT). For each of the 2 schedules being studied, groups of 3 to 6 subjects will be enrolled into dose-escalation cohorts. As long as fewer than 33% of subjects experience DLTs in a given cohort, escalation will continue by 30 mg increments of oprozomib onto the next designated cohort(s). A minimum of 6 subjects must be treated at each MTD to establish the dose as the MTD with and without step-up dosing.

Subjects will be evaluated for DLTs according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. Subjects with stable disease (SD) or better may continue treatment. Intrasubject dose escalation to the recommended Phase 2 dose may be permitted once that dose has been determined and after discussion between the treating physician and the **Sponsor** study medical monitor.

Phase 2: The Phase 2 portion will use the Phase 2 dose determined for each schedule, unless the sponsor determines that, based on Phase 1b data, 1 or both of the schedules should not proceed with development.

Oprozomib Tablet

In the Phase 1b portion of the study, oprozomib doses in combination with dexamethasone will be escalated in sequential groups of 3 subjects with expansion up to 6 subjects if a DLT is observed. The initial cohort of the study with Oprozomib Tablets will be entered at a dose level of 210 mg oprozomib and 20 mg dexamethasone for both schedules. All subsequent cohorts will be escalated or de- escalated by 30 mg of oprozomib until the MTD is reached.

In the event that the initial cohort that received the 210 mg dose is found to exceed the MTD (the highest dose at which a DLT is observed in fewer than 2 of 6 subjects), dosing will proceed at 180 mg or lower, as agreed with the Cohort Safety Review Committee.

Oprozomib ER Tablet

A new oprozomib tablet will be introduced into the study with Amendment 3. The Oprozomib ER Tablet is being developed to have a more consistent dissolution profile by decreasing variability through an improved release process. In addition, administration of a single tablet, instead of multiple tablets as in the case of Oprozomib Tablets, will be used in doses up to 270 mg. (Currently, all doses given are composed of multiple Oprozomib Tablets. For example, the 270 mg dose is made up of three 90 mg Oprozomib Tablets.) The use of fewer tablets provides a smaller surface-to-volume ratio, resulting in a slower dissolution in vitro, and is predicted to have a lower maximum plasma concentration (C_{max}) and similar area under the curve (AUC).

The current gastrointestinal (GI) toxicity is likely mediated by local proteasome inhibition and variability (caused by prior formulation and multiple tablets) in the release of drug substance in the current formulation. Thus, it is hypothesized that the formulation change and single-tablet dosage may decrease local intraluminal oprozomib levels at any one location in the GI tract and thereby decrease GI toxicity. Preliminary PK data on file from the single-agent oprozomib study suggest systemic toxicity is related to C_{max}; therefore, a lower C_{max} may reduce systemic toxicity.

Switch from Oprozomib Tablets to Oprozomib ER Tablets

When subjects switch from Oprozomib Tablets to Oprozomib ER Tablets, intensive PK sampling should be obtained on Day 1 in the cycle prior to switching and on Day 1 of the following cycle (i.e., first day with Oprozomib ER Tablet) at the scheduled time points described above. The time between the 2 days of PK collection for switching to the Oprozomib ER tablet will be 1 cycle or 14 days.

The introduction of Oprozomib ER Tablets into the study and determination of MTD of this formulation for the 5/14 and 2/7 schedules are described below:

5/14 Schedule

For the 5/14 once-daily dosing schedule, Oprozomib ER Tablets will be introduced with step-up dosing as described below. Determination of the MTD for step-up dosing will proceed in the following manner:

- The first cohort will enroll 6 subjects using step-up dosing. Subjects will receive 1 cycle at the 150 mg dose and then step-up to the 180 mg dose for subsequent cycles (150/180 mg). The DLT period will begin in Cycle 2 (the first cycle of dosing at the step-up dose level).
- For the next cohort, 6 subjects will be dosed with continuous dosing of 180 mg of Oprozomib ER Tablets and assessed for DLTs to determine safety of this dose level.
- Further escalation will be based on the following:
  - If < 2 DLTs are observed in the continuous dosing cohort of 180 mg in Cycle 1, dose escalation may continue but will revert to step-up dosing (i.e., 150/210 mg, 150/240 mg, etc.) unless an alternate RP2D has been determined by the CSRC and sponsor.
  - If $\geq$ 2 DLTs are observed, further escalation will not be conducted.

2/7 Schedule

For the 2/7 once-daily dosing schedule, Oprozomib ER Tablets will be introduced into subsequent cohorts where no subjects have been enrolled unless the MTD for continuous dosing for Oprozomib Tablets has been previously determined prior to the introduction of the new tablets. One of the following 2 scenarios will be utilized to introduce Oprozomib ER Tablets into the dose escalation schema:

- If the MTD for continuous dosing has not been established for Oprozomib Tablets, Oprozomib ER Tablets will be introduced at the next new dose level

	specified by the preexisting dose-escalation plan. Dose escalation will continue in 30 mg increments until the MTD for continuous dosing for Oprozomib ER Tablets is established, as determined by the CSRC and sponsor. • If the MTD for continuous dosing has been established with Oprozomib Tablets, Oprozomib ER tablets will be introduced at the MTD in a cohort of 6 subjects. Escalation beyond this dose can only occur using step-up dosing as described below if there are < 2 DLTs in the 6 subjects in this cohort enrolled with Oprozomib ER Tablets as determined by the CSRC and sponsor. Once the MTD for continuous dosing for Oprozomib ER Tablets has been established, step-up dosing will be introduced into dose escalation. Subsequent 2/7 cohorts will be dosed at the 240 mg for 1 cycle then step-up to the dose level to be studied. The rationale for this initial dose is based on safety and tolerability of this dose level in the current study, as no DLTs were observed in this cohort of 3 evaluable subjects at this dose level. The 240 mg dose is 2 dose levels below the single agent MTD, which was found to be 300 mg in Study 2011-001. **Subjects on active treatment will continue with Oprozomib ER Tablets under protocol Amendment 4. No changes in drug product, dosage, or treatment regimen occurred in this protocol amendment from the previous version.** Determination of the MTD for step-up dosing will be evaluated in the following manner: • The first step-up dosing cohort will start with 1 cycle of 240 mg, and then starting with Cycle 2, subjects will step-up to the MTD from continuous dosing for subsequent cycles. • All subsequent cohorts will also begin dosing at 240 mg for 1 cycle and then will be escalated in Cycle 2 to the step-up dose level to be studied, by 30 mg increments until the MTD is defined with Oprozomib ER Tablets, unless an alternate R2PD is determined by the CSRC and the sponsor. The DLT period will begin in Cycle 2 (the first cycle of dosing at the step-up dose level). **Phase 2**: The Phase 2 portion of the study will include approximately 40 subjects at the recommended dose for each schedule, to better characterize the safety and tolerability, activity, and PK/PDn of the regimen and treatment schedule. The Phase 2 portion of the study for 1 or both treatment schedules will be initiated at the sponsor's discretion. **Dose-Limiting Toxicities:** During the Phase 1b portion, assessment of DLTs will occur at the following times: • The first 14 days of treatment with continuous dosing (Cycle 1), or • The first 14 days of treatment with the step-up dose to be studied (Cycle 2) Any subject who develops DLT after receiving at least 1 dose of oprozomib during the DLT assessment period will be considered evaluable. Any subject who does not develop a DLT but has not received all planned doses of oprozomib and dexamethasone during the DLT assessment period will be considered unevaluable and will be replaced. "Study drug-related" is defined as a reasonable likelihood of clinical causality based on time of event, biology, and dechallenge improvement, and that the adverse event (AE) was not likely explained by the subject's clinical state, underlying disease, concomitant medication, or study/non-study procedure. For the purposes of this study, a DLT is defined as any of the following treatment-related events occurring in the first 14 days of treatment, with treatment at the dose to be studied (i.e., Cycle 1 for continuous dosing or Cycle 2 for step-up dosing):

	Any ≥ Grade 3 nonhematologic AE with the following exceptions or qualifications: • ≥ Grade 4 abnormalities in serum creatinine or electrolytes will be considered a DLT • ≥ Grade 3 acute kidney injury, defined as serum creatinine > 3 × baseline or > 4.0 mg/dL of any duration will be considered a DLT • 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 ($5\text{-}HT_3$) antagonist and aprepitant for nausea and vomiting, loperamide (e.g., Imodium), and diphenoxylate/atropine (e.g., Lomotil) for diarrhea • Grade 3 fatigue lasting > 14 days will be considered at DLT • Asymptomatic Grade 3 hypophosphatemia lasting less than 24 hours will not be considered a DLT • ≥ Grade 3 dexamethasone-related toxicities will not be considered DLTs **Any of the following hematologic AEs will be considered a DLT:** • Grade 4 neutropenia: Absolute neutrophil count (ANC) < 500 cells/mcL lasting ≥ 7 days • Febrile neutropenia: Any single temperature ≥ 38.3°C or a sustained temperature of ≥ 38.0°C for more than 1 hour with ≥ Grade 3 neutropenia (ANC < 1000 cells/mcL) • Grade 3/4 thrombocytopenia, as follows: o Grade 3 thrombocytopenia of any duration with Grade 2 bleeding or requiring platelet transfusion o Grade 4 lasting ≥ 7 days o Grade 4 lasting < 7 days with Grade 2 bleeding, or if platelet counts are lower than 10,000 cells/mcL, requiring a platelet transfusion **The following will not be considered a DLT:** • Grade 4 anemia • Grade 4 thrombocytopenia lasting < 7 days with platelet counts above 10,000 cells/mcL without clinically significant bleeding and with or without transfusion **Pharmacokinetics:** Blood samples for determination of plasma concentrations of oprozomib and its metabolite(s) will be drawn at the time points specified in the PK/PDn appendices according to continuous or step-up dosing; blood volumes are detailed in the Laboratory Manual. At a minimum, the following PK parameters will be calculated: C_{max}, time to maximum concentration (T_{max}), and AUC. Samples may also be used for biomarker assessment. When subjects switch from Oprozomib Tablet to Oprozomib ER Tablet, they will have intensive PK collection on Day 1 of the cycle prior to switching, and on Day 1 of the subsequent cycle when the new formulation is administered. **Pharmacodynamics and Proteomics:** Blood samples for the determination of proteasome inhibition by oprozomib and proteomic analyses will be drawn at the time points specified in the PK/PDn appendices; blood volumes are detailed in the Laboratory Manual. **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 who consent to optional genomic biomarker analysis. These analyses will be performed on a sample of bone marrow aspirate, blood, and saliva obtained at baseline. No additional bone marrow samples will be required

	for the baseline analysis. At the time of progression, analysis will also be performed on a sample of the bone marrow aspirate. **Activity:** Response assessments will be performed every 4 weeks based on IMWG-URC and EBMT (for nCR and MR) criteria. Overall response rate and CBR will be determined based on subjects' best overall response. **Safety:** All subjects will be closely monitored for AEs and study drug tolerability. The safety and tolerability of oprozomib will be assessed through documentation of AEs graded according to NCI-CTCAE (Version 4.03), blood counts, serum chemistries, vital signs, and electrocardiograms (ECGs).
Duration of study/treatment periods:	The total study duration is expected to be approximately 36 months. Approximately 22 to 26 months may be required to enroll all subjects in both phases. **Phase 1b:** It is estimated that enrollment will take approximately 8–16 months. Subjects will be treated in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason. Subjects must complete a visit approximately 4 weeks after the last cycle of treatment to allow for safety follow-up within 30 days after the last dose of oprozomib. **Phase 2:** It is estimated that enrollment will take approximately 10–12 months. Subjects will be treated in 14-day cycles and may continue treatment until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason. Subjects with progression will be considered to have completed the study 30 days after the last dose of oprozomib. Note: For subjects who discontinue treatment for reasons other than progression in either study phase, disease assessments **will no longer be required under protocol Amendment 4.**.
Number of investigational sites:	Approximately 12 sites in the United States (US) Approximately 4 sites in France
Study population:	The study population will consist of multiple myeloma patients requiring therapy who have relapsed and/or are refractory to their last therapy and have been treated with at least 1, but not more than 5, lines of multiple myeloma therapy. Prior therapy must have consisted of at least 1 regimen that included lenalidomide and/or bortezomib. Patients should be considered to be appropriate candidates for a clinical study by their treating physicians. • Relapsed patients must have previously achieved ≥ MR on at least 1 line of therapy as assessed by the treating physician. • Refractory patients are allowed, but it is not required that patients be refractory to their last therapy. • Primary refractory patients are allowed in the Phase 1b portion of the study only.
Sample size:	For the Phase 1b portion of the study, it is estimated that approximately 60 subjects (approximately 30 subjects per treatment schedule) will be required to determine the recommended Phase 2 dose for each treatment schedule. This is based on an estimate that up to 5 cohorts will be enrolled per treatment schedule, with up to 6 evaluable subjects per cohort. The Phase 2 portion of each dose schedule will be initiated at the sponsor's discretion. Approximately 80 additional evaluable subjects (approximately 40 subjects per treatment schedule) will be enrolled at the recommended dose. The total sample size for the study will depend on the number of dose levels required to establish the recommended dose for each schedule and the number of schedules initiated in the Phase 2 portion of the study.

Planned number of subjects:	The total number of subjects planned for this study is approximately 140 subjects.
Test product, dose, and mode of administration:	Oral Oprozomib Tablet in strengths of 60, 90, and 120 mg Oral Oprozomib ER tablet in strengths of 150,180, 210, 240, and 270 mg Oral dexamethasone 20 mg in tablet strengths of 4 and 6 mg
Reference therapy, dose, and mode of administration:	Not applicable
Type of control:	Not applicable
Treatment regimen:	Oprozomib will be administered at the assigned dose for each cohort, as follows: • Days 1–5 of a 14-day cycle with 20 mg dexamethasone on Days 1, 2, 8, and 9, or • Days 1, 2, 8, and 9 of a 14-day cycle with 20 mg dexamethasone on Days 1, 2, 8, and 9 All subjects with SD or better may continue treatment until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.
Main inclusion criteria:	1. Diagnosis of multiple myeloma with measureable disease as indicated by 1 or more of the following: a. Serum M-protein ≥ 500 mg/dL b. Urine M-protein ≥ 200 mg/24 hours c. Only for subjects without measurable serum and urine M-protein, serum free light chain: Involved free light chain (FLC) level ≥ 10 mg/dL, provided serum FLC ratio is abnormal 2. Patients requiring therapy who have relapsed and/or are refractory to their last therapy and have been treated with at least 1, but not more than 5, lines of multiple myeloma therapy. Prior therapy must have consisted of at least 1 regimen that included lenalidomide and/or bortezomib. Patients should be considered to be appropriate candidates for a clinical study by their treating physicians. Relapsed patients must have previously achieved ≥ MR on at least 1 line of therapy, as assessed by the treating physician. Refractory patients are allowed, but it is not required that patients be refractory to their last therapy. Primary refractory patients are allowed in the Phase 1b portion of the study only. 3. Males and females ≥ 18 years of age 4. Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0–2 5. Adequate hepatic function, with bilirubin ≤ 1.5 times the upper limit of normal (ULN) in the absence of Gilbert's disease or hemolysis, aspartate aminotransferase (AST) ≤ 3 times ULN, and alanine aminotransferase (ALT) ≤ 3 times ULN 6. Absolute neutrophil count ≥ 1000 cells/mcL, hemoglobin ≥ 7.0 g/dL, and platelet count ≥ 30,000 cells/mcL: 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 and granulocyte-macrophage colony-stimulating factor (G-CSF and GM-CSF) support for at least 1 week and of pegylated G-CSF for ≥ 2 weeks prior to first dose. c. Patients may receive red blood cell (RBC) transfusions or receive

	supportive care with erythropoietin or darbepoetin in accordance with institutional guidelines. 7. Calculated or measured creatinine clearance (CrCl) of ≥ 30 mL/minute calculated using the formula of Cockcroft and Gault ([140 − Age] × Mass (kg) / [72 × creatinine mg/mL]). Multiply result by 0.85 if female. 8. Uric acid, if elevated, must be corrected to within laboratory normal range before dosing. 9. Patients must sign a written informed consent form in accordance with federal, local, and institutional guidelines. 10. Female patients of childbearing potential must have a negative serum or urine pregnancy test within 3 days prior to receiving the first dose of study drug and agree to use effective methods of contraception during the study and for 3 months following the last dose of study drug. Postmenopausal females (> 45 years old and without menses for > 1 year) and surgically sterilized females are exempt from these requirements. Male patients must use an effective barrier method of contraception during the study and for 3 months following the last dose if sexually active with a female of childbearing potential. 11. Prior carfilzomib is not required but is allowed if a patient had at least 2 cycles of carfilzomib alone or in combination with a dose of at least 20/27 mg/m^2, as long as the patient: a. Had at least a partial response to prior carfilzomib therapy b. Was not removed from carfilzomib therapy due to toxicity, unless approved by the medical monitor c. Was not removed from carfilzomib therapy for progressive disease nor experienced progressive disease within 6 months after any prior carfilzomib therapy
Main exclusion criteria:	1. Radiation therapy within 2 weeks prior to first dose; localized radiation therapy within 1 week prior to first dose 2. Immunotherapy/standard myeloma therapy within 2 weeks prior to first dose (except for antibody therapy, where 6 weeks are required, and alkylator therapy, where 3 weeks are required); prior stem cell transplant (SCT) therapy (autologous SCT within the prior 8 weeks; allogeneic SCT within the prior 16 weeks). Patients with prior allogeneic SCT should not have evidence of moderate-to-severe graft-versus-host disease (GvHD). 3. 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. 4. Glucocorticoid therapy within 14 days prior to enrollment that exceeds a cumulative dose of 160 mg of dexamethasone or equivalent 5. Participation in an investigational therapeutic study within 3 weeks prior to first dose 6. Prior oprozomib exposure 7. Known hypersensitivity/toxicity or intolerance to dexamethasone 8. Major surgery within 3 weeks prior to first dose 9. Congestive heart failure ([CHF] 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 10. Uncontrolled hypertension or uncontrolled diabetes

	11. Active infection requiring systemic antibiotics, antivirals, or antifungals within 2 weeks prior to first dose 12. Known or suspected human immunodeficiency virus (HIV) infection or patients who are HIV seropositive 13. Active hepatitis A, B, or C infection 14. History of previous clinically significant GI bleed in the last 6 months prior to first dose 15. Significant neuropathy (Grade 3, Grade 4, or Grade 2 with pain) at the time of the first dose 16. 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 of Gleason Score of 6 or less with stable prostate specific antigen levels, or cancer considered cured by surgical resection 17. Plasma cell leukemia 18. Female patients who are pregnant or nursing 19. Inability to swallow medication, inability or unwillingness to comply with the drug administration requirements, or GI condition that could interfere with the oral absorption or tolerance of treatment 20. Any contraindication to oral hydration (e.g., significant preexisting comorbidity or fluid restriction) 21. Any clinically significant psychiatric or medical condition that in the opinion of the investigator could increase patient risk or interfere with protocol adherence or a patient's ability to give informed consent
Schedule of treatment and assessments:	Refer to Appendix A, Appendix B, Appendix C, and Appendix D in the study protocol for the schedule of study assessments.
Criteria for evaluation:	
Efficacy variables:	Disease response assessments will be done every 4 weeks for the first year through Cycle 26 and then every 8 weeks thereafter according to the IMWG-URC. In addition, nCR and MR will be assessed as per the modified EBMT criteria.
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 variables:	**Pharmacokinetics**: Blood samples will be drawn for plasma concentration of oprozomib and its metabolite(s) at various time points during the study based on whether subjects are treated with continuous or step-up dosing. Pharmacokinetic parameters, including but not limited to C_{max}, T_{max}, and AUC, will be calculated. **Pharmacodynamics**: Blood samples will be drawn for PDn assessments of proteasome inhibition in whole blood and peripheral blood mononuclear cells (PBMCs) via a fluorogenic substrate assay or enzyme-linked immunosorbent assay. **Proteomics**: Analysis of proteomic biomarkers that may predict for response following treatment with oprozomib will be performed. Proteomic biomarkers will be measured in PBMCs and plasma. Global proteomic profiling using mass spectrometry will be conducted on plasma samples and isolated PBMCs taken before and after study drug administration and analyzed for changes in specific protein levels (e.g., cytokines). **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.

	Biomarker analyses will be performed on bone marrow aspirates, blood, and saliva samples. Whole genome sequencing (WGS), whole exome sequencing (WES), whole transcriptome sequencing, and/or other methods of nucleic acid 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 germ line 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 activation of NF-KappaB transcription factors as well as in genes involved in immunoglobulin production and plasma cell protein homeostasis. Immunoglobulin levels in tumor cells will be quantified by enzyme-linked immunosorbent assay (ELISA) or other protein quantification methods. These data will also be used to derive hypotheses about mechanisms of drug response, resistance, and safety.
Statistical Methods:	The design of the Phase 1b portion of the study will focus on determining the MTD, RP2D, and safety of oprozomib (along with assessing selected PK/PDn parameters) and will employ a 3+3 design that will allow for possible dose de-escalation. A listing of subjects who experience a DLT during the Phase 1b portion will be generated along with the results associated with the PK/PDn parameters being considered. All subjects who receive at least 1 dose of study treatment will be considered evaluable for both the efficacy and the safety analyses (Safety Population). Additional efficacy analyses will be performed using the response-evaluable population, defined as subjects who are included in the safety evaluable population, have a baseline disease assessment and at least 1 postbaseline disease assessment, or dropped out due to AE prior to first postbaseline disease assessment. Efficacy endpoints include evaluation of response at each dose level and at the recommended Phase 2 dose for each schedule. An estimate of the ORR at the recommended dose(s) and its 1-sided 95% exact binomial confidence interval will be determined by each schedule. Additionally, the ORR and CBR will be determined along with the associated 2-sided 95% exact binomial confidence intervals for each cohort and schedule. Analyses for time-to-event(s) endpoints (DOR, PFS, and TTP) will be performed using the Kaplan-Meier method. Medians and other quartiles for each time-to-event endpoint will be estimated with the corresponding 2-sided 95% confidence intervals. Time to response will be assessed using descriptive statistics. Extent of exposure to the study treatment will be summarized using descriptive statistics. The number and percentage of subjects experiencing 1 or more AEs will be summarized by relationship to study treatment and severity. Laboratory parameters, vital signs, and ECGs will be summarized using descriptive statistics.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
2/7	2 consecutive days every 7 days
5/14	5 consecutive days every 14 days
5-HT3	5-hydroxytryptamine type-3
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APEX trial	Assessment of Proteasome Inhibition for Extending Remissions Investigators trial
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}inf}$	area under the curve extrapolated to infinity
$AUC_{0\text{-}\tau}$	area under the curve at the last measurable time point
BPNS	Brief Peripheral Neuropathy Screen
CBC	complete blood count
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CHF	congestive heart failure
C_{max}	maximum plasma concentration
CR	complete response
CrCl	creatinine clearance
CRF	Case Report Form
CSRC	Cohort Safety Review Committee
CYP3A	cytochrome P450 3A
Dex	Dexamethasone
DLT	dose-limiting toxicity
DOR	duration of response
EBMT	European Group for Blood and Marrow Transplantation
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
ER	extended release
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FLC	free light chain

Abbreviation	Definition
G-CSF	granulocyte colony stimulating factor
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
GM-CSF	granulocyte macrophage-colony stimulating factor
GvHD	graft-versus-host disease
H_0	null hypothesis
HA	alternative hypothesis
HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose
IB	investigator's brochure
IC_{50}	50% inhibition concentration
ICF	informed consent form
ICH	International **Council for** Harmonisation
IEC	Independent Ethics Committee
IMWG-URC	International Myeloma Working Group - Uniform Response Criteria
IND	Investigational New Drug
IRB	Institutional Review Board
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MPD	maximum protocol dose
MR	minimal response
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
nCR	near complete response
NF-κB	nuclear factor kappa light chain enhancer of activated B cells
NHL	non-Hodgkin lymphoma
NSCLC	non-small cell lung cancer
OPZ	Oprozomib
ORR	overall response rate
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PDn	pharmacodynamics
PDn/P	blood draw for pharmacodynamic and proteomic analyses
PFS	progression-free survival
PK	pharmacokinetic(s)

Abbreviation	Definition
PR	partial response
PRN	pro re nata (as needed)
QRS interval	beginning of the Q wave to the termination of the S wave, representing the time for ventricular depolarization
QT	the interval from the beginning of the Q wave to the beginning of the T wave, measured from the beginning of the QRS complex to the end of the T wave
QTc	corrected QT interval
QTc prolongation	prolongation of the interval between the start of the Q wave and the end of the T wave in the heart's electrical cycle (A prolonged QT interval is a biomarker for ventricular tachyarrhythmias and a risk factor for sudden death)
RBC	red blood cell
RP2D	Recommended Phase 2 Dose
RR	R to R interval: the interval from the beginning of one R wave to the beginning of the next
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCR	stringent complete response
SCT	stem cell transplant
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
T_{max}	time to maximum plasma concentration
TTP	time to progression
TTR	time to response
ULN	upper limit of normal range
UPEP	urine protein electrophoresis
US	United States
VGPR	very good partial response
WBC	white blood cell
WD	withdrawal
WES	whole exome sequencing
WGS	whole genome sequencing
WM	Waldenström macroglobulinemia

1. INTRODUCTION

This is a Phase 1b/2 clinical trial of the oral proteasome inhibitor oprozomib in combination with dexamethasone in subjects with a relapsed and/or refractory multiple myeloma. See Section 3 for a complete description of the study design. The study began in July 2013. The maximum tolerated dose (MTD) of oprozomib was not reached on either schedule but is currently ongoing.

The protocol has been amended as new data have become available and ongoing safety results have been reviewed. A summary of changes for all amendments is included in Appendix K of each version of the protocol and the main purpose for each amendment is summarized below.

Version	Main Purpose of Amendment
Amendment 1	• Changed the starting dose from 150 mg to 210 mg • Changed the inclusion/exclusion criteria
Amendment 2	• Provided guidance to investigators regarding prophylaxis, monitoring, and treatment of tumor lysis syndrome • Updated DLT criteria
Amendment 3	• Introduce the Oprozomib ER tablet broadly in the study. • Introduce step-up dosing in the dose escalation to determine if tolerability and safety are improved. This approach is based on preclinical data suggesting this schedule may be better tolerated than continuous dosing (see Section 1.3). • Include the use of the results of the safety and tolerability of step-up dosing in the determination of the recommended Phase 2 dose. • Provide additional safety guidance and exclusion criteria regarding GI hemorrhage as toxicities were observed in subjects treated with oprozomib on the 5/14 schedule (5 consecutive days every 14 days bimonthly) at 240 mg.
DLT = dose-limiting toxicity	

The main purpose of the current amendment (Amendment **4**) is to:

Pare down data collection for subjects on active treatment due to the completion of this study's analysis and abbreviated clinical study report.

1.2 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.

1.3 RELEVANT NONCLINICAL 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 United States (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 proapoptotic activity across a broad panel of tumor-derived cell lines in culture. The antitumor efficacy of oprozomib has been tested in immunocompromised mice implanted with a variety of human tumor cell lines, including models of 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 to rats orally for 2 complete cycles of daily dosing for 5 days with 9 days rest, at doses of 120, 180, and 240 mg/m^2 (20, 30, and 40 mg/kg). 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) and was also noted 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) using the same schedule of administration. A dose of 120 mg/m^2 (6 mg/kg) was determined to be the highest nonseverely 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 were 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 with 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 (QTc) prolongations in any animals.

Schedules with and without step-up dosing were conducted in rats. Rats did not tolerate a schedule of 50 mg/kg given on the 2 consecutive day weekly schedule. Rats did tolerate up to 60 mg/kg daily when initiated at a lower dose of 30 mg that was then stepped-up to 50 mg on Week 2 and then 60 mg on Week 3. This suggests increased tolerability using a step-up approach. This is consistent with preclinical and clinical observations showing that CFZ

tolerability was increased with step-up schedule.

Oprozomib does not absorb light within the range of natural sunlight (molar extinction coefficient less than 1000 L mol^{-1} cm^{-1} for wavelengths between 290 to 700 nm), and therefore is unlikely to have any adverse photoeffects.

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

1.4 RELEVANT CLINICAL BACKGROUND

The following enrollment safety and efficacy information for the Oprozomib studies below as of 31 March 2014 is as follows:

1.4.1 STUDY 2009-003: SOLID TUMORS

Once-Daily Dosing Group

The first-in-human clinical study (Study 2009-003 using Oprozomib in Capsules) was initiated in May 2010 and was an open-label, dose-escalation study in subjects with recurrent or relapsed advanced solid tumors. The primary objectives of this ongoing study were to evaluate the safety, tolerability, and MTD of oprozomib. Samples for PK and pharmacodynamics (PDn) analysis were also collected at various time points during Cycles 1 and 2. The dose for the initial cohort was 30 mg orally, once daily, for 5 consecutive days every 14 days (bimonthly), with cycles repeated every 14 days. Doses were escalated in subsequent cohorts by 30 mg as follows: 60, 90, 120, 150, and 180 mg. A once-daily dosing schedule was used for the first 6 cohorts treated.

Twenty-five subjects received oprozomib on a 5 consecutive day bimonthly schedule with once-daily dosing (n = 3 for each dose from 30 to 120 mg, n = 7 for the 150 mg cohort, and n = 6 for the 180 mg cohort). All 25 subjects who received a once-daily dose of Oprozomib in Capsules were included in the safety population. The median duration of study treatment in the once-daily dosing group was 29 days (range: 5–249 days). The median number of 14-day treatment cycles was 3 (range: 1–18 cycles), and the median total dose received was 1650 mg (range: 150–7740 mg). All subjects are off study; reasons for study discontinuation included

progressive disease (18 subjects, 72.0%), withdrawal of consent (3 subjects, 12.0%), adverse event (AE)/toxicity (1 subject, 4.0%), and "Other" reasons (3 subjects, 12.0%). The latter category includes subject decision in 1 subject and lack of clinical benefit in 2 subjects.

One subject in the 180 mg cohort experienced a dose-limiting toxicity (DLT) of Grade 3 vomiting and dehydration, and a second subject in the same dose cohort experienced a DLT of Grade 3 hypophosphatemia, prompting the expansion of the 150 mg cohort to 7 subjects in total. The MTD for the once-daily dosing group receiving the powder in capsule formulation was determined to be 150 mg.

Twenty-four subjects (96.0%) experienced at least 1 treatment-emergent AE. The most frequent AEs seen in ≥ 25% of subjects included nausea (23 subjects, 92.0%), vomiting (20 subjects, 80.0%), fatigue (14 subjects, 56.0%), diarrhea (13 subjects, 52.0%), decreased appetite (11 subjects, 44.0%), and abdominal pain, dehydration, and anemia (7 subjects each, 28.0%).

The majority of treatment-emergent AEs were gastrointestinal and Grade 1 or Grade 2 in severity. The only ≥ Grade 3 AEs occurring in more than 1 subject were Grade 3 dehydration (3 subjects, 12.0%) and Grade 3 vomiting, hyponatremia, and hypophosphatemia (2 subjects each, 8.0%). One subject (4.0%) experienced a Grade 4 treatment-emergent AE of hyperuricemia that resolved after 13 days; no action was taken with study drug.

Seven subjects (28.0%) experienced at least 1 treatment-emergent serious adverse event (SAE). There were no Grade 4 or Grade 5 SAEs in the once-daily dosing group. Grade 3 dehydration (experienced by 2 subjects, 8.0%) was the only SAE experienced by more than 1 subject.

One subject (4.0% overall) in the 150 mg cohort discontinued study treatment due to the occurrence of Grade 3 nausea and vomiting which did not require hospitalization.

Clinically significant laboratory abnormalities reported as AEs included Grade 3 anemia (n = 1), hypophosphatemia (n = 2), and lymphocytopenia (n = 1). As mentioned previously, there was also 1 Grade 4 AE of hyperuricemia.

Plasma concentrations of oprozomib following oral administration typically reached a maximum within 120 minutes and were undetectable within 24 hours. Exposure to oprozomib appears to

increase in a dose-proportional manner up to 150 mg. The diol, PR-176, is a major plasma metabolite for all subjects. The bioavailability of oprozomib is reflected by potent target inhibition at levels similar to those observed with carfilzomib (Badros 2010, Papadopoulos 2011, Zhou 2009). Proteasome inhibition ≥ 80% was observed in both whole blood and peripheral mononuclear cells for two-thirds of the subjects receiving doses ≥ 90 mg.

Twice-daily Dosing Group

In an effort to reduce gastrointestinal toxicity, subjects enrolled under Amendment 4 received oprozomib as a split daily dose, 4 to 6 hours apart. Nineteen subjects have received treatment on a 5 consecutive day bimonthly schedule with twice-daily dosing (n = 4 for the 120 mg cohort; n = 3 for the 150 mg cohort; n = 7 for the 180 mg cohort; and n = 5 for the 210 mg cohort).

All 19 enrolled subjects received at least 1 dose of Oprozomib in Capsules and comprised the safety population. The median duration of study treatment in the twice-daily dosing group was 47 days (range: 5–116 days). The median number of 14-day treatment cycles was 4 (range: 1–8 cycles), and the median total dose received was 3000 mg (range: 1050−6300 mg). All subjects are off study; reasons for study discontinuation included progressive disease (11 subjects, 57.9%), AE/toxicity (3 subjects, 15.8%), symptomatic deterioration (1 subject, 5.3%), and "Other" reasons (4 subjects, 21.1%), the latter including subject decision/preference (3 subjects) and lack of clinical benefit and toxicity (1 subject).

One subject in the 180 mg cohort experienced a DLT of Grade 3 hypophosphatemia, prompting the expansion of the 180 mg cohort to 7 subjects (1 subject did not complete Cycle 1 for reasons other than DLT and was therefore replaced). No additional DLTs were observed in this cohort. Two additional DLTs were recorded in the 210 mg cohort (120 mg, 90 mg), including 1 subject with Grade 5 gastrointestinal hemorrhage and 1 subject with Grade 3 hallucinations. The MTD for the once-daily dosing group receiving the powder in capsule formulation was determined to be 180 mg.

Nineteen subjects (100.0%) experienced at least 1 treatment-emergent AE. The AEs most frequently seen in ≥ 25% of subjects included vomiting (18 subjects, 94.7%); nausea (17 subjects, 89.5%); diarrhea (14 subjects, 73.7%); fatigue, constipation, and decreased appetite

(7 subjects each, 36.8%); and pyrexia, dysgeusia, and anemia (5 subjects each, 26.3%).

Most AEs were gastrointestinal and Grades 1 and 2 in severity, although 1 subject in the 210 mg cohort died within 30 days of discontinuing study drug due to a gastrointestinal bleed. Grade 3 anemia, fatigue, and lymphocyte count decreased were the only ≥ Grade 3 AEs occurring in more than 1 subject. Four subjects (21.1%) experienced Grade 3 anemia, and 2 subjects (10.5%) experienced Grade 3 lymphocyte count decreased and Grade 3 fatigue, respectively. No Grade 4 AE occurred in the twice-daily dosing group.

A lower incidence of gastrointestinal AEs was reported in Cycle 2 when subjects were fed (11 subjects, 57.9%) compared with Cycle 1 when subjects fasted (19 subjects, 100%). Fewer subjects participated in Cycle 2 than Cycle 1 due to discontinuations. Notable differences included less vomiting (Cycle 2: 9 subjects, 47.4%; Cycle 1: 14 subjects, 73.7%); less nausea (Cycle 2: 4 subjects, 21.1%; Cycle 1: 13 subjects, 68.4%); less diarrhea (Cycle 2: 6 subjects, 31.6%; Cycle 1: 10 subjects, 52.6%); and less pyrexia (Cycle 2: 1 subject, 5.3%; Cycle 1: 4 subjects , 21.1%). No other apparent differences in the incidence of other AEs were reported in Cycle 2 compared with Cycle 1. Additional data, ideally with a more robust crossover design, will be needed to assess the true effect of food on GI tolerability especially in light of preclinical data suggesting improved tolerability over time, such as the data supporting a step-up dosing regimen.

A total of 8 subjects (42.1%) experienced at least 1 treatment-emergent SAE. No SAE was experienced by more than 1 subject.

Three subjects (15.8%) discontinued study treatment due to AEs. One subject in the 120 mg cohort discontinued study treatment due to Grade 1 vomiting. One subject in the 180 mg cohort discontinued study treatment due to SAEs of Grade 3 nausea and vomiting. As mentioned previously, 1 subject in the 210 mg cohort was discontinued from study due to a Grade 5 gastrointestinal bleed. There were no treatment-emergent laboratory abnormalities ≥ Grade 4.

Preliminary PDn in subjects' whole blood samples demonstrates that the levels of proteasome inhibition with the twice-daily dose are similar to those with the equivalent single dose.

1.4.2 STUDY 2011-001: HEMATOLOGIC MALIGNANCIES

Safety

As of 21 January 2014, the Phase 1b portion of Study 2011-001 had completed enrollment; 61 response-evaluable subjects with hematologic malignancies had 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. In the Phase 1 portion of the study (as of 21 January 2014):

- Thirty-two (32) subjects have been enrolled on the 5 consecutive day bimonthly 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 selected for the Phase 2 portion of the study 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 consecutive day weekly 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, 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 the Phase 2 portion of the study for the 2/7 schedule.

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 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 Investigator's Brochure (Version 6). There were 2 cases of renal failure. There were also 2 Grade 5 GI hemorrhages at the 240 mg dose on the 5-consecutive-days bimonthly schedule.

Efficacy

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.

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

Formulation/Schedule (n)	Dose Range (mg)	ORR (≥ PR)	Clinical Benefit Rate (≥ MR)
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 (≥ MR)	Major Response (≥ PR)
Tablets 5/14 (11)	150–270	63.6%	54.5%
Tablets 2/7 (7)	150–330	42.9%	14.3%

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

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

1.4.3 STUDY 2012-001: OPROZOMIB IN COMBINATION WITH DEXAMETHASONE IN MULTIPLE MYELOMA

2012-001 is the study on which this protocol amendment is based. See Section 3.1 for information on study methodology.

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).

- 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.

Efficacy

Three response-evaluable subjects received Oprozomib Tablets on a 5 consecutive day bimonthly schedule with daily dosing, and all 3 subjects had SD as their best response. Seven response-evaluable subjects have received Oprozomib Tablets administered orally, once daily, on a 2 consecutive day weekly schedule. Four subjects had SD as the best response and 3 subjects had a partial response ([PR] confirmed or unconfirmed).

1.4.4 STUDY OPZ003: OPROZOMIB IN COMBINATION WITH LENALIDOMIDE AND DEXAMETHASONE IN MULTIPLE MYELOMA

Safety

The OPZ003 Phase 1b/2 study, assessing oprozomib in combination with lenalidomide and dexamethasone, is currently enrolling in the Phase 1b portion of the study in newly diagnosed subjects with multiple myeloma. As of 21 January 2014, three subjects have been enrolled. Two subjects remain on study. One subject, a 65-year-old female, experienced a treatment-related SAE of syncope during treatment at the 210 mg dose level. The subject discontinued treatment, and the SAE resolved. Subsequently, the subject experienced a second event of syncope. The dose level in this study has since been de-escalated to 180 mg and syncope has been identified as an event of interest for oprozomib.

Efficacy

No efficacy data are available at this time.

1.4.5 ADDITIONAL STUDIES WITH OPROZOMIB

Oprozomib is being studied in other Phase 1/2 trials intended to characterize the safety and

activity in combination with other anti-myeloma and solid tumor agents. Please see the Investigator's Brochure for additional details.

1.5 STUDY DESIGN RATIONALE

The objectives of this Phase 1b/2 study (Protocol 2012-001) are to define the MTD (Phase 1b), evaluate safety and tolerability (Phases 1b and 2), and evaluate the activity, PK, PDn, and biomarkers (Phases 1b and 2), and select the Recommended Phase 2 Dose (RP2D) of oprozomib administered in combination with dexamethasone in subjects with relapsed and/or refractory multiple myeloma with and without step-up dosing. All treatments will be administered orally, and all subjects will be treated in 14-day treatment cycles. Oprozomib Tablets or Extended Release (ER) Tablets will be administered in single daily doses unless otherwise determined by the sponsor.

Two schedules will be evaluated:

1. Treatment for 5 consecutive days bimonthly (Days 1, 2, 3, 4, and 5 of a 14-day cycle) with dexamethasone on Days 1, 2, 8, and 9 with both continuous and step-up dosing of oprozomib; and
2. Treatment for 2 consecutive days weekly (Days 1, 2, 8, and 9 of a 14-day cycle) with dexamethasone on Days 1, 2, 8, and 9 with both continuous and step-up dosing of oprozomib.

Treatment cycles will be repeated until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason (see Section 8).

The rationale for administration of oprozomib in combination with dexamethasone is provided in Section 1.5.1.

1.5.1 DOSE RATIONALE

Oprozomib Tablet

The starting dose of 210 mg (for the initial cohort of the study) given once daily on either the 5 consecutive day bimonthly or the 2 consecutive day weekly schedule in subjects with hematologic malignancies is supported by the clinical data collected for subjects exposed to Oprozomib Tablets in current and completed clinical studies.

Preliminary safety results from Study 2011-001 demonstrate the following:

- Subjects have tolerated 180 mg tablets in the 5 consecutive day bimonthly schedule without the occurrence of 2 DLTs and with no other significant safety concerns.
- Subjects have tolerated up to 240 mg tablets in the 2 consecutive day weekly schedule without the occurrence of 2 DLTs 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 day bimonthly schedule without occurrence of DLTs or the occurrence of other significant safety concerns.

In a previous study with bortezomib in relapsed refractory multiple myeloma subjects, the addition of steroids to a proteasome inhibitor has demonstrated a reduction in GI toxicity when compared to single agent (Jagannath 2006). In Study 2011-001, the addition of low doses of dexamethasone appeared to reduce GI toxicity. It is anticipated that Oprozomib Tablets will have lower GI toxicity in combination with dexamethasone than single-agent oprozomib, and therefore Oprozomib Tablets may be safely administered at the same level as oprozomib monotherapy.

As of 14 April 2014, three DLTs have been observed in the 5/14 once-daily dosing schedule at 210 mg using Oprozomib Tablets: 1 subarachnoid hemorrhage, 1 prolonged Grade 4 thrombocytopenia, and 1 Grade 3 transaminitis. The 180 mg cohort has expanded to 5 subjects without any DLTs. One additional subject will be enrolled to establish 180 mg as the MTD with Oprozomib Tablets.

Oprozomib ER Tablet

A new oprozomib tablet will be introduced into the study with Amendment 3. The Oprozomib ER Tablet is being developed to have a more consistent dissolution profile by decreasing variability through an improved release process. In addition, administration of a single Oprozomib ER Tablet, instead of multiple tablets as in the case of Oprozomib Tablets, will be used in doses up to 270 mg. (Currently, all doses given are composed of multiple Oprozomib Tablets. For example, the 270 mg dose is made up of three 90 mg Oprozomib Tablets.) The use of fewer tablets provides a smaller surface-to-volume ratio, resulting in a slower dissolution in vitro, and is predicted to have a lower maximum plasma concentration (C_{max}) and similar AUC. The current GI toxicity is likely mediated by local proteasome inhibition and variability (caused

by prior formulation and multiple tablets) in the release of drug substance in the current formulation. Thus, it is hypothesized that the formulation change and single-tablet dosage may decrease local intraluminal oprozomib levels at any one location in the GI tract and thereby decrease GI toxicity. Preliminary PK data on file from the single-agent oprozomib study suggest systemic toxicity is related to C_{max}; therefore, a lower C_{max} may reduce systemic toxicity.

Switching from Oprozomib Tablets to Oprozomib ER Tablets

When current subjects switch over to Oprozomib ER Tablets, they will continue the same dose and schedule that they were receiving with the Oprozomib Tablet. Intensive PK sampling should be obtained on Day 1 in the cycle prior to switching and on Day 1 of the following cycle (i.e., first day with Oprozomib ER Tablet) at the scheduled time points described in Section 7.4 for Cycle 1, Day 1 for patients on the step-up dosing regimen (i.e., predose to 7 hours postdose). The time between the 2 days of PK collection for switching to the Oprozomib ER tablet will be 1 cycle or 14 days. (see Section 7.4.1 for PK sampling requirements before and after the switch).

Step-Up Dosing

Step-up dosing has been better tolerated than continuous dosing in animal studies (see Section 1.3). Carfilzomib has been approved using a step-up dosing regimen that minimizes adverse events associated with initial doses. Based on this information, cohorts re-escalating after identification of the MTD with Oprozomib Tablets will receive step-up dosing.

Protocol Amendment 4

No changes in drug product, dosage, or treatment regimen occurred in this protocol amendment from the previous version.

1.5.2 SCHEDULE RATIONALE

The optimal schedule of administration of oprozomib is under investigation. Early development focused on the 5 consecutive day bimonthly (either once or twice daily) schedule in 14-day treatment cycles. The most significant AEs noted with the 5 consecutive day bimonthly schedule are related to GI toxicities. To potentially address those toxicities, a 2 consecutive

day weekly schedule is also being examined. Preclinical studies have shown that oprozomib administered once daily for 2 consecutive days has activity against a number of tumor cell lines. Therefore, for subjects enrolled in this study, the MTD will be determined for both the 5 consecutive day bimonthly schedule and for the 2 consecutive day weekly schedule. The Phase 2 portion of this study will be initiated at the sponsor's discretion using the recommended dose determined from 1 or both dosing schedules. The Phase 2 portion of the study will evaluate the safety and tolerability, PK, PDn, and activity of oprozomib; these data will be used to plan for the further development of oprozomib.

1.6 STUDY RATIONALE

The clinical activity of proteasome inhibition in hematologic malignancies has been demonstrated in the clinical setting, including multiple myeloma. Specifically, bortezomib, which is a covalent, slowly reversible inhibitor that primarily targets the chymotrypsin-like activity of the proteasome, was the first of the proteasome inhibitors that was shown to be cytotoxic to several tumor types. Because of the benefit of bortezomib observed in subjects with relapsed or refractory myeloma in Phase 1 and 2 studies, the drug received accelerated approval by the US Food and Drug Administration (FDA) and was made available to patients with advanced myeloma in May 2003 (Dispenzieri 2005). Full approval of bortezomib for multiple myeloma was based on the results of the Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial (Richardson 2005).

Carfilzomib (Kyprolis), which received accelerated approval in July 2012, is an irreversible inhibitor of the epoxyketone class (proteasome) that is selective and structurally distinct from bortezomib (O'Connor 2009). Proteasome inhibition by bortezomib is slowly reversible. Consequently, proteasome inhibition is more sustained with carfilzomib than with bortezomib (Demo 2007; Suzuki 2011). In comparison to bortezomib, carfilzomib exhibits equal potency, but greater selectivity for the chymotrypsin-like activity of the proteasome. In cell culture, carfilzomib is more cytotoxic than bortezomib following brief treatments that mimic the in vivo PK of both molecules (Demo 2007).

Phase 1 development of carfilzomib included 2 studies, PX-171-001 and PX-171-002, that explored 2 different dosing schedules (daily dosing for 5 consecutive days within Week 1 and

9 days rest; and daily dosing for 2 consecutive days for 3 weeks [Days 1, 2, 8, 9, 15, 16] and 12 days rest).

Data collected in these 2 studies suggested that the 2 consecutive day weekly schedule was better tolerated and demonstrated clinically meaningful response rates. Subsequent Phase 2 and Phase 3 carfilzomib studies have utilized this dosing schedule and have provided data indicating both tolerability and efficacy in advanced stage, heavily pretreated multiple myeloma subjects.

Oprozomib, an orally available structural analogue of carfilzomib, is a synthetic small-molecule peptide that specifically functions as an irreversible and highly selective 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. The studies discussed above demonstrate the treatment potential for proteasome inhibition in multiple myeloma. There is also a continued need for more effective agents and those that can be administered orally, which would improve compliance and patient convenience and potentially prolong treatment duration.

Dexamethasone will be administered in this study based on data from the SUMMIT trial (Richardson 2003) and an expanded access trial (Mikhael 2009), in which dexamethasone was shown to have synergistic effects with proteasome inhibitors. Preclinical studies also suggest the potential therapeutic advantage of dexamethasone combined with carfilzomib (Kuhn 2007) and bortezomib (Hideshima 2001) in multiple myeloma. In earlier clinical studies, dexamethasone was shown to mitigate GI AEs temporally associated with single-agent oprozomib.

2. STUDY OBJECTIVES

The Phase 1b portion of this study will determine the MTD of oprozomib in subjects with multiple myeloma when administered orally once daily, in combination with dexamethasone. A dose-escalation plan is being followed in Phase 1b to determine the recommended Phase 2 dose for each treatment schedule. The Phase 2 portion will use the recommended Phase 2 dose determine for each schedule, unless the sponsor determines that based on Phase1b data, 1 or both of the schedules should not proceed with development. The Phase 2 portion of this study will further evaluate the safety and activity of oprozomib in combination with dexamethasone.

2.1 PRIMARY OBJECTIVES

Phase 1b

- To determine the MTD and the RP2D of oprozomib given orally, once daily, on 2 different schedules: 5 consecutive days every 14 days (bimonthly, 5/14) or 2 consecutive days every 7 days (weekly; 2/7) for a 14-day treatment cycle, both schedules given in combination with dexamethasone
- To evaluate safety and tolerability

Phase 2

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

2.2 SECONDARY OBJECTIVES

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

2.3 EXPLORATORY OBJECTIVES

- To evaluate PDn and proteomic biomarkers
- To evaluate genomic biomarkers that may predict for response and resistance following treatment with proteasome inhibitors

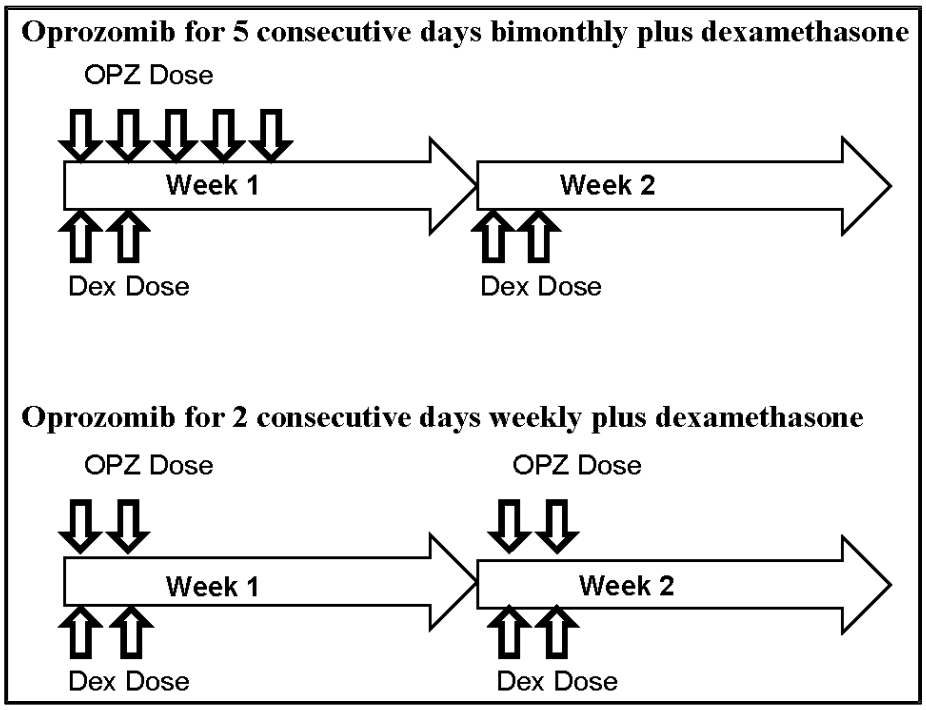
3. EXPERIMENTAL PLAN

3.1 STUDY DESIGN

This study is an open-label, Phase 1b/2, multicenter study in which subjects will receive oprozomib administered orally once daily in combination with dexamethasone on 2 different treatment schedules. Subjects will receive oprozomib on Days 1 to 5 of a 14-day treatment cycle in combination with 20 mg dexamethasone on Days 1, 2, 8, and 9; or oprozomib on

Days 1, 2, 8, and 9 of a 14-day treatment cycle in combination with 20 mg dexamethasone on Days 1, 2, 8, and 9 (Figure 1). Both the Phase 1b and the Phase 2 portions of this study will be open to patients with relapsed and/or refractory multiple myeloma. Primary refractory patients are allowed in the Phase 1b portion of the study only.

Figure 1 Dosing Regimens



OPZ = oprozomib; Dex = dexamethasone.

Treatment will be administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason (see Section 8).

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

3.1.1 PHASE 1B PORTION

Subjects will be evaluated for DLTs according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. Subjects with stable disease (SD) or better may continue treatment. Intrasubject dose escalation to the recommended Phase 2 dose may be permitted once that dose has been determined and after

discussion between the treating physician and the **Sponsor** study medical monitor.

The purpose of the Phase 1b portion of the study is to determine the MTD, RP2D, safety, and PK/PDn of oprozomib administered orally once daily in combination with dexamethasone, in subjects with relapsed and/or refractory multiple myeloma, using a 3 + 3 dose-escalation scheme with and without step-up dosing. The maximum tolerated dose is defined as the highest dose level at which fewer than 33% of subjects have a DLT.

For each of the 2 schedules being studied, groups of 3 to 6 subjects will be enrolled into dose-escalation cohorts. As long as fewer than 33% of subjects experience a DLT in a given cohort, escalation will continue by 30 mg increments of oprozomib onto the next designated cohort(s). A minimum of 6 subjects must be treated at the MTD to establish the dose as the MTD with and without step-up dosing.

Assessment of DLTs will occur during the first 14 days of treatment with continuous dosing (Cycle 1) or during the first 14 days of treatment at the step-up dose to be studied (Cycle 2), considered the assessment period. Any subject who develops a DLT during the assessment period after receiving at least 1 dose of oprozomib in the assessment period will be considered evaluable. Any subject who does not develop a DLT during the assessment period, but has not received all planned doses of oprozomib and dexamethasone, will be considered unevaluable and will be replaced.

3.1.2 DOSE-ESCALATION PLAN

Oprozomib Tablets

Prior to Amendment 3, oprozomib doses were escalated in sequential groups of 3 subjects with expansion up to 6 subjects, if a DLT was observed using Oprozomib Tablets. The initial cohorts of the study will be entered at a dose level of 210 mg for both schedules. All subsequent cohorts will be escalated by 30 mg until the MTD is determined.

In the event that the initial cohort that received the 210 mg dose is found to exceed the MTD (the highest dose at which a DLT is observed in fewer than 2 of 6 subjects), dosing will proceed at 180 mg or lower, as agreed with the Cohort Safety Review Committee.

Oprozomib ER Tablets

The introduction of Oprozomib ER Tablets into the study and determination of MTD of this formulation for the 5/14 and 2/7 schedules are described below:

5/14 Schedule

For the 5/14 once-daily dosing schedule, Oprozomib ER Tablets will be introduced with step-up dosing as described below. Determination of the MTD for step-up dosing will proceed in the following manner:

- The first cohort will enroll 6 subjects using step-up dosing. Subjects will receive 1 cycle at the 150 mg dose and then step-up to the 180 mg dose for subsequent cycles (150/180 mg). The DLT period will begin in Cycle 2 (the first cycle of dosing at the step-up dose level).
- For the next cohort, 6 subjects will be dosed with continuous dosing of 180 mg (Table 4, Cohort 502) of Oprozomib ER Tablets and assessed for DLTs to determine safety of this dose level.
- Further escalation will be based on the following:
  - If < 2 DLTs are observed in the continuous dosing cohort of 180 mg in Cycle 1, dose escalation may continue but will revert to step-up dosing (i.e., 150/210 mg, 150/240 mg, etc.) unless an alternate RP2D has been determined by the CSRC and sponsor.
  - If > 2 DLTs are observed, further escalation will not be conducted.

2/7 Schedule

For the 2/7 once daily dosing schedule, Oprozomib ER Tablets will be introduced into subsequent cohorts where no subjects have been enrolled unless the MTD for continuous dosing for Oprozomib Tablets has been previously determined prior to the introduction of the new tablets. One of the following 2 scenarios will be utilized to introduce Oprozomib ER Tablets into the dose escalation schema:

- If the MTD for continuous dosing has not been established for Oprozomib Tablets, Oprozomib ER Tablets will be introduced at the next new dose level specified by the preexisting dose-escalation plan (Table 3). Dose escalation will continue in 30 mg increments until the MTD for continuous dosing for Oprozomib ER Tablets is established as determined by the CSRC and sponsor.

- If the MTD for continuous dosing has been established with Oprozomib Tablets, Oprozomib ER Tablets will be introduced at the MTD in a cohort of 6 subjects (Table 5, Cohort 601). Escalation beyond this dose can only occur using step-up dosing as described below if there are < 2 DLTs in the 6 subjects in this cohort enrolled with Oprozomib ER Tablets as determined by the CSRC and sponsor.

Once the MTD for continuous dosing for Oprozomib ER Tablets has been established, step-up dosing will be introduced into dose escalation. Subsequent 2/7 cohorts will be dosed at the 240 mg for 1 cycle then step-up to the dose level to be studied. The rationale for this initial dose is based on safety and tolerability of this dose level in the current study, as no DLTs were observed in this cohort of 3 evaluable subjects at this dose level. The 240 mg dose is 2 dose levels below the single agent MTD, which was found to be 300 mg in Study 2011-001.

Determination of the MTD for step-up dosing will be evaluated in the following manner:

- The first step-up dosing cohort will start with 1 cycle of 240 mg, and then starting with Cycle 2, subjects will step-up to the MTD from continuous dosing for subsequent cycles.
- All subsequent cohorts will also begin dosing at 240 mg for 1 cycle and then will be escalated in Cycle 2 to the step-up dose level to be studied, by 30 mg increments until the MTD is defined with Oprozomib ER Tablets, unless an alternate R2PD is determined by the CSRC and the sponsor. The DLT period will begin in Cycle 2 (the first cycle of dosing at the step-up dose level).

Additional details regarding dose escalation can be found in the Cohort Management Plan.

Table 3: Dose-Escalation Schemes Using Oprozomib Tablets for 5 Consecutive Days Bimonthly and Using Oprozomib Tablets and Oprozomib Extended Release Tablets for 2 Consecutive Day Weekly Schedules

Cohorts		Oprozomib Daily Dose (mg)	Dexamethasone Dose (mg)
5 Consecutive Day Bimonthly Schedule	2 Consecutive Day Weekly Schedule		
-301[a]	-401[a]	180	20
301	401	210	20
NA	402	240	20
NA	403	270	20
NA	404	300	20
NA	403	330	20
NA	404[b]	360	20

CSRC = Cohort Safety Review Committee; DLT = dose-limiting toxicity; MTD = maximum tolerated dose; NA = not applicable.

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 -301 or -401 will proceed at 180 mg, or a lower dose as agreed with the CSRC and sponsor, and may be expanded up to 6 evaluable subjects.

[b] Additionally, subsequent cohorts of 3 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 fewer than 2 of 6 evaluable subjects) is defined.

Table 4: Dose-Escalation Schemes Using Oprozomib Extended Release Tablets: 5 Consecutive Day Bimonthly Schedule

5 Consecutive Day Bimonthly Schedule	Oprozomib Daily Dose Cycle 1 (mg)	Oprozomib Daily Dose to be Studied Cycles 2+ (mg)	Dexamethasone Dose (mg)
Step-up dosing with initial 1 cycle of 150 mg			
501[a]	150	180	20
Continuous dosing			
502	180	180	20
Step-up dosing with initial 1 cycle of 150 mg			
503	150	210	20
504	150	240	20
505	150	270	20

[a] Cohort will be dosed at 150 mg for 1 cycle and then increased to the step-up dose to be studied on Cycle 2 for the 5/14 once-daily dosing schedule. This is just an example and not meant to be all encompassing for further dose escalation beyond 270 mg. Dose-limiting toxicity period will be 1 cycle (Cycle 1 for continuous dosing or Cycle 2 for step-up dosing).

Table 5: Dose-Escalation Schemes for Oprozomib Extended Release Tablets: 2 Consecutive Day Weekly Schedule

2 Consecutive Day Weekly Schedule	Oprozomib Daily Dose Cycle 1 (mg)	Oprozomib Daily Dose to be Studied Cycles 2+ (mg)	Dexamethasone Dose (mg)
Cohort for continuous dosing			
601 Repeat at continuous dosing MTD[b] unless MTD achieved with OPZ ER Tablets	MTD	MTD[b]	20
Step-up dosing with initial 1 cycle 240 mg[a]			
602	240	MTD[b]	20
603	240	MTD[b] + 30	20
604	240	MTD[b] + 60	20
605	240	MTD[b] + 90	20

[a] Cohorts will be dosed at 240 mg for 1 cycle and then increased to the step-up dose to be studied on Cycle 2 for the 2/7 once-daily dosing schedule. Dose-limiting toxicity period will be 1 cycle (Cycle 1 for continuous dosing or Cycle 2 for step-up dosing).

[b] MTD for continuous dosing is to be determined.

3.1.3 PHASE 2 PORTION

The purpose of the Phase 2 portion of the study is to evaluate the safety, tolerability, and activity of oprozomib. The activity of the recommended Phase 2 dose will be determined for 1 or both treatment schedules (Days 1, 2, 8, and 9, and Days 1–5 of 14-day treatment schedules). In addition, the PK, PDn, proteomic biomarkers, and (optionally) genomic biomarkers will also be evaluated in this study.

3.2 NUMBER OF CENTERS

Approximately 12 sites in the US and 4 sites in France will be recruited for participation in the protocol. Sites that do not enroll subjects within 6 months of site initiation may be terminated.

3.3 NUMBER OF SUBJECTS

The total number of subjects planned for this study is approximately 140 relapsed and/or refractory multiple myeloma subjects.

3.3.1 PHASE 1B PORTION

For the Phase 1b portion of the study, it is estimated that approximately 60 evaluable subjects (30 for the 2/7 once-daily dosing schedule and 30 for the 5/14 once-daily dosing treatment

schedule) will be required to determine the recommended Phase 2 dose for each treatment schedule. This is based on an estimate that approximately 5 cohorts will be enrolled per treatment schedule, with up to 6 evaluable subjects per cohort.

3.3.2 PHASE 2 PORTION

Approximately 40 subjects will be enrolled per schedule in the Phase 2 portion of the study.

3.4 ESTIMATED STUDY DURATION

The total study duration is expected to be approximately 36 months. Approximately 22 to 26 months may be required to enroll all subjects (4–8 months to enroll Phase 1b subjects with the Oprozomib Tablets, 4–8 months to enroll Phase 1b subjects with the Oprozomib ER Tablets, and 10–12 months to enroll Phase 2 subjects). Subjects will be treated in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason (see Section 8); responding subjects (SD or better) may continue on treatment.

Subjects who continue on treatment and whose disease has not progressed 6 months after starting study treatment will reduce the frequency of their visits (on Day 1 of their next scheduled cycle) to every 4 weeks instead of every 2 weeks, with adequate drug supply for 2 cycles of treatment starting with Cycle 13. Disease response will be assessed every 8 weeks (4 cycles) after 1 year (26 cycles) on therapy.

Subjects must complete a visit approximately 4 weeks after the last cycle of treatment to allow for safety follow-up within 30 days after the last dose of oprozomib.

For subjects who discontinue treatment for reasons other than progression, disease assessments **will no longer be required under protocol amendment 4**.

4. PATIENT SELECTION

The study population will consist of multiple myeloma patients requiring therapy who have relapsed and/or are refractory to their last therapy and have been treated with at least 1, but not more than 5, lines of multiple myeloma therapy. Prior therapy must have consisted of at least 1 regimen that included lenalidomide and/or bortezomib. Patients should be considered to be appropriate candidates for a clinical study by their treating physicians.

- Relapsed patients must have previously achieved ≥ MR on at least 1 line of therapy as assessed by the treating physicians.
- Refractory patients are allowed, but it is not required that patients be refractory to their last therapy.
- Primary refractory patients are allowed in the Phase 1b portion of the study only.

The following definitions will be used to classify multiple myeloma disease state:

- Refractory multiple myeloma: Disease that is nonresponsive while on primary or salvage therapy or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve minimal response (MR) or development of progressive disease (PD) while on therapy.
- Relapsed and refractory myeloma: Disease that is nonresponsive while on salvage therapy, or progresses within 60 days of last therapy in patients who have achieved MR or better at some point previously before progressing in their disease course.
- Primary refractory myeloma: Disease that is nonresponsive in patients who have never achieved an MR or better with any therapy. It includes patients who never achieve MR or better in whom there is no significant change in M-protein and no evidence of clinical progression, as well as primary refractory PD where patients meet criteria for true PD.
- Relapsed multiple myeloma: Previously treated myeloma that progresses and requires the initiation of salvage therapy but does not meet the criteria for either "primary refractory myeloma" or "relapsed-and-refractory myeloma."

4.1 INCLUSION CRITERIA

1. Diagnosis of multiple myeloma with measureable 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. Only for subjects without measurable serum and urine M-protein, serum free light chain: Involved free light chain (FLC) level ≥ 10 mg/dL, provided serum FLC ratio is abnormal
2. Patients requiring therapy who have relapsed and/or are refractory to their last therapy and have been treated with at least 1, but not more than 5, lines of multiple myeloma

therapy. Prior therapy must consist of at least 1 regimen that included lenalidomide and/or bortezomib. Patients should be considered to be appropriate candidates for a clinical study by their treating physicians. Relapsed patients must have previously achieved ≥ MR on at least 1 line of therapy as assessed by the treating physician. Refractory patients are allowed, but it is not required that patients be refractory to their last therapy. Primary refractory patients are allowed in the Phase 1b portion of the study only.

3. Males and females ≥ 18 years of age
4. Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0–2
5. Adequate hepatic function, with bilirubin ≤ 1.5 times the upper limit of normal (ULN) in the absence of Gilbert's disease or hemolysis, aspartate aminotransferase (AST) ≤ 3 times ULN, and alanine aminotransferase (ALT) ≤ 3 times ULN
6. Absolute neutrophil count (ANC) ≥ 1000 cells/mcL, hemoglobin ≥ 7.0 g/dL, and platelet count ≥ 30,000 cells/mcL:
    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) and granulocyte-macrophage colony-stimulating factor (GM-CSF) support for at least 1 week and of pegylated G-CSF for ≥ 2 weeks prior to first dose.
    c. Patients may receive red blood cell (RBC) transfusions or receive supportive care with erythropoietin or darbepoetin in accordance with institutional guidelines.
7. Calculated or measured creatinine clearance (CrCl) rate of ≥ 30 mL/min calculated using the formula of Cockcroft and Gault [(140 − age) × mass (kg) / (72 × serum creatinine mg/dL)]. Multiply result by 0.85 if female.
8. Uric acid, if elevated, must be corrected to within laboratory normal range before dosing
9. Patients must sign written informed consent form (ICF) in accordance with federal, local, and institutional guidelines
10. Female patients of childbearing potential must have a negative serum or urine pregnancy test within 3 days prior to receiving the first dose and agree to use effective methods of contraception during the study and for 3 months following the last dose of study drug. Postmenopausal females (> 45 years old and without menses for > 1 year) and surgically sterilized females are exempt from these requirements. Male patients must use an effective barrier method of contraception during the study and for 3 months following the last dose if sexually active with a female of childbearing potential.

11. Prior carfilzomib is not required but is allowed if a patient had at least 2 cycles of carfilzomib alone or in combination with a dose of at least 20/27 mg/m^2, as long as the patient:

    a. Had at least a partial response to prior carfilzomib therapy

    b. Was not removed from carfilzomib therapy due to toxicity, unless approved by the medical monitor

    c. Was not removed from carfilzomib therapy for progressive disease nor experienced progressive disease within 6 months after any prior carfilzomib therapy.

4.2 EXCLUSION CRITERIA

1. Radiation therapy within 2 weeks prior to first dose; localized radiation therapy within 1 week prior to first dose
2. Immunotherapy/standard myeloma therapy within 2 weeks prior to first dose (except for antibody therapy, where 6 weeks is required, and alkylator therapy, where 3 weeks is required); prior stem cell transplant (SCT) therapy (autologous SCT within the prior 8 weeks; allogeneic SCT within the prior 16 weeks). Patients with prior allogeneic SCT should not have evidence of moderate to severe graft-versus-host disease (GvHD), as defined in Filipovich (2005)
3. 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.
4. Glucocorticoid therapy within 14 days prior to enrollment that exceeds a cumulative dose of 160 mg of dexamethasone or equivalent
5. Participation in an investigational therapeutic study within 3 weeks prior to first dose
6. Prior oprozomib exposure
7. Known hypersensitivity/toxicity or intolerance to dexamethasone
8. Major surgery within 3 weeks prior to first dose
9. Congestive heart failure ([CHF] 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
10. Uncontrolled hypertension or uncontrolled diabetes
11. Active infection requiring systemic antibiotics, antivirals, or antifungals within 2 weeks prior to first dose
12. Known or suspected human immunodeficiency virus (HIV) infection or patients who are HIV seropositive

13. Active hepatitis A, B, or C infection
14. History of previous clinically significant GI bleed in the last 6 months prior to first dose
15. Significant neuropathy (Grade 3, Grade 4, or Grade 2 with pain) at the time of the first dose
16. 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 of Gleason Score 6 or less with stable prostate specific antigen levels, or cancer considered cured by surgical resection
17. Plasma cell leukemia
18. Female patients who are pregnant or nursing
19. Inability to swallow medication, inability or unwillingness to comply with the drug administration requirements, or GI condition that could interfere with the oral absorption or tolerance of treatment
20. Any contraindication to oral hydration (e.g., significant preexisting comorbidity or fluid restriction)
21. Any clinically significant psychiatric or medical condition that, in the opinion of the investigator, could increase patient risk or interfere with protocol adherence or a patient's ability to give informed consent

5. SUBJECT ENROLLMENT

The Screening period for a particular subject commences after the subject signs the ICF. The ICF must be signed before any study-specific tests may be performed. Every subject who signs an ICF will be assigned a study number.

After a subject has been screened and has successfully fulfilled all eligibility criteria, the site representative will submit the completed Inclusion/Exclusion Checklist to **the Sponsor**. Please see the Study Reference Manual for contact information.

Each subject will be assigned a study- and site-specific sequential number by the site staff. This number will be used to identify each subject throughout the clinical study and will be used on all study documentation related to that subject.

Documentation must include start and stop dates for prior treatment. Disease progression must be documented with appropriate disease assessment parameters. Copies of all Screening

laboratory results are required.

Subjects who initially fail Screening but subsequently become eligible may still be enrolled in the study.

Sites that do not enroll a single subject within the first 6 months of initiating the study may be terminated at the discretion of the sponsor.

6. TREATMENT PROCEDURES

6.1 DRUG ADMINISTRATION

Oprozomib Tablets will be supplied containing 60, 90, or 120 mg of oprozomib. Oprozomib ER Tablets will be supplied containing 150, 180, 210, 240, or 270 mg of oprozomib. Both types of tablets will be administered in single daily doses (Table 3, Table 4, and Table 5). Refer to the Pharmacy Manual for handling, administration, and storage instructions.

Oprozomib will be administered orally, once daily, on either the 5 consecutive day bimonthly schedule or the 2 consecutive day weekly schedule for each 14-day treatment cycle (Figure 1), either at the single-dose level (i.e., continuous dosing) or step-up dose level, and the treatments will be repeated until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason (see Section 8). Oprozomib will be administered in combination with dexamethasone at 20 mg orally (or intravenously, if tablets are unavailable or subject cannot tolerate tablets) on Days 1, 2, 8, and 9 for both treatment schedules. On oprozomib dosing days (i.e., on Days 1 and 2 for both schedules and Days 8 and 9 for the 2 consecutive day weekly schedule), dexamethasone must be taken at least 30 minutes prior to oprozomib. On days in which PK sampling is taken after a dose, oprozomib must be taken in the fasted state (at least 2 hours after a meal and fasting for at least 2 hours after dosing). On all other days, including non-PK days and days in which only a predose PK sample is taken, it is recommended that oprozomib is administered with food (i.e., within approximately 30 minutes after eating).

Subjects may be premedicated pro re nata (as needed [PRN]) with a 5-hydroxytryptamine type-3 ($5\text{-}HT_3$) inhibitor, such as ondansetron or granisetron, before administration of the first dose of oprozomib each day and around the clock. Procedures for dose reductions and adjustments are summarized in Section 6.4.

In the Phase 1b portion, subjects will be dosed in treatment cohorts in escalating order (see Section 3.1.2: Table 3, Table 4, and Table 5 for doses/cohorts, and see Section 6.2 for methods of dose escalation to the MTD), as determined by the CSRC and sponsor, only after the safety of the previous dose level has been established or until an MTD has been determined.

In the Phase 2 portion, subjects will be dosed at the recommended Phase 2 dose, as defined in the Phase 1b portion of the study (see Section 3.1.2: Table 3, Table 4, and Table 5 for doses/cohorts, and see Section 6.2 for methods of dose escalation to the MTD).

6.1.1 SWITCHING TO OPROZOMIB ER TABLETS FROM OPROZOMIB TABLETS

When subjects on Oprozomib Tablets switch to the Oprozomib ER Tablets, additional PK assessment will be obtained before and after changing formulations (Section 7.4.1).

6.2 PHASE 1B

6.2.1 SAFETY CONSIDERATIONS FOR PHASE 1B

Treatment cohorts will be dosed in escalating order (see Section 3.1.2: Table 3, Table 4, and Table 5) as determined by the CSRC and sponsor, only after the safety of the previous dose level has been established or until an MTD has been determined; de-escalation may be performed after the MTD is exceeded and for individual subjects based on tolerability.

Subsequent cohorts may initiate treatment at the starting dose (of 150 mg for 5/14 or 240 mg for 2/7) but will not be dosed at the step-up dose to be studied until safety data are obtained from at least 3 evaluable subjects in the previous cohort at the step-up dose for Cycle 2. Rules for dose escalation are presented in Section 6.2.2. Safety will be evaluated based on the incidence, relatedness, and severity of AEs, clinical laboratory test results, electrocardiograms (ECGs), and other relevant clinical findings as provided by the investigators. A review of safety data for each cohort will be conducted by the CSRC and sponsor when all of the above data are available.

The CSRC, which comprises**the Sponsor**'s medical monitor,**the Sponsor**'s drug safety representative, and the investigators, will review all clinical and laboratory data and must agree whether dose escalation to the next cohort is appropriate. As PK data from each treatment cohort become available, they may also be reviewed by the CSRC. All available clinical data

will be considered for dose-escalation decisions.

6.2.2 DOSE-ESCALATION RULES

The planned and contingent dose levels are provided in Section 3.1.2 (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	Next cohort of 3 subjects treated at the next planned 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 next lower dose level, unless 6 subjects have already been treated at that dose level.
1 of 6	Next cohort of 3 subjects treated at the next planned higher dose level.
≥ 2 of 6	Dose escalation stops. Additional subjects may be treated at the next lower dose level, for a minimum of 6 subjects treated at that dose level.
Highest dose with < 2 of 6	Maximum tolerated dose

Source: Modified from Simon 1997.
DLT = Dose-limiting toxicity.

Intrasubject dose escalation to the recommended Phase 2 dose may be permitted once that dose has been determined and after discussion between the treating physician and the **Sponsor** medical monitor.

6.3 DOSE-LIMITING TOXICITY

Subjects will be evaluated for DLT according to the NCI-CTCAE (Version 4.03). Subjects with SD or better may continue treatment.

During the Phase 1b portion, assessment of DLTs will occur during the first 14 days of treatment with continuous dosing (Cycle 1) or during the first 14 days of treatment with the step-up dose to be studied during the 2-week assessment period (Cycle 2). Any subject who develops a DLT during the assessment period after receiving at least 1 dose of oprozomib in the

assessment period will be considered evaluable. Any subject who does not develop a DLT, but has not received all planned doses of oprozomib and dexamethasone, will be considered unevaluable and will be replaced.

Guidelines for withholding study treatment, including treatment delays, reintroduction, and discontinuation, are described in Section 6.4.1. "Study drug-related" is defined as a reasonable likelihood of clinical causality based on time of event, biology, and dechallenge improvement, and that the AE was not likely explained by the subject's clinical state, underlying disease, concomitant medication, or study/nonstudy procedure. For the purposes of this study, a DLT is defined as any of the following treatment-related events occurring in the first 14 days of treatment, with treatment at the dose to be studied (i.e., Cycle 1 for continuous dosing or Cycle 2 for step-up dosing):

Any ≥ Grade 3 nonhematologic AE, with the following exceptions or qualifications:

- ≥ Grade 4 abnormalities in serum creatinine or electrolytes will be considered a DLT.
- ≥ Grade 3 acute kidney injury, defined as serum creatinine > 3 × baseline or > 4.0 mg/dL of any duration will be considered a DLT.
- 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-HT_3 antagonist and aprepitant or fosaprepitant for nausea and vomiting, and loperamide (e.g., Imodium), and diphenoxylate/atropine (e.g., Lomotil) for diarrhea.
- Grade 3 fatigue lasting > 14 days will be considered a DLT.
- Asymptomatic Grade 3 hypophosphatemia lasting less than 24 hours will not be considered a DLT.
- ≥ Grade 3 dexamethasone-related toxicities will not be considered DLTs.

Any of the following hematologic AEs will be considered a DLT:

- Grade 4 neutropenia: ANC < 500 cells/mcL lasting ≥ 7 days
- 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 < 1000 cells/mcL)
- Grade 3/4 thrombocytopenia
    - Grade 3 thrombocytopenia of any duration with Grade 2 bleeding or requiring platelet transfusion
    - Grade 4 lasting ≥ 7 days

- Grade 4 lasting < 7 days with Grade 2 bleeding, or if platelet counts are lower than 10,000 cells/mcL, requiring a platelet transfusion

Note: The following will not be considered a DLT:

- Grade 4 anemia
- Grade 4 thrombocytopenia lasting < 7 days with platelet counts above 10,000 cells/mcL without clinically significant bleeding and with or without transfusion

6.4 DOSE REDUCTIONS/ADJUSTMENTS

6.4.1 OPROZOMIB DOSING DELAYS, MODIFICATIONS, AND REINTRODUCTION

The dose of oprozomib should be held and/or reduced according to the guidelines described below. Dose reduction should be continued until resolution of toxicity (per Table 6 and Table 7). Subjects having severe toxicity will be allowed 3 dose reductions in 30 mg increments to a maximum reduction of 90 mg with a minimum dose of 150 mg. A final dose reduction will be managed by reducing dose intensity by schedule, if fewer than 3 dose reductions have occurred and subjects are currently dosed at 150 mg.

- Subjects on the 5/14 schedule who have had fewer than 3 reductions down to a dose of 150 mg may reduce the intensity on the next reduction by changing from 5 to 3 consecutive days for every 14-day cycle.
- Subjects on the 2/7 schedule who have had fewer than 3 reductions down to a dose of 150 mg may reduce the intensity on the next reduction by changing from 2 consecutive doses to 1 day weekly for every 14-day cycle.
- Exceptions to the dose modification guidelines are permitted after written approval from the **Sponsor** study medical monitor.

6.4.1.1 Dose Modification for Hematologic Toxicities

Table 7 summarizes hematologic toxicities and oprozomib dosing actions that should occur in the event of toxicities.

Table 7: Guidelines for Dose Modification for Hematologic Toxicities

Toxicity	**Oprozomib Dosing Action**
ANC ≥ 500 cells/mcL	Continue at full dose
ANC < 500 cells/mcL for less than 7 days	Hold dose. When ANC ≥ 500 cells/mcL, resume at full dose.
ANC < 500 cells/mcL for 7 days or longer	Hold dose. When ANC > 500 cells/mcL, resume at 1 dose decrement.
Grade 3 febrile neutropenia	Hold dose. When ANC ≥ 1000 cells/mcL and fever has resolved, resume at 1 dose decrement.
Platelet count < 50,000 cells/mcL and ≥ 25,000 cells/mcL *without evidence of bleeding*	Continue at full dose
Platelet count < 50,000 cells/mcL and ≥ 25,000 cells/mcL *with evidence of bleeding*	Hold dose. When platelet count returns to > 50,000 cells/mcL and bleeding stops, resume at 1 dose decrement.
Platelet count < 25,000 cells/mcL for < 7 days *without evidence of bleeding*	Hold dose. When platelet count ≥ 25,000 cells/mcL, resume at full dose.
Platelet count < 25,000 cells/mcL for ≥ 7 days *with or without evidence of bleeding*	Hold dose. When platelet count ≥ 25,000 cells/mcL, resume at 1 dose decrement.

ANC = absolute neutrophil count.

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

- Non-treatment-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.
- If required by continued or recurrent toxicity, a second or third dose reduction may be permitted down to a minimum dose of 150 mg after discussion with the **Sponsor** medical monitor. If the subject has not had 3 reductions but is at a dose level of 150 mg, an additional reduction may occur via reducing dose intensity (see Section 6.4.1). No more than 3 dose reductions will be permitted in an individual subject on study; if toxicity continues, the subject should be removed from the study.
- If the subject tolerates the reduced dose for 1 cycle, the subject's dose may be escalated to the dose prior to the dose reduction.
- If there is no resolution of toxicity after 2 weeks of withholding treatment (up to 3 weeks if an infection is being treated), the subject will be discontinued from the study.

6.4.1.2 Dose Reduction for Nonhematologic Toxicities

Table 8 summarizes nonhematologic toxicities and oprozomib dosing actions that should occur in the event of toxicities.

Table 8: Guidelines for Dose Modification for Nonhematologic Toxicities

Toxicity	**Oprozomib Dosing Action**
Tumor Lysis Syndrome, defined as abnormalities in at least 3 of the following 4 categories: (1) Increase in creatinine, uric acid, 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 oprozomib until all abnormalities in serum chemistries have resolved to baseline, then resume at full doses.
Grade 3 nonhematologic toxicity	Hold dose until toxicity resolved to ≤ Grade 1 or has returned to baseline. Resume study drug at 1 dose decrement.
Grade 4 nonhematologic toxicity	Discontinue dosing.
Grade 2 neuropathy with pain or ≥ Grade 3 neuropathy	Hold dose until toxicity resolved to ≤ Grade 1 or has returned to baseline. Resume study drug at 1 dose decrement.
Grade 3 nausea, vomiting, diarrhea and/or constipation without optimal supportive care	Continue dosing, but administer optimal supportive care.
Grade 3 nausea, vomiting, diarrhea and/or constipation with optimal supportive care	Hold dose until toxicity resolved to ≤ Grade 1 or has returned to baseline. Resume study drug at 1 dose decrement.
Grade 3 fatigue lasting < 14 days	Continue dosing.
Grade 3 fatigue lasting ≥ 14 days	Hold dose until toxicity has resolved to ≤ Grade 1 or has returned to baseline. Resume study drug at 1 dose decrement.
Grade 1 or 2 GI hemorrhage	DELAY until Grade 0 DECREASE one dose level for Grade 2
Grades 3 or 4 GI hemorrhage	Discontinue dosing

GI = gastrointestinal; LDH = lactate dehydrogenase.

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

- Non-treatment-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.
- If required by continued or recurrent toxicity, a second or third dose reduction down to a minimum of 150 mg may be permitted after discussion with the **Sponsor** medical monitor. If the subject has not had 3 reductions but is at a dose level of 150 mg, an additional reduction may occur via reducing dose intensity (see Section 6.4.1). No more than 3 dose reductions will be permitted in an individual subject on study; if toxicity continues, the subject should be removed from the study.
- If the subject tolerates the reduced dose for 1 cycle, the subject's dose may be escalated

to the dose prior to the dose reduction.

- If there is no resolution of toxicity after 2 weeks of withholding treatment (up to 3 weeks for infection treatment), the subject will be discontinued from the study.
- Subjects with Grade 3 or 4 GI hemorrhage should not be rechallenged. Oprozomib should be permanently discontinued. Endoscopy should be considered for all subjects who develop GI hemorrhage.

6.4.1.3 Infections

Subjects with active systemic infections of any kind should have dosing withheld until the infection has resolved. After the infection has resolved, treatment may continue at the original dose. If there is no resolution of infection after 3 weeks, the subject will be discontinued from the study.

6.4.1.4 Congestive Heart Failure

Acute development or exacerbation of CHF or new onset of decreased left ventricular ejection fraction in a subject (as defined by an increase of NCI-CTCAE ≥ 1 grade from baseline), whether or not drug related, requires withholding of the dose until resolution. After the CHF has resolved or returned to baseline, treatment may continue at a dose reduced by 30 mg, with the approval of the **Sponsor** medical monitor, or the subject may be discontinued from the study. If there is no resolution of CHF after 2 weeks, the subject will be discontinued from the study.

6.4.1.5 Conditions Not Requiring Dose Reduction

The following conditions are exceptions to the above guidelines. Oprozomib does not need to be held or dose reduced in the following cases:

- Grade 3 nausea, vomiting, constipation, or diarrhea (unless persisting despite optimal treatment with antiemetics or antidiarrheals)
- Grade 3 fatigue (unless persisting for > 14 days)
- Asymptomatic Grade 3 hypophosphatemia lasting less than 24 hours

6.4.1.6 Dosing Delays

Dosing delays are not permitted in the DLT assessment period. If the timing of later cycles must be adjusted for reasons unrelated to toxicity (e.g., holidays or subject requests), the cycle must be started no sooner than 1 day before or no later than 14 days after the originally scheduled

next cycle, unless permission is granted by the medical monitor. If subjects miss more than 4 weeks of oprozomib, they will be restarted at 150 mg for the 5/14 schedule or 240 mg for the 2/7 schedule using the step-up dose scheme with 1 cycle at the dose level described for each schedule, and then step-up to their last dose level prior to the therapy hold. Schedule adjustments may be made only at the beginning of each cycle; and adjustments may not be made mid-cycle. If possible, future cycles should revert back to the original day of dosing for the schedule.

6.4.2 DEXAMETHASONE: DOSING DELAYS, MODIFICATIONS, AND REINTRODUCTION

Guidelines for dexamethasone dose modifications are summarized in Table 9. In the event oprozomib is permanently discontinued, dexamethasone should also be discontinued (refer to Section 8).

Table 9: Treatment Guidelines for Dexamethasone-related Toxicity

Body System	Symptom	Recommended Action
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, or gastritis Grades 1 and 2 (requiring medical management)	Continue dexamethasone at same dose and treat with therapeutic doses of H_2 blockers or proton pump inhibitor. May consider adding sucralfate or other anti-ulcer treatment as clinically indicated. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, or gastritis ≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms return to baseline. Restart dexamethasone at 1 dose decrement along with concurrent therapy with H_2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone permanently.
Gastrointestinal	Acute pancreatitis	Discontinue dexamethasone permanently.
General disorders	Edema ≥ Grade 3 (≥ 30% limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self-care ADL)	Hold dexamethasone until symptoms return to baseline. Give 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.
Psychiatric Disorders	Confusion or mood alteration ≥ Grade 2 (interfering with function ± interfering with ADL)	Hold dexamethasone until symptoms return to baseline. 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 ADL)	Hold dexamethasone until symptoms return to baseline. Restart dexamethasone at 1 dose decrement. If weakness persists, decrease dose by 1 more dose level. Discontinue dexamethasone permanently if symptoms persist.
Metabolism and Nutrition Disorders	Hyperglycemia ≥ Grade 3 (fasting glucose > 250 mg/dL)	Hold dexamethasone until glucose is ≤ Grade 2 (< 250 mg/dL) and treat with insulin or other hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by 1 dose level until ≤ Grade 2 (< 250 mg/dL)
All Other	Other nonhematologic toxicity ≥ Grade 3 considered 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, hold dexamethasone dose until toxicity has resolved to Grade 2 or less or to baseline, and resume dexamethasone dose by 1 more dose decrement. If toxicity recurs despite 2 dose decrements, discontinue dexamethasone permanently.

ADL = activities of daily living.

Two dose-reduction levels are defined for dexamethasone, as illustrated in Table 10.

Table 10: Dose Decrements for Dexamethasone

Nominal Dose	Reduced Dexamethasone Doses	
	Dose -1	Dose -2
20 mg	12 mg	8 mg

Dexamethasone will be permanently discontinued after 2 dose reductions in the event of an additional dexamethasone-related DLT. At the investigator's discretion, dexamethasone dosing may be tapered prior to complete discontinuation, according to institutional practice. If the dexamethasone dose is reduced during the previous cycle, the lower dose level will be continued on Day 1 of the new cycle. If the reduced dose level is well tolerated for a complete cycle, the subject may, at the investigator's discretion, be rechallenged at the start of the next cycle with the dose level given prior to the reduction. If myeloma treatment doses of dexamethasone as noted in Table 9 are discontinued, antiemetic doses of dexamethasone, generally considered to be 4 mg on the days of dosing, may be continued if tolerable per investigator discretion.

6.4.3 MISSED DOSES

Subjects must receive all planned doses in the DLT assessment period in order to be assessed for DLT in Phase 1. Planned doses that are missed can be made up if they are received within the same calendar day of scheduled administration. If a subject misses more than 2 consecutive cycles after completing the DLT assessment period for reasons other than toxicity, the subject will be discontinued unless it is determined that the subject was benefiting from therapy and that the medical monitor permits the subject to resume therapy. See Section 6.4.1.6 for information on cycle delays.

6.5 SAFETY GUIDANCE FOR INVESTIGATORS

Based on the experience in nonclinical studies of oprozomib and available Phase 1 clinical data in subjects with solid tumors and hematologic malignancies, the following guidance is recommended but not mandated to investigators unless otherwise noted in the dose reduction guidelines:

- Subjects with active systemic infections of any kind should not be dosed with oprozomib until infection has resolved. Subjects with neutrophil counts related to their infection of ANC < 500 cells/mcL should not be treated until the neutrophil count has recovered to > 1500 cells/mcL.
- For platelet counts < 25,000 cells/mcL, oprozomib dosing should be held until platelet count is ≥ 25,000 cells/mcL independent of platelet transfusions for 1 week. Consideration of dose reduction of oprozomib should be given if it is thought that oprozomib may have caused the thrombocytopenia.

- Subjects should have anemia corrected in accordance with the institutional guidelines, which can include transfusions or support with erythropoietin or darbepoetin.
- Based on the high incidence of nausea and vomiting that has been observed to date, it is recommended that subjects treated with oprozomib receive prophylactic antiemetics that would typically be utilized to prevent nausea and vomiting prior to moderately to highly emetogenic therapies.
- Prophylactic treatment for diarrhea is not recommended; however, subjects who experience diarrhea should be treated with antidiarrheals and may be given prophylaxis once they are known to have diarrhea related to administration of oprozomib.
- Hypophosphatemia has been observed in a few subjects treated with oprozomib. Severe hypophosphatemia has also been observed in subjects treated with other proteasome inhibitors, including carfilzomib (data on file), bortezomib (Messinger 2010), and MLN 9708 (Richardson 2012). This typically has been transient and not associated with clinical symptoms. Subjects should be monitored carefully for electrolyte abnormalities, and electrolytes should be replaced as needed.
- Cases of TLS have been observed with proteasome inhibitors, including oprozomib. It is recommended that all subjects begin vigorous oral hydration (1.5–2.0 liters/day) the day before and on days of oprozomib dosing until instructed that the risk of TLS has abated. Allopurinol prophylaxis and close monitoring of fluid and electrolyte balance are recommended for subjects with renal functional impairment and for those with a high tumor burden. For specific recommendations, see Section 6.6.1.
- Gastrointestinal hemorrhage has been reported in subjects treated with oprozomib, including fatalities. Subjects with Grades 3 and 4 GI hemorrhage should not be rechallenged with oprozomib and should be permanently discontinued. Endoscopy should be considered for any subject developing GI hemorrhage.

See Section 6.4.1 for additional information and recommendations for dose adjustments required for specific hematologic and nonhematologic toxicities.

6.6 CONCOMITANT MEDICATIONS

Concomitant medications are defined as any prescription or over-the-counter preparations, including vitamins and supplements. All concomitant medications taken by the subject from 30 days before Day 1 until 30 days after the subject's last dose of study drug must be recorded on the electronic case report form (eCRF).

In vitro tests indicate 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, as a precaution, 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.

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 G. Investigators should consider switching to an alternative drug or be alert to the need for dose adjustment.

Plasmapheresis is not permitted at any time during the Screening period or while the subject is receiving study treatment. If a subject who has started screening procedures requires plasmapheresis or is anticipated to require plasmapheresis during or after the screening period, this patient will be considered a screen failure. Subjects requiring plasmapheresis while on study treatment will discontinue study treatment and will enter Long-Term Follow-up for survival. Subjects requiring plasmapheresis must have 2 serum samples (for serum protein electrophoresis [SPEP] and immunofixation) and at least one 24-hour urine sample (for urine protein electrophoresis [UPEP] and immunofixation) obtained prior to the procedure.

6.6.1 REQUIRED/RECOMMENDED CONCOMITANT MEDICATIONS/TREATMENTS

Contraception

Female subjects of childbearing potential must agree to use effective methods of contraception during the study and for 3 months following the last dose of drug. Postmenopausal females (> 45 years old and without menses for > 1 year) and surgically sterilized females are exempt. Male subjects must use an effective barrier method of contraception unless surgically sterile during the study and for 3 months following the last dose if sexually active with a female of childbearing potential.

Nausea

Subjects will be premedicated PRN with a 5-HT_3 inhibitor, such as ondansetron or granisetron, prior to administration of the first dose of oprozomib each day and around the clock during the days of dosing, with additional doses throughout the cycle as needed to prevent and treat nausea. Additional antiemetics may be used if needed.

Shingles

Valacyclovir or an equivalent antiviral is recommended for the duration of treatment to prevent herpes zoster (additional prophylaxis is at the investigator's discretion).

Acid-related Disorders

Lansoprazole or other oral proton-pump inhibitor is required unless a subject has hypersensitivity or intolerance to proton-pump inhibitors for the duration of treatment to prevent peptic disease or other acid related GI toxicities.

Tumor Lysis Syndrome

Monitoring and Prophylaxis Guidelines: Oral hydration of 1.5 to 2 liters per 24 hours should be instituted in all subjects 24 through 48 hours prior to initiation of therapy in every cycle and continued throughout days of oprozomib 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: International Staging System 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. Laboratory abnormalities include increases in serum creatinine > 50% over baseline, 2-fold increases of lactate dehydrogenase (LDH) above the ULN, uric acid increase above the ULN, phosphate > 50% increase about the ULN, potassium > 30% above the ULN, or decreases in serum calcium from baseline. Subjects with such abnormalities should be re-evaluated as clinically indicated, and the medical monitor should be consulted if there are anticipated delays in treatment.

Treatment Guidelines for TLS

If TLS occurs, serial monitoring of cardiac rhythm, hydration status of the subject, and

laboratory assessments should be instituted. Correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and 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 therapeutic abnormalities consistent with TLS.

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

Orthostatic Hypotension

Orthostatic hypotension has been reported in subjects taking oprozomib. The following guidelines should be employed in the management of subjects exhibiting orthostatic hypotension. Etiology should be sought, whether neurogenic, non-neurogenic or iatrogenic. Dose modifications should be taken in accordance with Table 5 and Table 6.

- For those subjects with orthostatic hypotension who are taking antihypertensive medications, the subject's dosage and use of antihypertensive agents should be evaluated and reassessed on an ongoing basis while on study.
- Fluid intake should be assessed to confirm the subject is getting appropriate hydration in accordance with protocol requirements of six to eight, 8-ounce glasses of fluids in the 24 to 48 hours prior to dosing and on all days of oprozomib dosing.
- Fluid status should be repleted to normal levels in subjects with orthostatic hypotension.
- If protocol requirements for oral intake of fluids are already being met, additional measures should be taken to increase blood pressure as per investigator discretion, such as increased oral intake, fludrocortisone (Fluorinef) or midodrine or others depending on the etiology. Holding the dose during toxicity and dose reduction upon resolution may be a consideration (see Table 7).
- Ongoing monitoring of fluid status is warranted and should be managed per investigator discretion.
- In addition, vital signs monitoring may be extended beyond the time periods specified in the Schedules of Assessments (Appendix A, Appendix B, Appendix C, and Appendix D).

6.6.2 ALLOWED CONCOMITANT MEDICATIONS

Subjects may receive RBC or platelet transfusions, if clinically indicated, per institutional guidelines. Subjects who require repeated platelet transfusion support should be discussed with the **Sponsor** medical monitor.

Subjects may receive erythropoietin or darbepoetin therapy, if clinically indicated, per institutional guidelines.

Subjects may receive antiemetics, antidiarrheals, and/or laxatives as necessary.

Colony-stimulating factors (e.g., G-CSF, GM-CSF) may be used if neutropenia occurs but should not be given prophylactically and should be administered only after the DLT assessment period in Phase 1b but anytime during the Phase 2 portion of the study.

Palliative radiation therapy is permitted, if clinically indicated, in consultation with the **Sponsor** medical monitor.

6.6.3 EXCLUDED CONCOMITANT MEDICATIONS

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

Glucocorticoid therapy that exceeds a cumulative dose of 160 mg of dexamethasone is not permitted within 14 days prior to enrollment. During the study, glucocorticoid therapy (in addition to dexamethasone) is permitted only at the discretion of the medical monitor to treat a concurrent medical condition (e.g., asthma, inflammatory bowel disease, or as an antiemetic, etc.).

7. STUDY TESTS AND OBSERVATIONS

The Schedule of Assessments for subjects treated on Days 1 to 5 of a 14-day cycle is provided in Appendix A and Appendix B, and that for subjects treated on Days 1, 2, 8, and 9 of a 14-day cycle is provided in Appendix C and Appendix D.

For subjects with SD or better after at least 12 cycles of therapy who are on a steady dose for ≥ 2 cycles and are tolerating oprozomib, study assessments may be performed every **4** cycles, and **4** cycles of study medication may be dispensed from the study site at a time starting with Cycle 13.

7.1 VITAL SIGNS ASSESSMENTS

Vital sign measurements include orthostatic blood pressure, pulse rate, respiration rate, and temperature. Subjects should lie down for approximately 5 minutes and then have blood

pressure and pulse rate measured consistently in 1 arm or the other. This should be followed by having the subject stand and the blood pressure and pulse rate measurements should be repeated at 1 and 3 minutes. Any drop of 20 mm/Hg systolic 10 mm/Hg diastolic, or lightheadedness/dizziness between supine and standing blood pressure measurements would indicate orthostatic hypotension. Usually an increase in pulse rate of 10 beats/min is also associated with, but not required for, diagnosis of orthostatic hypotension. If the subject has orthostatic hypotension, please see Section 6.6.1.

7.2 CENTRAL ECG ASSESSMENTS

For the Phase 2 portion, assessment of QT/QTc interval will be done via central ECGs on 10 subjects on each schedule.

- 12-lead ECGs will be serially recorded digitally and read centrally
- On Cycle 1, Day 1, 12-lead ECG will be recorded in a supine position after 5−10 minutes of rest at the following time points:
    - Within 15 minutes prior to oprozomib dose
    - 30 minutes after oprozomib dose
    - 1 hour, 2 hours, 4 hours, and 6 hours after oprozomib dose
    - Note that ECG data collection will occur within 5 minutes prior to the corresponding PK time points where appropriate.
- The R to R interval (the interval from the beginning of one R wave to the beginning of the next; [RR]), PR, and the interval from the beginning of the Q wave to the beginning of the T wave (QT) intervals and beginning of the Q wave to the termination of the S wave, representing the time for ventricular depolarization (QRS) duration will be analyzed and QTc will be calculated using standard methods, including Fridericia's formulas.

Note: If 1 schedule does not proceed to Phase 2, central ECGs should be performed on 20 subjects assessed in the chosen schedule.

7.3 NEUROLOGIC ASSESSMENTS

For neurologic assessments, the Brief Peripheral Neuropathy Screen (BPNS), which is included in Appendix J should be performed, and neurologic events should be evaluated according to the NCI-CTCAE grading (Version 4.03).

7.4 PHARMACOKINETIC, PHARMACODYNAMIC, AND PROTEOMIC STUDIES

Pharmacokinetic sampling time points are listed below for each treatment schedule and study phase. See Appendix I for time points, and refer to the Laboratory Manual for collection volumes, processing, and shipping of PK samples. At a minimum, the following PK parameters will be calculated: C_{max}, time to maximum plasma concentration (T_{max}), and AUC.

Pharmacodynamic and proteomic sampling time points are listed below for each treatment schedule and study phase. See Appendix I for time points, and refer to the Laboratory Manual for collection volumes and processing and shipping of PDn and proteomic samples. A fluorogenic substrate assay or enzyme-linked immunosorbent assay (ELISA) will be used to measure proteasome activity in whole blood and peripheral blood mononuclear cells (PBMCs). Global proteomic profiling using mass spectrometry will be conducted on plasma sample and isolated PBMCs taken prior to and after oprozomib administration and analyzed for changes in specific protein levels (e.g., cytokines).

7.4.1 PHASE 1B: PHARMACOKINETIC STUDIES

For the Phase 1b portion, PK samples will be collected at the following time points for both treatment schedules:

Continuous Dosing Subjects:

Cycles 1 and 2, Day 1

- Predose
- 15 minutes postdose
- 30 minutes postdose
- 1 hour postdose
- 2 hours postdose
- 4 hours postdose
- 6 hours postdose
- 8 hours postdose

Cycle 1, Day 2

- Predose

Step-up Dosing Subjects:

Cycles 1 and 2, Day 1

- Predose
- 15 minutes postdose
- 30 minutes postdose
- 1 hour postdose
- 2 hours postdose
- 4 hours postdose
- 6 hours postdose
- 7 hours postdose

Cycles 1 and 2, Day 2

- Predose

Samples must be taken within 5 minutes of intended collection times for 15- and 30-minute and 1- and 2-hour time points and within 15 minutes thereafter. Note: Oprozomib must be taken in the fasted state (at least 2 hours after a meal and fasting for at least 2 hours after dosing) on days in which PK sampling is taken after a dose. On all other days including non-PK days and days in which only a predose PK sample is taken, it is recommended that oprozomib is administered with food (i.e., within approximately 30 minutes after eating). Pharmacokinetic time points are also summarized in Appendix I, and blood volumes are detailed in the Laboratory Manual.

Switching from Oprozomib Tablets to Oprozomib ER Tablets

When subjects switch from Oprozomib Tablets to Oprozomib ER Tablets, intensive PK sampling should be obtained on Day 1 in the cycle prior to switching and on Day 1 of the following cycle (i.e., first day with Oprozomib ER Tablet) at the scheduled time points described above for step-up dosing subjects on Cycle 1, Day 1. The time between the 2 days of PK collection for switching to the Oprozomib ER tablet will be 1 cycle or 14 days.

7.4.2 PHASE 1B: PHARMACODYNAMIC AND PROTEOMIC STUDIES

Blood samples for PDn analyses will be drawn as described above, but no samples for proteomic analyses will be collected. Samples must be taken within 15 minutes of intended collection time points between 4 and 8 hours postdose. Pharmacodynamic and proteomic time points are also summarized in Appendix I, and blood volumes are detailed in the Laboratory Manual.

Continuous Dosing Subjects:

Cycles 1 and 2, Day 1

- Predose
- 4 hours postdose
- 8 hours postdose

Cycle 1, Day 2

- Predose

Step-up Dosing Subjects:

Cycles 1 and 2, Day 1

- Predose
- 4 hours postdose
- 6 hours postdose

Cycles 1 and 2, Day 2

- Predose

7.4.3 PHASE 2: PHARMACOKINETIC STUDIES

For the Phase 2 portion of the study, PK blood samples will be drawn from all subjects from the 5 consecutive day bimonthly and 2 consecutive day weekly schedules at the following time points unless collection is discontinued at the sponsor's discretion:

Cycles 1 and 2, Day 1

- Predose
- 15 minutes postdose
- 30 minutes postdose
- 1 hour postdose
- 2 hours postdose
- 4 hours postdose
- 6 hours postdose
- 7 hours postdose

Cycles 1 and 2, Day 2

- Predose

Samples on Cycle 1, Day 1 and Cycle 2, Day 1 must be taken within 5 minutes of intended collection time for 15-and 30-minute and 1- and 2-hour time points and within 15 minutes thereafter. Note: Oprozomib must be taken in the fasted state (at least 2 hours after a meal and fasting for at least 2 hours after dosing) on days in which PK sampling is taken after a dose. On all other days including non-PK days and days in which only a predose PK sample is taken, it is recommended that oprozomib is administered with food (i.e., within approximately 30 minutes after eating). Pharmacokinetic time points are detailed in Appendix I, and blood volumes are detailed in the Laboratory Manual. Samples may also be used for biomarker assessment.

7.4.4 PHASE 2: PHARMACODYNAMIC AND PROTEOMIC STUDIES

For the Phase 2 portion of the study, PDn and proteomic samples will be collected from all subjects from the 5 consecutive day bimonthly and 2 consecutive day weekly schedules at the following time points unless collection is discontinued at the sponsor's discretion:

Oprozomib Administered Once Daily on the 5 consecutive day bimonthly schedule

Cycles 1 and 2, Day 1

- Predose
- 4 hours postdose

- 6 hours postdose

Cycles 1 and 2, Day 2

- Predose

Oprozomib Administered Once Daily on the 2 consecutive day weekly schedule

Cycles 1 and 2, Day 1

- Predose
- 4 hours postdose
- 6 hours postdose

Cycles 1 and 2, Day 2

- Predose

Samples must be taken within 15 minutes of the intended collection time for 4- and 6-hour time points. Pharmacodynamic and proteomic time points are also summarized in Appendix I and blood volumes are detailed in the Laboratory Manual.

7.4.5 GENOMIC EVALUATIONS

Analysis of genetic and gene expression biomarkers that may potentially predict for response and resistance following treatment with proteasome inhibitors will be conducted on all subjects who consent to optional genomic biomarker analysis. These analyses will be performed on 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, as well as bone marrow aspirate at the time of progression.

The schedule for genomic sampling is outlined in Appendix A for subjects treated on Days 1 to 5 of the 14-day cycle and in Appendix B for subjects treated on Days 1, 2, 8, and 9 of the 14-day cycle.

7.5 LABORATORY EVALUATIONS FOR SAFETY

The schedule for laboratory evaluations for safety is outlined in Appendix A and Appendix B for subjects treated on the Days 1–5 of the 14-day cycle treated and in Appendix C and

Appendix D for subjects treated on Days 1, 2, 8, and 9 of the 14-day cycle. The laboratory tests included in the full chemistry panel are listed in Table 11.

Table 11: 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

Source: Appendix A, Appendix B, Appendix C, and Appendix D.

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; absolute or percentage will be acceptable), RBC count, and platelet count.

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

The pregnancy test can be performed using urine or serum and must be done within 3 days prior to first dose for females of childbearing potential.

7.6 DISEASE RESPONSE ASSESSMENTS

The schedules of disease assessments for subjects treated on either treatment schedule are provided in Appendix E. Beginning with Cycle 3, assessments are to be completed every 4 weeks for the first year while on study drug and then changed to every 8 weeks (4 cycles) after Cycle 26. Subjects enrolled in the Phase 2 portion of the study will be evaluated for disease response following the IMWG-URC; evaluations will also include MR and nCR from EBMT criteria (Appendix F).

Disease response will be assessed by the investigator.

7.7 ASSESSMENTS AT END OF STUDY TREATMENT OR EARLY DISCONTINUATION

Early discontinuation and End-of-Study assessments must be performed any time 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, disease assessments **will no longer be required under protocol Amendment 4**.

8. STUDY TREATMENT DISCONTINUATION

Subjects may discontinue from the study at any time. Subjects who discontinue from study treatment will be monitored for AEs for 30 days after the last dose of oprozomib. In the Phase 1b portion of the study, additional subjects may be enrolled to replace discontinued subjects to reach the target population of MTD-evaluable subjects for each cohort.

For the purposes of estimation of response rate, subjects who discontinue from study treatment before completing a full 14-day cycle (Cycle 1) at the dose or step-up dose to be studied (Cycle 2), do not receive all scheduled doses without a DLT, do not have evaluable disease at Screening, or do not complete a response assessment will be considered unevaluable.

The Sponsor may elect to discontinue the study or either schedule at any time.

The investigator may remove a subject from study treatment for the following reasons:

- Subject with disease progression
- Subject with unacceptable toxicity
- Noncompliance with study procedures
- Need of treatment with medications not allowed by the study protocol
- Subject no longer consents to participate in the study
- Intercurrent illness that interferes with study assessments
- Female subject who becomes pregnant, in which case treatment must be immediately discontinued

The Sponsor 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 and/or stabilize, and according to the investigator's judgment, there is no need for further follow-up. 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.

9. ADVERSE EVENTS

9.1 ADVERSE EVENTS 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 treatment related. In addition to new events, any increase in the severity or frequency of a preexisting condition that occurs after the subject signs a consent form for participation is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction. All reported AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

Laboratory findings should not be recorded as AEs unless corrective action is required (e.g., transfusions, initiation of antibiotics or treatment regimens, hydration) or the event is deemed clinically significant by the treating physician.

Any condition, laboratory abnormality, or physical finding with an onset date prior to the subject signing consent for study participation is considered to be preexisting in nature and part of the subject's medical history.

An unexpected AE is any AE, the specificity or severity of which is not consistent with the current Investigator's Brochure (IB) or prescribing information for a marketed compound; or that adds significant information on specificity or severity of a known, already-documented AE. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected."

Whenever possible, the NCI-CTCAE (Version 4.03) should be used to describe the event and for assessing the severity of AEs (National Cancer Institute 2010). **The National Cancer Institute Common Terminology Criteria for Adverse Events does not use to the term "intermittent" and this term must not be used to describe AEs.** Any AEs representing a change in the NCI-CTCAE grade need to be reported on the AE eCRF. For AEs not adequately addressed in the NCI-CTCAE, the table below (Table 12) may be used.

Table 12: Adverse Event Severity Grades

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 ADL
GRADE 3 - Severe	Medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
GRADE 4 - Life-threatening	Life-threatening consequences; urgent intervention indicated
GRADE 5 - Fatal	Death related to AE

ADL = activities of daily living; AE = adverse event.

9.2 CAUSALITY

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 onset of the AE 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 responds to withdrawal of the study medication (dechallenge) and/or recurs with rechallenge (when clinically feasible); and/or
  - The AE cannot be reasonably attributed to concurrent/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 medication, study or non-study procedure; and/or
  - The time of occurrence of the AE is not reasonably related to administration of study treatment; and/or
  - The event is unlikely to be related to the investigational product(s)

9.3 ADVERSE EVENTS REPORTING PROCEDURES

9.3.1 GENERAL PROCEDURES

All AEs (e.g., any new event or worsening in severity or frequency of a preexisting condition or laboratory finding) with an onset date after the subject signs consent for study participation must be promptly documented on the AE eCRF. Details of the event must include severity, relationship to study drug, duration, action taken, and outcome. Whenever possible, reporting specific diagnosis is preferred rather than individual signs or symptoms. Serious adverse events will be recorded on the AE eCRF *and* on the SAE reporting form (see Section 9.5, Serious Adverse Event Reporting and Documentation Requirements).

All AEs occurring from the time that the subject signs the ICF and through 30 days after the last administered dose of study drug will be reported, regardless of whether new chemotherapy regimens are initiated. In addition, the investigator should report any AE that may occur after this time period that is believed to have a reasonable possibility of being associated with study drug. If a subject discontinues the study prior to receiving any study drug, AEs must be

captured until it is documented that the subject fails to enroll in the study.

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. Adverse events that completely resolve and then recur should be recorded as new AEs. For subjects who complete the End-of-Study Assessment less than 30 days following their last dose of protocol-defined therapy, 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 drug 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 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 FDA Form 1572.

9.3.2 DISEASE PROGRESSION

Signs and symptoms associated with disease progression will be reported as SAEs if the sign or symptom meets the seriousness criteria (e.g., death, hospitalization). Signs and symptoms clearly associated with disease progression will be reported as AEs only if the event is judged by the investigator to be atypical or accelerated or if the investigator considers the sign or symptom to be caused by the study drug. If there is any uncertainty regarding causality, the event should be recorded in the eCRF as an AE.

All deaths that occur from the time that ICF is signed until 30 days after the last dose of study drug is administered are to be reported as SAEs (see Section 9.4). **Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, metastatic, pancreatic cancer). Note: The term "disease progression" should not be used to describe the disease related event or adverse event.** Additional details of the event (such as the primary and contributory causes of death) should be reported on the Death eCRF.

Discontinuation of treatment due to either disease progression or deterioration of myeloma malignancy should be recorded on the Treatment Discontinuation eCRF as "Disease Progression."

9.4 SERIOUS ADVERSE EVENTS DEFINITIONS

An SAE is an event 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 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 any nonacute, unrelated cause such as an elective surgery)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in the offspring of an exposed subject
- Is an important medical event that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it jeopardizes the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

9.5 SERIOUS ADVERSE EVENT REPORTING AND DOCUMENTATION REQUIREMENTS

Amgen Global Patient Safety must be notified within 24 hours of the investigator, designee, or site personnel knowledge of the event. To report an SAE to **Amgen Global Patient** Safety, please refer to the SAE reporting guidelines **below**.

The primary mechanism for reporting serious adverse events will be the electronic data capture system (EDC) via the Safety Report Form. If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an electronic Serious Adverse Contintency Report Form (see Appendix K) within 24 hours of the investigator's knowledge of the event. The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the EDC system will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken offline, then the site can report this information on a paper Serious Adverse Event Report Form (see Appendix K).

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

New or updated information will be recorded in the originally completed Event CRF.

The investigator will submit any updated serious adverse even data to Amgen Global Patient Safety within 24 hours of receipt of the information.

The investigator is responsible for notifying the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) in accordance with local regulations, of all SAEs. The sponsor may request additional source documentation pertaining to the SAE. If a subject is permanently discontinued from the study because of an SAE, this information must be included in the initial or follow-up SAE report form as well as the Study Discontinuation eCRF.

All SAEs occurring from the time that the subject signs consent for study participation and through 30 days after the last administered dose of study drug will be reported, regardless of whether new chemotherapy regimens are initiated (see Section 9.2 for additional information). All SAEs, regardless of relationship to study drug, must be followed to resolution or to stabilization if improvement or resolution is not expected.

9.6 PREGNANCY

If a subject or **spouse or** partner of a subject becomes pregnant during treatment or up to 30 days following administration **of study treatment**, **Amgen Global Patient Safety and** the **medical monitor must be notified** within 24 hours of **the investigator, designee, or site personnel** learning of the pregnancy. **On notification to Amgen, the investigator must obtain a separate information release and authorization form for the use and disclosure of health information of the pregnant spouse or partner of a patient. If the patient becomes pregnant while taking oprozomib, oprozomib must be immediately discontinued. Patients,**

spouses, or partners will be followed through the outcome of the pregnancy. The investigator will be required to complete an Amgen Pregnancy Notification Worksheet and report the information as specified below. To report a pregnancy to Amgen Global Patient Safety, please refer to the pregnancy reporting guidelines below.

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- **Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 30 days after stopping oprozomib.**
- **Information will be recorded on the Pregnancy Notification Worksheet (Appendix L). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws.**
- **After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 30 days after stopping oprozomib. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).**
- **Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.**
- **While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.**
- **If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.**
- **Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator will be reported to Amgen Global Patient Safety as described in Section 9.5. While the**

investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.

- **Any female subject who becomes pregnant while participating will discontinue study treatment.**

Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- **In the event a male subject fathers a child during treatment, and for an additional 90 days after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Worksheet (Appendix L). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws.**
- **The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.**
- **After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.**
- **Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).**
- **Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.**

<u>Collection of Lactation Information</u>

- **Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 30 days after stopping oprozomib.**
- **Information will be recorded on the Lactation Notification Worksheet (Appendix M) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.**
- **Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 16.**
- **With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 30 days after discontinuing protocol-required therapies.**

10. STATISTICAL CONSIDERATIONS

This section describes the statistical analysis that will be employed for assessing each of the safety and efficacy endpoints considered in the study. Specifics of the analyses will be provided in the Statistical Analysis Plan (SAP). Any other changes made to the planned analyses after the protocol and SAP have been finalized, along with an explanation as to when and why they occurred, will be described in the clinical study report, in which any post hoc exploratory analyses also will be clearly identified.

10.1 STUDY ENDPOINTS

Primary Endpoints

Phase 1b

- Dose-limiting toxicities identified to determine the MTD and RP2D, defined as the highest dose at which < 33% of subjects experience DLTs after 1 cycle (14 days Cycle 1 for continuous dosing and Cycle 2 for step-up dosing) of treatment.
- Safety and tolerability

Phase 2

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

Secondary Endpoints

Phase 1b/2

- Pharmacokinetics of Oprozomib Tablets and Oprozomib ER Tablets

Phase 2

- Clinical benefit response status, to determine whether a subject has a best response of sCR, CR, VGPR, or PR, as defined by IMWG-URC, and MR or nCR per EBMT criteria (Appendix H)
- 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
- Progression-free survival, defined as the time from the start of treatment to disease

progression or death due to any cause

- Time to progression, defined as the time from first dose to disease progression
- Time to response, defined as time from the start of study treatment until the start of the first confirmed response (PR or better).

Exploratory Endpoints

Phase 1b/2

- Pharmacodynamics and proteomic biomarkers
- Genomic biomarkers that may potentially predict for response and resistance following treatment with proteasome inhibitors

10.2 SAMPLE SIZE CONSIDERATIONS

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

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

$$H_0: \ ORR_{Cd} \leq 15\% \quad H_A: \ ORR_{Cd} > 15\%$$

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

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

10.3 STATISTICAL ANALYSIS

10.3.1 ANALYSIS POPULATIONS

All subjects who receive at least 1 dose of study treatment will be considered evaluable for both the efficacy and safety analyses (Safety Population). Additional efficacy analyses will be performed using the Response-evaluable Population, defined as subjects who are included in the safety evaluable population and have a baseline disease assessment and at least 1 postbaseline disease assessment, or who dropped out due to AE prior to first postbaseline disease assessment.

10.3.2 EFFICACY ANALYSIS

An estimate of the ORR and its 1-sided 95% exact binomial confidence interval for the recommended Phase 2 dose group(s) will be determined. Additionally, the ORR and CBR along with the associated 2-sided 95% exact binomial confidence intervals will be determined for each dose cohort (within each schedule), including the recommended Phase 2 dose group (dose-escalation cohort + Phase 2 cohort). Responses will be defined using the IMWG-URC for sCR, CR, VGPR, or PR, and the EBMT for MR and nCR.

Analysis for time-to-events endpoints (PFS, DOR, and TTP) will be performed using the Kaplan-Meier method. Medians and other quartiles for each time-to-event endpoints will be estimated with the corresponding 2-sided 95% confidence intervals.

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

Table 13: Date of Progression or Censoring for Duration of Response and Progression Free Survival

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

PD = progressive disease.

The mean, standard deviation, median, minimum, and maximum will be calculated for time to response (TTR).

10.3.3 SAFETY ANALYSIS

Safety and tolerability assessments will include extent of exposure to study treatment, AEs (including the DLT assessment period DLTs and SAEs), laboratory values, vital sign results, and ECGs. Safety data will be examined on an ongoing basis to ensure subject safety.

Extent of exposure to the study treatment will be summarized using descriptive statistics (n, mean, standard deviation, median, and range). Percent of subjects and number of cycles with dose holds and reductions will be calculated by treatment group.

Adverse events will be coded using MedDRA. Treatment-emergent AEs are defined as AEs occurring from the first dose of study treatment through 30 days after the last dose of study treatment. An AE that is present before the first administration of study treatment and subsequently worsens in severity between the first dose of study treatment and 30 days after the last dose of study treatment is also considered to be treatment emergent. Adverse events will be summarized by MedDRA system organ class and preferred term for the number and percentage of subjects who experienced the event. A subject reporting the same AE more than once will be counted only once when calculating (1) within a given system organ class and (2) within a given system organ class and preferred term combination. For such cases, the

maximum NCI-CTCAE toxicity grade and strongest causal relationship to study treatment for the event will be used in the incidence calculations. Treatment-emergent AEs will be tabulated to examine their frequency, severity, and relationship to study treatment. Additional summaries will be provided for SAEs and events resulting in the permanent discontinuation of treatment. All AEs will also be included in individual subject listings.

A listing of subjects who experience a DLT during the DLT assessment period of the dose- escalation portion will be generated along with the results associated with the PK/PDn parameters considered.

Laboratory parameters will be summarized using descriptive statistics and by postdose shifts relative to baseline. Vital sign results will also be summarized descriptively for each scheduled protocol time point. Changes will be calculated relative to the values collected at baseline, defined as the last assessment taken prior to the first dose of study drug on Day 1 of Cycle 1.

The analysis of the locally performed ECGs will involve descriptive statistics.

10.4 PHARMACOKINETIC, PHARMACODYNAMIC, AND PROTEOMIC ANALYSES

10.4.1 PHARMACOKINETIC ANALYSES

Blood samples will be collected to measure plasma concentration of oprozomib and potential metabolite(s), as detailed in Section 7.2 and Appendix I.

The following PK parameter estimates will be determined when possible for Oprozomib Tablets and Oprozomib ER Tablets and/or metabolite(s):

- C_{max} (observed)
- T_{max} (observed)
- Area under the curve at the last measurable time point ($AUC_{0-\tau}$)
- Area under the curve extrapolated to infinity (AUC_{0-inf})

Unless otherwise specified, the PK parameters will be estimated based on noncompartmental methods. These estimates will be summarized descriptively by dose cohort and formulation. Dose proportionality across dose levels will be analyzed. Exploratory analyses may be performed to evaluate the relationship between the estimated PK parameters and selected safety,

biomarker, or clinical effect endpoints. Individual plasma PK samples may also be used to assess the changes in endogenous markers of hepatic CYP3A activity upon oprozomib dosing.

10.4.2 PHARMACODYNAMIC AND PROTEOMIC ANALYSES

Blood samples will be collected for PDn and proteomic analyses from subjects in all portions of the study as detailed in Section 7.2 and Appendix I.

The extent of inactivation of proteasome activity after oprozomib dosing in RBCs and PBMCs will be monitored as a PDn parameter. Proteasome activity will be measured in RBCs and PBMCs isolated from the blood samples. A fluorogenic substrate assay will be used to measure proteasome activity in samples, and a site-specific ELISA that quantitates drug binding to the active sites of the proteasome may also be performed to further characterize target binding. The extent of proteasome inactivation will be determined by comparing the activity of the postdose oprozomib samples with the samples taken before dosing. Exploratory analyses may be performed to evaluate the relationship between the RBC or PBMC PDn and selected safety, biomarker, PK, or clinical effect endpoints.

In the Phase 2 portion, blood samples for PDn and proteomics will be taken prior to and after oprozomib administration. The plasma samples and the PBMCs will be analyzed for changes in specific protein levels. The plasma samples for proteomics will be drawn and processed in the same manner as the PK samples.

10.4.3 GENOMIC ANALYSES

Whole genome sequencing (WGS), whole exome sequencing (WES), and 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 isolated from PBMCs) to distinguish germ line mutations from somatic mutations in tumor cell samples. Data will be analyzed to examine 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 cells (NF-κB) transcription factors, as well as genes involved in immunoglobulin production and plasma cell protein homeostasis. Immunoglobulin levels in tumor cells will be quantified by ELISA or other protein

quantification methods. These data will also be used to derive new hypotheses about mechanisms of drug response, resistance, and safety.

11. INVESTIGATIONAL PRODUCT

11.1 OPROZOMIB DRUG PRODUCT

11.1.1 DESCRIPTION

Oprozomib is a synthetic small molecule peptide bearing the chemical name N-((S)-3-methoxy-1-((S)-3-methoxy-1-((S)-1-((R)-2-methyloxiran-2-yl)-1-oxo-3-phenylpropan-2-ylamino)-1-oxopropan-2-ylamino)-1-oxopropan-2-yl)-2-methylthiazole-5-carboxamide. The molecular formula is $C_{25}H_{32}N_4O_7S$ and the molecular weight is 532.61. 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.

11.1.2 FORMULATION

Oprozomib will be provided as a tablet containing 60, 90, or 120 mg of oprozomib drug substance for oral administration, or as an extended release (ER) tablet containing 150, 180, 210, 240, or 270 mg of oprozomib. Both Oprozomib Tablets and Oprozomib ER Tablets are intended to release greater than or equal to 75% (quantity) of the total dose of oprozomib over approximately 8 hours.

Oprozomib Tablets are white to off-white, film-coated, round, biconvex tablets 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 are debossed with “5” on one side and contain 120 mg of oprozomib.

Oprozomib ER Tablets are white to off-white, oval-shaped tablets manufactured at 5 dosage strengths:

- Oprozomib 150 mg ER Tablets are debossed with "H" on one side and contain 150 mg of oprozomib
- Oprozomib 180 mg ER Tablets are debossed with "I" on one side and contain 180 mg of oprozomib
- Oprozomib 210 mg ER Tablets are debossed with "J" on one side and contain 210 mg of oprozomib
- Oprozomib 240 mg ER Tablets are debossed with "K" on one side and contain 240 mg of oprozomib
- Oprozomib 270 mg ER 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 8 dosage strengths.

No changes in drug product, dosage, or treatment regimen occurred in this protocol amendment from the previous version.

11.1.3 HOW SUPPLIED

Oprozomib Tablets will be supplied containing 60, 90, or 120 mg of oprozomib. Oprozomib ER Tablets will be supplied containing 150, 180, 210, 240, and 270 mg of oprozomib. Details may be found in the Pharmacy Manual.

11.1.4 STORAGE CONDITIONS

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.

11.2 ACCOUNTABILITY

The Sponsor 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 **the Sponsor** 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.

11.3 DEXAMETHASONE DRUG PRODUCT

11.3.1 DESCRIPTION

Dexamethasone, a synthetic adrenocortical steroid, is a white to practically white, odorless, crystalline powder (Roxanne Laboratories, Inc. 2007).

11.3.2 HOW SUPPLIED

Dexamethasone is a commercially available drug, available both as tablets for oral administration and as various sterile formulations for parenteral administration (Roxanne Laboratories, Inc. 2007).

11.3.3 STORAGE CONDITIONS

Dexamethasone is to be stored at controlled room temperature 20°C to 25°C (68°F to 77°F). Consult the package insert of the respective product for additional storage and usage instructions (Roxanne Laboratories, Inc. 2007).

11.3.4 ACCOUNTABILITY

Sites will be required to record and document subject compliance regarding dexamethasone dosing.

12. REGULATORY OBLIGATIONS

12.1 INFORMED CONSENT

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 ICF. Local and/or institutional requirements may require disclosure of additional information in the ICF. Any changes to the ICF must be submitted to the sponsor or its designated representative for approval, prior to submission to the IRB/IEC. The IRB/IEC will review the ICF for approval. A copy of the approved form must be submitted to the sponsor or its designated representative prior to initiation of the study.

Before any study procedure is implemented, informed consent shall be documented by the use of a written ICF 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 ICF will be given to the subject or subject's legally authorized representative. The original signed ICF must be maintained by the investigator and available for inspection by Onyx, its designated representative, or regulatory authority at any time.

12.2 COMPLIANCE WITH LAWS AND REGULATIONS

The study will be conducted in accordance with FDA and International **Council for** Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, any applicable local health authority, and IRB or IEC requirements.

This study must have the approval of a properly constituted IRB/IEC. Before the investigational drug is shipped to the investigator, the investigator or designee will provide **the**

Sponsor with a copy of the IRB/IEC approval letter stating that the study protocol and any subsequent amendments and ICFs have been reviewed and approved.

The investigator or designee will be responsible for obtaining annual IRB/IEC approval throughout the duration of the study. Copies of the investigator's annual report to the IRB/IEC and copies of the IRB/IEC continuance of approval must be submitted to **the Sponsor** or designee.

The investigator is also responsible for notifying his or her IRB/IEC of any significant AEs that are serious and/or unexpected.

The Sponsor or its designated representatives will provide study sites with any Investigational New Drug (IND) safety reports generated, changes to the Investigator's Brochure, and any safety updates. The investigator is responsible for immediately notifying their IRB/IEC of any such updates.

The Sponsor will initiate in writing any substantive changes to this protocol as a protocol amendment. The amendment will be submitted to the IRB/IEC, together with a revised ICF, if applicable. Written documentation of IRB/IEC approval must be received before the amendment is implemented. On completion of the study, the investigator must provide the IRB/IEC with a summary of the study's outcome.

12.3 SUBJECT CONFIDENTIALITY

Subject medical information obtained as part of this study is confidential and must not be disclosed to third parties, except as noted below. The subject may request in writing that medical information be given to his/her personal physician.

The investigator/institution will permit direct access to source data and documents for Onyx, its designee, the FDA, and other applicable regulatory authorities. The access may consist of study-related monitoring, audits, IRB/IEC reviews, and FDA/regulatory authority inspections.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 Code of Federal Regulations (CFR) 164.508,

and, if and to the extent applicable, the principles set out in Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, and national legislation with regard to data privacy.

13. ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 PROTOCOL AMENDMENTS AND STUDY TERMINATION

All protocol amendments will be implemented by Onyx and must receive IRB/IEC approval before implementation, except where necessary to eliminate an immediate hazard to subjects. The investigator or designee must send a copy of the approval letter from the IRB/IEC, along with the revised ICF, to Onyx or its designated representatives.

Both Onyx and the investigator reserve the right to terminate the study according to the study contract. The investigator or designee should notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Onyx or it designated representatives.

13.2 STUDY DOCUMENTATION AND ARCHIVES

13.2.1 SOURCE DOCUMENTS

Source records are original documents, data, and records (e.g., medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical study. The investigator will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical study. Source records must be adequate to reconstruct all data transcribed onto the eCRFs.

13.2.2 CASE REPORT FORM COMPLETION

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 aspart of the case histories. These source documents may include subject diaries, laboratory reports, etc. Onyx will supply the eCRF, which will be completed in English.

The investigators 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; however, they can authorize subinvestigators listed on the FDA Form 1572 to sign/approve the data. More detailed instructions may be found in the Study Reference Manual.

13.2.3 ARCHIVAL OF RECORDS

According to 21 CFR 312.62(c), the investigators shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such indication, the investigator shall retain these records until 2 years after the investigation is discontinued and the FDA or applicable regulatory authorities are notified.

The investigator must retain protocols, amendments, IRB approvals, copies of the FDA Form 1572, signed and dated ICFs, medical records, eCRFs, drug accountability records, all correspondence, and any other documents pertaining to the conduct of the study.

13.3 STUDY MONITORING AND DATA COLLECTION

Following prequalification and initiation of the study site, periodic monitoring visits will be made by **the Sponsor**and/or its designated representative. The investigator must provide sufficient space and allocate sufficient time for the monitor to inspect subject source records, eCRFs, drug accountability records, and regulatory documents.

The purpose of clinical study monitoring is to verify the following:

- The rights and well-being of human subjects are protected
- The reported data are accurate, complete, and verifiable from source documents
- The conduct of the study is in compliance with the currently approved protocol, amendment(s), ICH GCPs, FDA CFR, and any other applicable regulatory requirements
- The monitor shall submit a written report to Onyx after each study site visit or study- related communication. Reports shall include a summary of what the monitor reviewed and significant findings, deviations and deficiencies, conclusions, and actions taken or to be taken to ensure site compliance.

The investigator must also permit study-related audits, IRB/IEC review, and regulatory inspections providing direct access to data and source documents pertaining to this study if so requested.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Routine study site monitoring
- eCRF review against source documents
- Data management quality control checks
- Sponsor medical review

The sponsor or its designee will be responsible for the design and distribution of the eCRFs and for data management. **The sponsor** or its designee will be responsible for the monitoring of the eCRFs. The clinical research organization, and/or **the Sponsor** and/or its designee will generate queries in the event of incomplete or inconsistent data to be reconciled by the study site.

14. REFERENCES

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Appendix A SCHEDULE OF STUDY ASSESSMENTS: SUBJECTS TREATED ON THE 5 CONSECUTIVE DAY BIMONTHLY SCHEDULE (DAYS 1 TO 5 OF EACH 14-DAY TREATMENT CYCLE), PHASE 1B

5/14 Phase 1b, Continuous Dosing Subjects

Visit	Screening D -14 to -1	Cycle 1 D 1	Cycle 1 D 2	Cycle 1 D 3, 4	Cycle 1 D 5	Cycle 2 D 1	Cycle 2 D 2	Cycle 2 D 5	Cycle 3+[r] D 1	End of Study/ Early Discontinuation[s]
Medical History	X									
Previous Treatment History	X									
Targeted Physical Examination[a]	X	X				X			X	X
Height	X									
Weight	X	X				X			X	X
Neurological Assessment (BPNS and CTCAE grading)	X								X[b]	X
Vital Signs[c]	X	X	X	X	X	X	X	X	X[d]	X
12–lead ECG (Local)[e]	X	X			X	X			X	X
Urinalysis[f]	X									X
Serum Chemistry[g]	X	X	X		X	X	X	X	X	X
CBC with Diff and Platelets[h]	X	X	X		X	X	X	X	X	X
Coagulation Tests	X									
Pregnancy Test[i]	X									
Blood for PK[j,k]		X	X			X				
Blood for PDn Assay[l]		X	X			X				
Administer Antiemetics[m]		X	X	X	X	X	X	X	X	
Oprozomib Dosing[n,o]		X	X	X	X	X	X	X	X	
Dexamethasone Dosing[p]		X	X			X	X		X	
AEs and Concomitant Medications[q]	←									→

Footnotes to Appendix A, 5/14 Phase 1b, Continuous Dosing Subjects

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BPNS = Brief Peripheral Neuropathy Screen; CBC = complete blood count; CRF = case report form; CTCAE = Common Terminology Criteria for Adverse Events; CrCL = creatinine clearance; Diff = differential; ECG = electrocardiogram; EOS = End of Study; PDn = pharmacodynamics; PK = pharmacokinetics.

[a] A physical examination can be performed every 4 cycles after subjects have been on study for more than 2 months**, if clinically indicated** (i.e., starting at Cycle 5, Day 1, then at Cycle 9, Day 1, etc.). The screening exam may be used for Cycle 1, Day 1 if obtained within 7 days of Cycle 1, Day 1.

[b] Neurological assessments (BPNS and CTCAE grading) will be performed at Screening, every 4 cycles starting from Cycle 5, Day 1, and at EOS. **Patients on active treatment under Amendment 4 will have this assessment performed only if clinically indicated and at EOS.**

[c] Measure blood pressure, pulse rate, orthostatic blood pressure and pulse rate, respiration rate, and temperature within 1 hour prior to dose and at 30 ± 5 min, 1 hour (± 15 min), and 2 hours (± 15 min) after each dose (Cycle 1, Days 1–5; and Cycle 2, Days 1, 2, and 5). Measure once at Screening and at EOS. Subjects should lie down for 5 minutes and then and have blood pressure and pulse measured. This should be followed by having the subject stand and the blood pressure and pulse should be repeated at 1 and 3 minutes. Any drop of 20 mm/Hg systolic, 10 mm/Hg diastolic or lightheadedness/dizziness would indicate orthostatic hypotension (usually an increase in pulse rate of 10 beats/min is associated but not required). At the investigator's medical discretion, vital signs monitoring may be extended beyond the time periods specified above. **Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated.**

[d] During Cycles 3 and higher, respiration rate, temperature, orthostatic blood pressure and pulse rate are required within 1 hour prior to first dose and within 30−60 minutes after first dose administration. Subjects should lie down for 5 minutes and then and have blood pressure and pulse measured. This should be followed by having the subject stand and the blood pressure and pulse should be repeated at 1 and 3 minutes. **Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated and at EOS.**

[e] Perform local ECGs at Screening, within 6 hours postdose on specified days with oprozomib dosing, and at EOS. Starting from Cycle 5, ECGs will be performed on Day 1 of every fourth cycle (i.e., starting at Cycle 5, Day 1, then at Cycle 9, Day 1, etc.).

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

[g] 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 at Screening, within 4 hours prior to dosing on specified days**. Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated** and at EOS. Calculate CrCL. Screening results may be used for Cycle 1, Day 1 if obtained within 72 hours of Cycle 1, Day 1.

[h] Hemoglobin, hematocrit, WBC count with differential (total neutrophils, lymphocytes, monocytes, eosinophils, basophils, absolute or percentage will be acceptable), RBC count, and platelet count. **Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated and at EOS.**

[i] A serum or urine pregnancy test is to be done within 3 days prior to first dose in females of childbearing potential only.

[j] Blood sampling for PK for continuous dosing subjects in the Phase 1b portion: Blood samples to measure oprozomib and its metabolite(s) will be collected on Cycle 1, Days 1 and 2 and Cycle 2, Day 1 for subjects given oprozomib at a single dose level. Samples on Cycles 1 and 2, Day 1 must be taken within 5 minutes of intended collection times for 15- and 30-minute and 1- and 2-hour time points and within 15 minutes for 4-, 6-, and 8-hour time points. Oprozomib must be taken in the fasted state (at least 2 hours after a meal and fasting for at least 2 hours after dosing) on days in which PK sampling is taken after a dose. On all other days including non-PK days and days in which only a predose PK sample is taken, it is recommended that oprozomib is administered with food (i.e., within approximately 30 minutes after eating). Sampling times and volumes are provided in the Laboratory Manual.

[k] When subjects switch from Oprozomib Tablets to Oprozomib ER Tablets, intensive PK sampling should be obtained on Day 1 in the cycle prior to switching and on Day 1 of the following cycle (i.e., first day with Oprozomib ER Tablet) at the scheduled time points described for the step-up dosing subjects in Phase 1b.

Footnotes to Appendix A, 5/14 Phase 1b, Continuous Dosing Subjects

[l] Blood sampling for PDn for continuous dosing subjects in the Phase 1b portion: Blood samples for determination of proteasome inhibition by oprozomib will be drawn on Cycle 1, Days 1 and 2 and Cycle 2, Day 1 for subjects given oprozomib at a single dose level. Samples must be taken within 15 minutes of intended collection time for all postdose time points. Sampling times and volumes are provided in the Laboratory Manual. Subjects may be premedicated PRN with a 5-HT3 inhibitor, such as ondansetron or granisetron, before administration of the first dose of oprozomib each day and throughout the day as needed.

[m] Subjects will be premedicated PRN with a 5-HT3 inhibitor, such as ondansetron or granisetron, before administration of the first dose of oprozomib each day and throughout the day as needed.

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

[o] Subjects on the 5 consecutive day bimonthly schedule will be provided with oprozomib dose for Days 1–5 of the 14-day cycle.

[p] Subjects will receive 20 mg of dexamethasone on Days 1, 2, 8, and 9 of each 14-day treatment cycle. Dexamethasone must be taken at least 30 minutes prior to oprozomib.

[q] 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 and continue 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.

[r] For patients with ≥ SD for at least 6 months (12 cycles), who are on a steady dose for ≥ 2 cycles, and are tolerating oprozomib, study assessments may be reduced to every **4** cycles (starting at Cycle 13, Day 1, then Cycle 15, Day 1, etc.) and **4** cycles of study medication can be provided at clinic visits. Subjects who do not meet these criteria should continue to have study assessments performed at every cycle.

[s] All 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.

5/14 Phase 1b, Step-up Dosing Subjects

Visit	Screening D -14 to -1	Cycle 1 D 1	Cycle 1 D 2	Cycle 1 D 3,4	Cycle 1 D 5	Cycle 2 D 1	Cycle 2 D 2	Cycle 2 D 5	Cycle 3+[r] D 1	End of Study/ Early Discontinuation[s]
Medical History	X									
Previous Treatment History	X									
Targeted Physical Examination[a]	X	X				X			X	X
Height	X									
Weight	X	X				X			X	X
Neurological Assessment (BPNS and CTCAE grading)	X								X[b]	X
Vital Signs[c]	X	X	X	X	X	X	X	X	X[d]	X
12–lead ECG (Local)[e]	X	X			X	X			X	X
Urinalysis[f]	X									X
Serum Chemistry[g]	X	X	X		X	X	X	X	X	X
CBC with Diff and Platelets[h]	X	X	X		X	X	X	X	X	X
Coagulation Tests	X									
Pregnancy Test[i]	X									
Blood for PK[j,k]		X	X			X	X			
Blood for PDn Assay and Proteomic Analyses[l]		X	X			X	X			
Administer Antiemetics[m]		X	X	X	X	X	X	X	X	
Oprozomib Dosing[n,o]		X	X	X	X	X	X	X	X	
Dexamethasone Dosing[p]		X	X			X	X		X	
AEs and Concomitant Medications[q]	←									→

Footnotes to Appendix A, 5/14 Phase 1b, Step-up Dosing Subjects

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BPNS = Brief Peripheral Neuropathy Screen; CBC = complete blood count; CRF = case report form; CTCAE = Common Terminology Criteria for Adverse Events; CrCL = creatinine clearance; ECG = electrocardiogram; Diff = differential; EOS = End of Study; PDn = pharmacodynamics; PK = pharmacokinetics.

[a] A physical examination may be performed every 4 cycles after subjects have been on study for more than 2 months **if clinically indicated**. (i.e., starting at Cycle 5, Day 1, then at Cycle 9, Day 1, etc.). The screening exam may be used for Cycle 1, Day 1 if obtained within 7 days of Cycle 1, Day 1.

[b] Neurological assessments (BPNS and CTCAE grading) will be performed at Screening, every 4 cycles starting from Cycle 5, Day 1, and at EOS. **Patients on active treatment under Amendment 4 will have this assessment performed only if clinically indicated and at EOS.**

[c] Measure blood pressure, pulse rate, orthostatic blood pressure and pulse rate, respiration rate, and temperature within 1 hour prior to dose and at 30 ± 5 min, 1 hour (± 15 min), and 2 hours (± 15 min) after each dose (Cycle 1, Days 1–5; and Cycle 2, Days 1, 2, and 5). Measure once at Screening and at EOS. Subjects should lie down for 5 minutes and then and have blood pressure and pulse measured. This should be followed by having the subject stand, and the blood pressure and pulse should be repeated at 1 and 3 minutes. Any drop of 20 mm/Hg systolic, 10 mm/Hg diastolic or lightheadedness/dizziness would indicate orthostatic hypotension (usually an increase in pulse rate of 10 beats/min is associated, but it is not required). At the investigator's medical discretion, vital signs monitoring may be extended beyond the time periods specified above. **Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated.**

[d] During Cycles 3 and higher, respiration rate, temperature, orthostatic blood pressure and pulse rate are required within 1 hour prior to first dose and within 30−60 minutes after first dose administration. Subjects should lie down for 5 minutes and then and have blood pressure and pulse measured. This should be followed by having the subject stand and the blood pressure and pulse should be repeated at 1 and 3 minutes. **Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated and at EOS.**

[e] Perform local ECGs at Screening, within 6 hourspostdose on specified days with oprozomib dosing, and at EOS. Starting from Cycle 5, ECGs will be performed on Day 1 of every fourth cycle (i.e., starting at Cycle 5, Day 1, then at Cycle 9, Day 1, etc.). **Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated and at EOS.**

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

[g] 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 at Screening, within 4 hours prior to dosing on specified days**. Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated** and at EOS. Calculate CrCL. Screening results may be used for Cycle 1, Day 1 if obtained within 72 hours of Cycle 1, Day 1.

[h] Hemoglobin, hematocrit, WBC count with differential (total neutrophils, lymphocytes, monocytes, eosinophils, basophils, absolute or percentage will be acceptable), RBC count, and platelet count**. Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated and at EOS.**

[i] A serum or urine pregnancy test is to be done within 3 days prior to first dose in females of childbearing potential only.

[j] Blood sampling for PK for step-up dosing subjects in the Phase 1b portion: Blood samples to measure oprozomib and its metabolite(s) will be collected on Cycle 1, Days 1 and 2 and Cycle 2, Days 1 and 2 for subjects given oprozomib using step-up dosing. Samples on Cycles 1 and 2, Day 1 must be taken within 5 minutes of intended collection times for 15- and 30-minute and 1- and 2-hour time points and within 15 minutes for 4-, 6-, and 7-hour time points. Oprozomib must be taken in the fasted state (at least 2 hours after a meal and fasting for at least 2 hours after dosing) on days in which PK sampling is taken after a dose. On all other days, including non-PK days and days in which only a predose PK sample is taken, it is recommended that oprozomib is administered with food (i.e., within approximately 30 minutes after eating). Sampling times and volumes are provided in the Laboratory Manual.

[k] When subjects switch from Oprozomib Tablets to Oprozomib ER Tabletsintensive PK sampling should be obtained on Day 1 in the cycle prior to switching and on Day 1 of the following cycle (i.e., first day with Oprozomib ER Tablet) at the scheduled time points described for the step-up dosing subjects in Phase 1b.

[1] Blood sampling for PDn for step-up dosing subjects in the Phase 1b portion: Blood samples for determination of proteasome inhibition by oprozomib will be drawn on Cycle 1, Days 1 and 2 and Cycle 2, Days 1 and 2 for subjects given oprozomib using step-up dosing. Samples must be taken within 15 minutes of the intended collection time for all postdose time points. Sampling times and volumes are provided in the Laboratory Manual.

Footnotes to Appendix A, 5/14 Phase 1b, Step-up Dosing Subjects

[m] Subjects will be premedicated PRN with a 5-HT3 inhibitor, such as ondansetron or granisetron, before administration of the first dose of oprozomib each day and throughout the day as needed.

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

[o] Subjects on the 5-consecutive-days bimonthly schedule will be provided with oprozomib dose for Days 1–5 of 14-day cycle.

[p] Subjects will receive 20 mg of dexamethasone on Days 1, 2, 8, and 9 of each 14-day treatment cycle. Dexamethasone must be taken at least 30 minutes prior to oprozomib.

[q] 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 and continue 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.

[r] For patients with ≥ SD for at least 6 months (12 cycles), who are on a steady dose for ≥ 2 cycles, and are tolerating oprozomib, study assessments may be reduced to every **4** cycles (starting at Cycle 13, Day 1, then Cycle 15, Day 1, etc.) and **4** cycles of study medication can be provided at clinic visits. Subjects who do not meet these criteria should continue to have study assessments performed at every cycle.

[s] All 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.

Appendix B SCHEDULE OF STUDY ASSESSMENTS: SUBJECTS TREATED ON THE 5 CONSECUTIVE DAY BIMONTHLY SCHEDULE (DAYS 1-5 OF EACH 14-DAY TREATMENT CYCLE), PHASE 2

5/14 Phase 2

Visit	Screening D -14 to -1	Cycle 1 D 1	Cycle 1 D 2	Cycle 1 D 3,4	Cycle 1 D 5	Cycle 2 D 1	Cycle 2 D 2	Cycle 2 D 5	Cycle 3+[r] D 1	End of Study/ Early Discontinuation[s]
Medical History	X									
Previous Treatment History	X									
Targeted Physical Examination[a]	X	X				X			X	X
Height	X									
Weight	X	X				X			X	X
Neurological Assessment (BPNS and CTCAE grading)	X								X[b]	X
Vital Signs[c]	X	X	X	X	X	X	X	X	X[d]	X
12–lead ECG (Local)[e]	X	X			X	X			X	X
ECG Central Lab[f]		X								
Urinalysis[g]	X									X
Serum Chemistry[h]	X	X	X		X	X	X	X	X	X
CBC with Diff and Platelets[i]	X	X	X		X	X	X	X	X	X
Coagulation Tests	X									
Pregnancy Test[j]	X									
Blood for PK[k]		X	X			X	X			
Blood for PDn Assay and Proteomic Analyses[l]		X	X			X	X			
Administer Antiemetics[m]		X	X	X	X	X	X	X	X	
Oprozomib Dosing[n,o]		X	X	X	X	X	X	X	X	
Dexamethasone Dosing[p]		X	X			X	X		X	
AEs and Concomitant Medications[q]	←									→

Footnotes to Appendix B, 5/14 Phase 2

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BPNS = Brief Peripheral Neuropathy Screen; CBC = complete blood count; CRF = case report form; CTCAE = Common Terminology Criteria for Adverse Events; CrCL = creatinine clearance; ECG = electrocardiogram; Diff = differential; EOS = End of Study; PDn = pharmacodynamics; PK = pharmacokinetics; QT = the interval from the beginning of the Q wave to the beginning of the T wave; QTc = the interval between the start of the Q wave and the end of the T wave.

[a] A physical examination may be performed every other month after subjects have been on study for more than 2 months **if clinically indicated** (i.e., starting at Cycle 5, Day 1, then at Cycle 9, Day 1, etc.). The screening exam may be used for Cycle 1, Day 1 if obtained within 7 days of Cycle 1, Day 1.

[b] Neurological assessments (BPNS and CTCAE grading) will be performed at Screening, every 4 cycles starting from Cycle 5, Day 1, and at EOS. **Patients on active treatment under Amendment 4 will have this assessment performed only if clinically indicated and at EOS.**

[c] Measure blood pressure, pulse rate, orthostatic blood pressure and pulse rate, respiration rate, and temperature within 1 hour prior to dose and at 30 minutes (± 5 min), 1 hour (± 15 min), and 2 hours (± 15 min) after each dose (Cycle 1, Days 1–5; and Cycle2, Days 1, 2, and 5). Measure once at Screening and at EOS. Subjects should lie down for 5 minutes and then have blood pressure and pulse measured. This should be followed by having the subject stand, and the blood pressure and pulse should be repeated at 1 and 3 minutes. Any drop of 20 mm/Hg systolic, 10 mm/Hg diastolic or lightheadedness/dizziness would indicate orthostatic hypotension (usually an increase in pulse rate of 10 beats/min is associated, but it is not required). At the investigator's medical discretion, vital signs monitoring may be extended beyond the time periods specified above. **Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated.**

[d] During Cycles 3 and higher, respiration rate, temperature, orthostatic blood pressure and pulse rate are required within 1 hour prior to first dose and within 30−60 minutes after first dose administration. Subjects should lie down for 5 minutes and then and have blood pressure and pulse measured. This should be followed by having the subject stand, and the blood pressure and pulse should be repeated at 1 and 3 minutes. **Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated.**

[e] Perform local ECGs at Screening, within 6 hours postdose on specified days with oprozomib dosing, and at EOS. Starting from Cycle 5, ECGs will be performed on Day 1 of every fourth cycle (i.e., starting at Cycle 5, Day 1, then at Cycle 9, Day 1, etc.). **Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated and at EOS.**

[f] Electrocardiograms Central Lab: Outside the requirements for local ECGs, assessment of QT/QTc interval will done via central ECGs on10 subjects on each schedule. Twelve-lead ECGs including QT/QTc interval will be performed in triplicate using an ECG machine provided by a central laboratory at the following time points during Cycle 1, Day 1: within 15 minutes prior to oprozomib dosing and at 30 minutes, 1, 2, 4 and 6 hours after oprozomib dosing.

[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) to be done at Screening, within 4 hours prior to dosing on specified days**. Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated** and at EOS. Calculate CrCl. Screening results may be used for Cycle 1, Day 1 if obtained within 72 hours of Cycle 1, Day 1.

[i] Hemoglobin, hematocrit, WBC count with differential (total neutrophils, lymphocytes, monocytes, eosinophils, basophils, absolute or percentage will be acceptable), RBC count, and platelet count**. Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated and at EOS.**

[j] A serum or urine pregnancy test is to be done within 3 days prior to first dose in females of childbearing potential only.

Footnotes to Appendix B, 5/14 Phase 2

[k] Blood sampling for PK for subjects in the Phase 2 portion: Blood samples for determination of plasma concentrations of oprozomib and its metabolite(s) will be drawn on Cycle 1, Days 1 and 2 and Cycle 2, Days 1and 2 for all subjects on the 5 consecutive day bimonthly schedule. Samples on Cycles 1 and 2, Day 1 must be taken within 5 minutes of intended collection time for 15-and 30-minute and 1- and 2-hour time points and within 15 minutes for 4-, 6-, and 7-hour time points. Oprozomib must be taken in the fasted state (at least 2 hours after a meal and fasting for at least 2 hours after dosing) on days in which PK sampling is taken after a dose. On all other days, including non-PK days and days in which only a predose PK sample is taken, it is recommended that oprozomib is administered with food (i.e., within approximately 30 minutes after eating). Sampling times and volumes are provided in the Laboratory Manual. Blood samples will be obtained for all subjects unless collection is discontinued at the sponsor's discretion. Samples may also be used for biomarker assessment.

[l] Blood sampling for PDn and proteomic analyses for subjects in the Phase 2 Portion: Blood samples for determination of proteasome inhibition by oprozomib and proteomic analyses will be drawn on Cycle 1, Days 1 and 2 and Cycle 2, Days 1 and 2 for all subjects on the 5 consecutive day bimonthly schedule.

Samples must be taken within 15 minutes of intended collection time for 4- and 6-hour time points. Sampling times and volumes are provided in the Laboratory Manual.

[m] Subjects will be premedicated PRN with a 5-HT3 inhibitor, such as ondansetron or granisetron, before administration of the first dose of oprozomib each day and throughout the day as needed.

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

[o] Subjects on the 5-consecutive-days bimonthly schedule will be provided with oprozomib doses for Days 1–5 of each 14-day cycle.

[p] Subjects will receive 20 mg of dexamethasone on Days 1, 2, 8, and 9 of each 14-day treatment cycle. Dexamethasone must be taken at least 30 minutes prior to oprozomib.

[q] 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 and continue 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.

[r] For patients with ≥ SD for at least 6 months (12 cycles), who are on a steady dose for ≥ 2 cycles, and are tolerating oprozomib, study assessments may be reduced to every **4** cycles (starting at Cycle 13, Day 1, then Cycle 15, Day 1, etc.) and **4** cycles of study medication can be provided at clinic visits. Subjects who do not meet these criteria should continue to have study assessments performed at every cycle.

[s] All 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.

Appendix C SCHEDULE OF STUDY ASSESSMENTS: SUBJECTS TREATED ON THE 2 CONSECUTIVE DAY WEEKLY SCHEDULE (DAYS 1, 2, 8, AND 9 OF EACH 14-DAY TREATMENT CYCLE), PHASE 1B

2/7 Phase 1b, Continuous Dosing Subjects

Visit	Screening D -14 to -1	Cycle 1 D 1	Cycle 1 D 2	Cycle 1 D 8	Cycle 1 D 9	Cycle 2 D 1	Cycle 2 D 2, 9	Cycle 3+[r] D 1	End of Study/ Early Discontinuation[s]
Medical History	X								
Previous Treatment History	X								
Targeted Physical Examination[a]	X	X				X		X	X
Height	X								
Weight	X	X				X		X	X
Neurological Assessment (BPNS and CTCAE grading)	X							X[b]	X
Vital Signs[c]	X	X	X	X	X	X	X	X[d]	X
12–lead ECG (Local)[e]	X	X			X	X		X	X
Urinalysis[f]	X								X
Serum Chemistry[g]	X	X	X	X	X	X	X	X	X
CBC with Diff and Platelets[h]	X	X	X	X	X	X	X	X	X
Coagulation Tests	X								
Pregnancy Test[i]	X								
Blood for PK[j,k]		X	X			X			
Blood for PDn Assay and Proteomic Analyses[l]		X	X			X			
Administer Antiemetics[m]		X	X	X	X	X	X	X	
Oprozomib Dosing[n,o]		X	X	X	X	X	X	X	
Dexamethasone Dosing[p]		X	X	X	X	X	X	X	
AEs and Concomitant Medications[q]	⟷								

Footnotes to Appendix C, 2/7 Phase 1b, Continuous Dosing Subjects

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BPNS = Brief Peripheral Neuropathy Screen; CBC = complete blood count; CRF = case report form; CTCAE = Common Terminology Criteria for Adverse Events; CrCL = creatinine clearance; ECG = electrocardiogram; Diff = differential; EOS = End of Study; PDn = pharmacodynamics; PK = pharmacokinetics.

[a] A physical examination may be performed every 4 cycles after subjects have been on study for more than 2 months **if clinically indicated** (i.e., starting at Cycle 5, Day 1, then at Cycle 9, Day 1, etc.). The screening exam may be used for Cycle 1, Day 1 if obtained within 7 days of Cycle 1, Day 1.

[b] Neurological assessments (BPNS and CTCAE grading) will be performed at Screening, every 4 cycles starting from Cycle 5, Day 1, and at EOS. **Patients on active treatment under Amendment 4 will have this assessments performed only if clinically indicated and at EOS.**

[c] Measure blood pressure, pulse rate, orthostatic blood pressure and pulse rate, respiration rate, and temperature within 1 hour prior to dosing and at 30 minutes (± 5 min), 1 hour (± 15 min) and 2 hours (± 15 min) after each dose (Cycle 1, Days 1, 2, 8 and 9; and Cycle 2, Days 1, 2, and 9). Measure once at Screening and at EOS. Subjects should lie down for 5 minutes and then have blood pressure and pulse measured. This should be followed by having the subject stand, and the blood pressure and pulse should be repeated at 1 and 3 minutes. Any drop of 20 mm/Hg systolic, 10 mm/Hg diastolic, or lightheadedness/dizziness would indicate orthostatic hypotension (usually an increase in pulse rate of 10 beats/min is associated, but it is not required). At the investigator's medical discretion, vital signs monitoring may be extended beyond the time periods specified above. **Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated.**

[d] During Cycles 3 and higher, respiration rate, temperature, orthostatic blood pressure and pulse rate are required within 1 hour prior to first dose and within 30– 60 minutes after first dose administration. Subjects should lie down for 5 minutes and then and have blood pressure and pulse measured. This should be followed by having the subject stand, and the blood pressure and pulse should be repeated at 1 and 3 minutes. **Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated.**

[e] Perform local ECGs at Screening, within 6 hours after dosing, on specified days with oprozomib dosing, and at EOS. Starting from Cycle 5, ECGs will be performed on Day 1 of every fourth cycle (i.e., starting at Cycle 5, Day 1, then at Cycle 9, Day 1, etc.). **Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated and at EOS.**

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

[g] 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) is to be done at Screening, within 4 hours prior to dosing on specified days**. Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated** and at EOS. Calculate CrCl. Screening results may be used for Cycle 1, Day 1 if obtained within 72 hours of Cycle 1, Day 1.

[h] Hemoglobin, hematocrit, WBC count with differential (total neutrophils, lymphocytes, monocytes, eosinophils, basophils, absolute or percentage will be acceptable), RBC count, and platelet count. **Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated and at EOS.**

[i] A serum or urine pregnancy test is to be done within 3 days prior to first dose in females of childbearing potential only.

[j] Blood sampling for PK for continuous dosing subjects in the Phase 1b portion: Blood samples to measure oprozomib and its metabolite(s) will be collected on Cycle 1, Days 1 and 2 and Cycle 2, Day 1 for subjects given oprozomib at a single dose level. Samples on Cycles 1 and 2, Day 1 must be taken within 5 minutes of intended collection times for 15- and 30-minute and 1- and 2-hour time points and within 15 minutes for 4-, 6-, and 8-hour time points. Oprozomib must be taken in the fasted state (at least 2 hours after a meal and fasting for at least 2 hours after dosing) on days in which PK sampling is taken after a dose. On all other days, including non-PK days and days in which only a predose PK sample is taken, it is recommended that oprozomib is administered with food (i.e., within approximately 30 minutes after eating). Sampling times and volumes are provided in the Laboratory Manual.

[k] When subjects switch from Oprozomib Tablets to Oprozomib ER Tablets, intensive PK sampling should be obtained on Day 1 in the cycle prior to switching and on Day 1 of the following cycle (i.e., first day with Oprozomib ER Tablet) at the scheduled time points described for step-up dosing subjects in Phase 1b.

[l] Blood sampling for PDn for continuous dosing subjects in the Phase 1b portion: Blood samples for determination of proteasome inhibition by oprozomib will be drawn on Cycle 1, Days 1 and 2 and Cycle 2, Day 1 for subjects given oprozomib at a single dose level. Samples must be taken within 15 minutes of the intended collection time for all postdose time points on Cycles 1 and 2, Day 1. Sampling times and volumes are provided in the Laboratory Manual.

[m] Subjects will be premedicated PRN with a 5-HT3 inhibitor, such as ondansetron or granisetron, before administration of the first dose of oprozomib each day and throughout the day as needed.

Footnotes to Appendix C, 2/7 Phase 1b, Continuous Dosing Subjects

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

[o] Subjects on 2 consecutive day weekly schedule will be provided with oprozomib dose for Days 1, 2, 8, and 9 of 14-day cycle.

[p] Subjects will receive 20 mg of dexamethasone on Days 1, 2, 8, and 9 of each 14-day treatment cycle. Dexamethasone must be taken at least 30 minutes prior to oprozomib.

[q] Record all AEs from the 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 and continue 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.

[r] For patients with ≥ SD for at least 6 months (12 cycles), who are on a steady dose for ≥ 2 cycles, and are tolerating oprozomib, study assessments may be reduced to every **4** cycles (starting at Cycle 13, Day 1, then Cycle 15, Day 1, etc.) and **4** cycles of study medication can be provided at clinic visits. Subjects who do not meet these criteria should continue to have study assessments performed at every cycle.

[s] All 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.

2/7 Phase 1b, Step-up Dosing Subjects

Visit	Screening D -14 to -1	Cycle 1 D 1	Cycle 1 D 2	Cycle 1 D 8	Cycle 1 D 9	Cycle 2 D 1	Cycle 2 D 2	Cycle 2 D 9	Cycle 3+[r] D 1	End of Study/Early Discontinuation[s]
Medical History	X									
Previous Treatment History	X									
Targeted Physical Examination[a]	X	X				X			X	X
Height	X									
Weight	X	X				X			X	X
Neurological Assessment (BPNS and CTCAE grading)	X								X[b]	X
Vital Signs[c]	X	X	X	X	X	X	X	X	X[d]	X
12–lead ECG (Local)[e]	X	X			X	X			X	X
Urinalysis[f]	X									X
Serum Chemistry[g]	X	X	X	X	X	X	X	X	X	X
CBC with Diff and Platelets[h]	X	X	X	X	X	X	X	X	X	X
Coagulation Tests	X									
Pregnancy Test[i]	X									
Blood for PK[j,k]		X	X			X	X			
Blood for PDn Assay and Proteomic Analyses[l]		X	X			X	X			
Administer Antiemetics[m]		X	X	X	X	X	X	X	X	
Oprozomib Dosing[n,o]		X	X	X	X	X	X	X	X	
Dexamethasone Dosing[p]		X	X	X	X	X	X	X	X	
AEs and Concomitant Medications[q]	←									→

Footnotes to Appendix C, 2/7 Phase 1b, Step-up Dosing Subjects

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BPNS = Brief Peripheral Neuropathy Screen; CBC = complete blood count; CRF = case report form; CTCAE = Common Terminology Criteria for Adverse Events; CrCL = creatinine clearance; ECG = electrocardiogram; Diff = differential; EOS = End of Study; PDn = pharmacodynamics; PK = pharmacokinetics.

[a] A physical examination can be performed every 4 cycles after subjects have been on study for more than 2 months **if clinically indicated** (i.e., starting at Cycle 5, Day 1, then at Cycle 9, Day 1, etc.). The screening exam may be used for Cycle 1, Day 1 if obtained within 7 days of Cycle 1, Day 1.

[b] Neurological assessments (BPNS and CTCAE grading) will be performed at Screening, every 4 cycles starting from Cycle 5, Day 1, and at EOS. **Patients on active treatment under Amendment 4 will have this assessment performed only if clinically indicated and at EOS.**

[c] Measure blood pressure, pulse rate, orthostatic blood pressure and pulse rate, respiration rate, and temperature within 1 hour prior to dosing and at 30 minutes (± 5 min), 1 hour (± 15 min) and 2 hours (± 15 min) after each dose (Cycle 1, Days 1, 2, 8 and 9; and Cycle 2, Days 1, 2, and 9). Measure once at Screening and at EOS. Subjects should lie down for 5 minutes and then have blood pressure and pulse measured. This should be followed by having the subject stand, and the blood pressure and pulse measurements should be repeated at 1 and 3 minutes. Any drop of 20 mm/Hg systolic, 10 mm/Hg diastolic, or lightheadedness/dizziness would indicate orthostatic hypotension (usually an increase in pulse of 10 beats/min is associated, but it is not required). At the investigator's medical discretion, vital signs monitoring may be extended beyond the time periods specified above. **Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated.**

[d] During Cycles 3 and higher, respiration rate, temperature, orthostatic blood pressure and pulse rate measurements are required within 1 hour prior to first dose and within 30-60 minutes after first dose administration. Subjects should lie down for 5 minutes and then and have blood pressure and pulse measured. This should be followed by having the subject stand and the blood pressure and pulse should be repeated at 1 and 3 minutes. **Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated.**

[e] Perform local ECGs at Screening, within 6 hours after dosing on specified days with oprozomib dosing, and at EOS. Starting from Cycle 5, ECGs will be performed on Day 1 of every fourth cycle (i.e., starting at Cycle 5, Day 1, then at Cycle 9, Day 1, etc.). **Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated and at EOS.**

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

[g] 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 at Screening, within 4 hours prior to dosing on specified days**. Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated** and at EOS. Calculate CrCl. Screening results may be used for Cycle 1, Day 1 if obtained within 72 hours of Cycle 1, Day 1.

[h] Hemoglobin, hematocrit, WBC count with differential (total neutrophils, lymphocytes, monocytes, eosinophils, basophils, absolute or percentage will be acceptable), RBC count, and platelet count**. Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated and at EOS.**

[i] A serum or urine pregnancy test is to be done within 3 days prior to first dose in females of childbearing potential only.

[j] Blood sampling for PK for step-up dosing subjects in the Phase 1b portion: Blood samples to measure oprozomib and its metabolite(s) will be collected on Cycle 1, Days 1 and 2 and Cycle 2, Days 1 and 2 for subjects given oprozomib using step-up dosing. Samples on Cycles 1 and 2, Day 1 must be taken within 5 minutes of intended collection times for 15- and 30-minute and 1- and 2-hour time points and within 15 minutes for 4-, 6-, and 7-hour time points. Oprozomib must be taken in the fasted state (at least 2 hours after a meal and fasting for at least 2 hours after dosing) on days in which PK sampling is taken after a dose. On all other days, including non-PK days and days in which only a predose PK sample is taken, it is recommended that oprozomib is administered with food (i.e., within approximately 30 minutes after eating). Sampling times and volumes are provided in the Laboratory Manual.

[k] When subjects switch from Oprozomib Tablets to Oprozomib ER Tablets, PK samples should be obtained on Day 1 in the cycle prior to switching and on Day 1 of the following cycle (i.e., first day with Oprozomib ER Tablet) at the scheduled time points described for the step-up dosing subjects in Phase 1b.

[1] Blood sampling for PDn for step-up dosing subjects in the Phase 1b portion: Blood samples for determination of proteasome inhibition by oprozomib will be drawn on Cycle 1, Days 1 and 2 and Cycle 2, Days 1 and 2 for subjects given oprozomib using step-up dosing. Samples must be taken within 15 minutes of intended collection time for all postdose time points on Cycles 1 and 2, Day 1. Sampling times and volumes are provided in the Laboratory Manual.

Footnotes to Appendix C, 2/7 Phase 1b, Step-up Dosing Subjects

[m] Subjects will be premedicated PRN with a 5-HT3 inhibitor, such as ondansetron or granisetron, before administration of the first dose of oprozomib each day and throughout the day as needed.

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

[o] Subjects on the 2 consecutive day weekly schedule will be provided with oprozomib dose for Days 1, 2, 8, and 9 of each 14-day cycle.

[p] Subjects will receive 20 mg of dexamethasone on Days 1, 2, 8, and 9 of each 14-day treatment cycle. Dexamethasone must be taken at least 30 minutes prior to oprozomib.

[q] Record all AEs from the 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 and continue 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.

[r] For patients with ≥ SD for at least 6 months (12 cycles), who are on a steady dose for ≥ 2 cycles, and are tolerating oprozomib, study assessments may be reduced to every **4** cycles (starting at Cycle 13, Day 1, then Cycle 15, Day 1, etc.) and **4** cycles of study medication can be provided at clinic visits. Subjects who do not meet these criteria should continue to have study assessments performed at every cycle.

[s] All 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.

Appendix D SCHEDULE OF STUDY ASSESSMENTS: SUBJECTS TREATED ON THE 2 CONSECUTIVE DAY WEEKLY SCHEDULE (DAYS 1, 2, 8, AND 9 OF EACH 14-DAY TREATMENT CYCLE), PHASE 2

2/7 Phase 2

Visit	Screening D -14 to -1	Cycle 1 D 1	Cycle 1 D 2	Cycle 1 D 8	Cycle 1 D 9	Cycle 2 D 1	Cycle 2 D 2	Cycle 2 D 9	Cycle 3+[r] D 1	End of Study/ Early Discontinuation[s]
Medical History	X									
Previous Treatment History	X									
Targeted Physical Examination[a]	X	X				X			X	X
Height	X									
Weight	X	X				X			X	X
Neurological Assessment (BPNS and CTCAE grading)	X								X[b]	X
Vital Signs[c]	X	X	X	X	X	X	X	X	X[d]	X
12–lead ECG (Local)[e]	X	X			X	X			X	X
ECG Central Lab[f]		X								
Urinalysis[g]	X									X
Serum Chemistry[h]	X	X	X	X	X	X	X	X	X	X
CBC with Diff and Platelets[i]	X	X	X	X	X	X	X	X	X	X
Coagulation Tests	X									
Pregnancy Test[j]	X									
Blood for PK[k]		X	X			X	X			
Blood for PDn Assay and Proteomic Analyses[l]		X	X			X	X			
Administer Antiemetics [m]		X	X	X	X	X	X	X	X	
Oprozomib Dosing[no]		X	X	X	X	X	X	X	X	
Dexamethasone Dosing[p]		X	X	X	X	X	X	X	X	
AEs and Concomitant Medications[q]	←									→

Footnotes to Appendix D, 2/7 Phase 2

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BPNS = Brief Peripheral Neuropathy Screen; CBC = complete blood count; CRF = case report form; CTCAE = Common Terminology Criteria for Adverse Events; CrCL = creatinine clearance; ECG = electrocardiogram; Diff = differential; EOS = End of Study; PDn = pharmacodynamics; PK = pharmacokinetics; QT = the interval from the beginning of the Q wave to the beginning of the T wave; QTc = the interval between the start of the Q wave and the end of the T wave.

[a] A physical examination can be performed every other month after subjects have been on study for more than 2 months**, if clinically indicated** (i.e., starting at Cycle 5, Day 1, then at Cycle 9, Day 1, etc.). The screening exam may be used for Cycle 1, Day 1 if obtained within 7 days of Cycle 1, Day 1

[b] Neurological assessments (BPNS and CTCAE grading) will be performed at Screening, every 4 cycles starting from Cycle 5, Day 1, and at EOS. **Patients on active treatment under Amendment 4 will have this assessment performed only if clinically indicated and at EOS.**

[c] Measure blood pressure, pulse rate, orthostatic blood pressure and pulse rate, respiration rate, and temperature within 1 hour prior to dosing and at 30 minutes (± 5 min), 1 hour (± 15 min) and 2 hours (± 15 min) after each dose (Cycle 1, Days 1, 2, 8 and 9; and Cycle 2, Days 1, 2, and 9). Measure once at Screening and at EOS. Subjects should lie down for 5 minutes and then have blood pressure and pulse measured. This should be followed by having the subject stand, and the blood pressure and pulse measurements should be repeated at 1 and 3 minutes. Any drop of 20 mm/Hg systolic, 10 mm/Hg diastolic, or lightheadedness/dizziness would indicate orthostatic hypotension (usually an increase in pulse rate of 10 beats/min is associated, but it is not required). At the investigator's medical discretion, vital signs monitoring may be extended beyond the time periods specified above. **Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated.**

[d] During Cycles 3 and higher, respiration rate, temperature, orthostatic blood pressure and pulse rate measurements are required within 1 hour prior to the first dose and within 30-60 minutes after first dose administration. Subjects should lie down for 5 minutes and then and have blood pressure and pulse measured. This should be followed by having the subject stand, and the blood pressure and pulse should be repeated at 1 and 3 minutes. **Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated.**

[e] Perform local ECGs at Screening, within 6 hours after dosing on specified days with oprozomib dosing, and at EOS. Starting from Cycle 5, ECGs will be performed on Day 1 of every fourth cycle (i.e., starting at Cycle 5, Day 1, then at Cycle 9, Day 1, etc.). **Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated and at EOS.**

[f] Electrocardiograms Central Lab: Outside the requirements for local ECGs, assessment of QT/QTc interval will done via central ECGs on 10 subjects on each schedule. Twelve-lead ECGs including QT/QTc interval will be performed in triplicate using an ECG machine provided by a central laboratory at the following time points during Cycle 1, Day 1: 15 minutes prior to oprozomib dosing and at 30 minutes, 1, 2, 4 and 6 hours after oprozomib dosing.

[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) to be done at Screening, within 4 hours prior to dosing on specified days**. Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated** and at EOS. Calculate CrCL. Screening results may be used for Cycle 1, Day 1 if obtained within 72 hours of Cycle 1, Day 1.

[i] Hemoglobin, hematocrit, WBC count with differential (total neutrophils, lymphocytes, monocytes, eosinophils, basophils, absolute or percentage will be acceptable), RBC count, and platelet count**. Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated and at EOS.**

[j] A serum or urine pregnancy test is to be done within 3 days prior to the first dose in females of childbearing potential only.

[k] Blood sampling for PK for subjects in the Phase 2 portion: Blood samples for determination of plasma concentrations of oprozomib and its metabolite(s) will be drawn on Cycle 1, Days 1 and 2, and Cycle 2, Days 1 and 2 for all subjects administered with a 2 consecutive day weekly schedule. Samples on Cycles 1 and 2, Day 1 must be taken within 5 minutes of intended collection time for 15-and 30-minute and 1- and 2-hour time points and within 15 minutes for the 4-, 6-, and 7-hour time points. Oprozomib must be taken in the fasted state (at least 2 hours after a meal and fasting for at least 2 hours after dosing) on days in which PK sampling is taken after a dose. On all other days, including non-PK days and days in which only a predose PK sample is taken, it is recommended that oprozomib is administered with food (i.e., within approximately 30 minutes after eating). Sampling times and volumes are provided in the Laboratory Manual. Blood samples will be obtained for all subjects unless collection is discontinued at the sponsor's discretion. Samples may also be used for biomarker assessment.

Footnotes to Appendix D, 2/7 Phase 2

[l] Blood sampling for PDn and proteomic analyses for subjects in the Phase 2 portion: Blood samples for determination of proteasome inhibition by oprozomib and proteomic analyses will be drawn on Cycle 1, Days 1 and 2 and Cycle 2, Days 1 and 2, for all subjects on the 2 consecutive day weekly schedule. Samples must be taken within 15 minutes of intended collection time for 4- and 6-hour time points. Sampling times and volumes are provided in the Laboratory Manual.

[m] Subjects will be premedicated PRN with a 5-HT3 inhibitor, such as ondansetron or granisetron, before administration of the first dose of oprozomib each day and throughout the day as needed.

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

[o] Subjects on the 2 consecutive day weekly schedule will be provided with oprozomib dose for Days 1, 2, 8, and 9 of each 14-day treatment cycle.

[p] Subjects will receive 20 mg of dexamethasone on Days 1, 2, 8, and 9 of each 14-day treatment cycle. Dexamethasone must be taken at least 30 minutes prior to oprozomib.

[q] Record all AEs from the 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 and continue 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.

[r] For patients with ≥ SD for at least 6 months (12 cycles), who are on a steady dose for ≥ 2 cycles, and are tolerating oprozomib, study assessments may be reduced to every **4** cycles (starting at Cycle 13, Day 1, then Cycle 15, Day 1, etc.) and **4** cycles of study medication can be provided at clinic visits. Subjects who do not meet these criteria should continue to have study assessments performed at every cycle.

[s] All 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.

Appendix E SCHEDULE OF STUDY ASSESSMENTS: DISEASE RESPONSE EVALUATIONS

Assessment	Screening -14 to -1	Cycle 2 Day 1	Every 2 Cycles Days 10–14	EOS/ WD[a]	At Progression	LTFU for subjects without PD
Disease response assessment labs						**Every 8 weeks**
SPEP[b]	X		X	X		X
Serum immunofixation	X		X	X		X
SFLC[b]	X	X[c]	X	X		X
24-hr Urine sample: UPEP[b,d] urine immunofixation	X		X	X		X
β2 microglobulin	X					
Skeletal survey[e]	X			X[f]		X[e]
Plasmacytoma evaluation[g]	X			X[f]		X[g]
Bone marrow aspirate and biopsy, cytogenetics, and FISH analyses[h]	X			X[f]		
Optional Genomic Biomarker samples[i]	X				X	

CT = computed tomography, lab = laboratory, EOS = End of Study, FISH = fluorescence in situ hybridization, LFTU = long-term follow-up; SFLC = serum free light chain; SPEP = serum protein electrophoresis, UPEP = urine protein electrophoresis, WD = withdrawal (from study), WM = Waldenström macroglobulinemia.

Footnotes apply to Phase 1b and Phase 2.

[a] All End of Study Treatment Assessments must be performed within 30 days following the subject's last administration of study drug and before initiation of any other treatment. For subjects who discontinue treatment for reasons other than progression, disease assessments **will no longer be required under Amendment 4**.

[b] After screening, disease response assessments should be done every 2 cycles after all study drug (oprozomib and dexamethasone) doses have been taken in that cycle (e.g., Cycle 2, Days 10–14) OR on Day 1 of the next scheduled cycle (e.g., Cycle 3, Day 1; Cycle 5, Day 1; Cycle 7, Day 1). However, the time of assessment(s) should precede the Day 1 dose. The times of assessments and study drug dose must be recorded in the source documents. All subjects are required to complete SFLC assessments at each time point noted above. For subjects with ≥ SD after being on study for 26 cycles, Days 10−14 OR predose on Cycle 27, Day 1 (the next assessment would be on Cycle 30, Days 10–14 OR Cycle 31, Day 1).

[c] For Cycle 2 only, SFLC specifically should be performed on Day 1. After this assessment, SFLC can be performed with the other assessments.

[d] UPEP (on a 24-hour collection) is required; no substitute method is acceptable.

[e] All patients are required to have a skeletal survey at Screening. Skeletal survey does not need to be repeated if previously done within 30 (± 15) days of consent. Skeletal survey includes lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. Repeat skeletal survey as clinically indicated and to confirm CR or document PD. Skeletal survey for EOS does not need to be repeated if done within the prior 30 days to prevent unnecessary

radiation exposure.

[f] Also if clinically indicated to confirm response or PD within 30 days of laboratory assessment. Cytogenetic analysis (Phase 1b only) and FISH from bone marrow samples will not be repeated after the Screening assessment. Bone marrow assessments and FISH analyses are to be performed at a central laboratory.

[g] Extramedullary plasmacytoma evaluation at baseline only required for patients with known or suspected plasmacytoma. Historical evaluation performed as part of standard of care may be used as long as it is within 30 days of C1D1 dosing. Extramedullary plasmacytoma evaluation to be repeated during treatment only to confirm a response of PR or better or to confirm PD, or as clinically indicated. The same technique (which may include clinical evaluation by palpation, ultrasound, x-ray, CT scan, MRI or PET) should be employed for each measurement as clinically appropriate.

[h] For the bone marrow aspirate or biopsy, quantitate percent plasma cell involvement at Screening and repeat when appropriate to confirm sCR, CR, or PD. Obtain bone marrow sample for cytogenetic analysis and FISH studies at Screening only. Screening bone marrow assessment does not need to be repeated if previously completed within 30 (± 15) days of the patient's providing consent and assuming that FISH and cytogenetics were obtained. Bone marrow assessments and FISH analyses are to be performed at a central laboratory.

[i] 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, as well as bone marrow aspirate at the time of progression (may be at time of treatment discontinuation or during long term follow-up).

Appendix F EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Grade	ECOG
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 M.D., Group Chair

Appendix G 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
Astemizolea	Ergotamine	Sirolimus
Cisapridea Cyclosporine	Fentanyl Pimozide	Tacrolimus Terfenadine[a]

[a] Not available in the United States.

Appendix H 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 disease	• Not meeting criteria for CR, VGPR, PR, or PD

Page 1 of 2

Footnoted defined on next page

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: • Serum M-component (absolute increase must be ≥ 0.5 g/dL) and/or • Urine M-component (absolute increase must be ≥ 200 mg per 24 hours) and/or • 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) • 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%) • Bone marrow plasma cell percentages (absolute % 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 2.65 mmol/L) attributed solely to the plasma cell proliferative disorder

Page 2 of 2

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, but these should be done within 30 days of the confirmatory assessment if appropriate for the response category.

[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 ≥ 1.0 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 based on M-protein, hypercalcemia, or FLC 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 are 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.

Definition of Minimal Response and Near-Complete Response per EBMT Criteria

Response Subcategory	Response Criteria
MR[a]	≥ 25 but < 49% reduction in serum M-protein and a 50-89% reduction in 24-hour urinary M-protein, which still exceeds 200 mg per 24 h
	For subjects with non-secretory myeloma only, 25-49% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed.
	25-49% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination)
	No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
nCR[a]	Immunofixation-positive response. Absence of M-protein on electrophoresis, independent of the immunofixation test status, stable bone disease, and a normal serum calcium concentration,

Sources: Bladé 1998, Kyle 2009, Richardson 2003.

EBMT = European Group for Blood and Marrow Transplantation; MR = minimal response; nCR = near- complete response.

[a] **Response categories (MR and nCR) 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.

Appendix I BLOOD SAMPLES FOR PHARMACOKINETIC AND PHARMACODYNAMIC/PROTEOMIC ANALYSES: SAMPLING TIMES

Phase 1b Sampling Time Points (continuous dosing subjects only)

		Time Point							
Cycle	**Day**	**Predose**	**15 min Postdose**	**30 min Postdose**	**1 hour Postdose**	**2 hours Postdose**	**4 hours Postdose**	**6 hours Postdose**	**8 hours Postdose**
Schedule: 5 Consecutive Days Bimonthly (Days 1–5 of Each 14-day Treatment Cycle)									
1	1	PK PDn	PK	PK	PK	PK	PK PDn	PK	PK PDn
1	2	PK PDn	—	—	—	—	—	—	—
2	1	PK PDn	PK	PK	PK	PK	PK PDn	PK	PK PDn
Schedule: 2 Consecutive Days Weekly (Days 1, 2, 8, and 9 of Each 14-day Treatment Cycle)									
1	1	PK PDn	PK	PK	PK	PK	PK PDn	PK	PK PDn
1	2	PK PDn	—	—	—	—	—	—	—
2	1	PK PDn	PK	PK	PK	PK	PK PDn	PK	PK PDn

PK = blood draw for pharmacokinetic analysis; PDn = blood draw for pharmacodynamic analyses; — indicates that no blood sample is obtained.

Note: Oprozomib must be taken in the fasted state (at least 2 hours after a meal and fasting for at least 2 hours after dosing) on days in which PK sampling is taken after a dose. On all other days including non-PK days and days in which only a predose PK sample is taken, it is recommended that oprozomib is administered with food (i.e., within approximately 30 minutes after eating). Subjects switching from Oprozomib Tablet to Oprozomib ER Tablet should follow Day 1 PK sampling as described for step-up dosing (predose to 7 hours postdose) on Day 1 of the cycle prior and Day 1 of the cycle subsequent to the switch.

Phase 1b Sampling Time Points (step-up dosing subjects only)

Time Point									
Cycle	**Day**	**Predose**	**15 min Postdose**	**30 min Postdose**	**1 hour Postdose**	**2 hours Postdose**	**4 hours Postdose**	**6 hours Postdose**	**7 hours Postdose**
Schedule: 5 Consecutive Days Bimonthly (Days 1–5 of Each 14-day Treatment Cycle)									
1	1	PK PDn	PK	PK	PK	PK	PK PDn	PK PDn	PK
1	2	PK PDn	—	—	—	—	—	—	—
2	1	PK PDn	PK	PK	PK	PK	PK PDn	PK PDn	PK
2	2	PK PDn	—	—	—	—	—	—	—
Schedule: 2 Consecutive Days Weekly (Days 1, 2, 8, and 9 of Each 14-day Treatment Cycle)									
1	1	PK PDn	PK	PK	PK	PK	PK PDn	PK PDn	PK
1	2	PK PDn	—	—	—	—	—	—	—
2	1	PK PDn	PK	PK	PK	PK	PK PDn	PK PDn	PK
2	2	PK PDn	—	—	—	—	—	—	—

PK = blood draw for pharmacokinetic analysis; PDn = blood draw for pharmacodynamic analyses; — indicates that no blood sample is obtained.

Note: Oprozomib must be taken in the fasted state (at least 2 hours after a meal and fasting for at least 2 hours after dosing) on days in which PK sampling is taken after a dose. On all other days including non-PK days and days in which only a predose PK sample is taken, it is recommended that oprozomib is administered with food (i.e., within approximately 30 minutes after eating).

Phase 2 Sampling Time Points

Time Point									
Cycle	**Day**	**Predose**	**15 min Postdose**	**30 min Postdose**	**1 hour Postdose**	**2 hours Postdose**	**4 hours Postdose**	**6 hours Postdose**	**7 hours Postdose**
Schedule: 5 Consecutive Days Bimonthly (Days 1–5 of Each 14-day Treatment Cycle)									
1	1	PK PDn/P	PK	PK	PK	PK	PK PDn/P	PK PDn/P	PK
1	2	PK PDn/P	—	—	—	—	—	—	—
2	1	PK PDn/P	PK	PK	PK	PK	PK PDn/P	PK PDn/P	PK
2	2	PK PDn/P	—	—	—	—	—	—	—
Schedule: 2 Consecutive Days Weekly (Days 1, 2, 8, and 9 of Each 14-day Treatment Cycle)									
1	1	PK PDn/P	PK	PK	PK	PK	PK PDn/P	PK PDn/P	PK
1	2	PK PDn/P	—	—	—	—	—	—	—
2	1	PK PDn/P	PK	PK	PK	PK	PK PDn/P	PK PDn/P	PK
2	2	PK PDn/P	—	—	—	—		—	—

PK = blood draw for pharmacokinetic analysis; PDn/P = blood draw for pharmacodynamic and proteomic analyses; — indicates that no blood sample is obtained.

Note: Oprozomib must be taken in the fasted state (at least 2 hours after a meal and fasting for at least 2 hours after dosing) on days in which PK sampling is taken after a dose. On all other days including non-PK days and days in which only a predose PK sample is taken, it is recommended that oprozomib is administered with food (i.e., within approximately 30 minutes after eating).

Appendix J ACTG BRIEF PERIPHERAL NEUROPATHY SCREENING TOOL

ACTG BRIEF PERIPHERAL NEUROPATHY SCREENING TOOL

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.

Vibration perception

- a. Great toe DIP joint perception of vibration in seconds
- b. Vibration perception score
- 0 = felt > 10 seconds (normal)
- 1 = felt 6−10 seconds (mild loss)
- 2 = felt < 5 seconds (moderate loss)
- 3 = not felt (severe loss)
- 8 = unable to or did not assess

R	L

4. Evaluate Deep Tendon Reflexes

With the subject seated, the examiner uses one hand to press upward on the ball of the foot, dorsiflexing the subject's ankle to 90 degrees. Using a reflex hammer, the examiner then strikes the Achilles tendon. The tendon reflex is felt by the examiner's hand as a plantar flexion of the foot, appearing after a slight delay from the time the Achilles tendon is struck. Use reinforcement by having the subject clench his/her fist before classifying the reflex as absent.

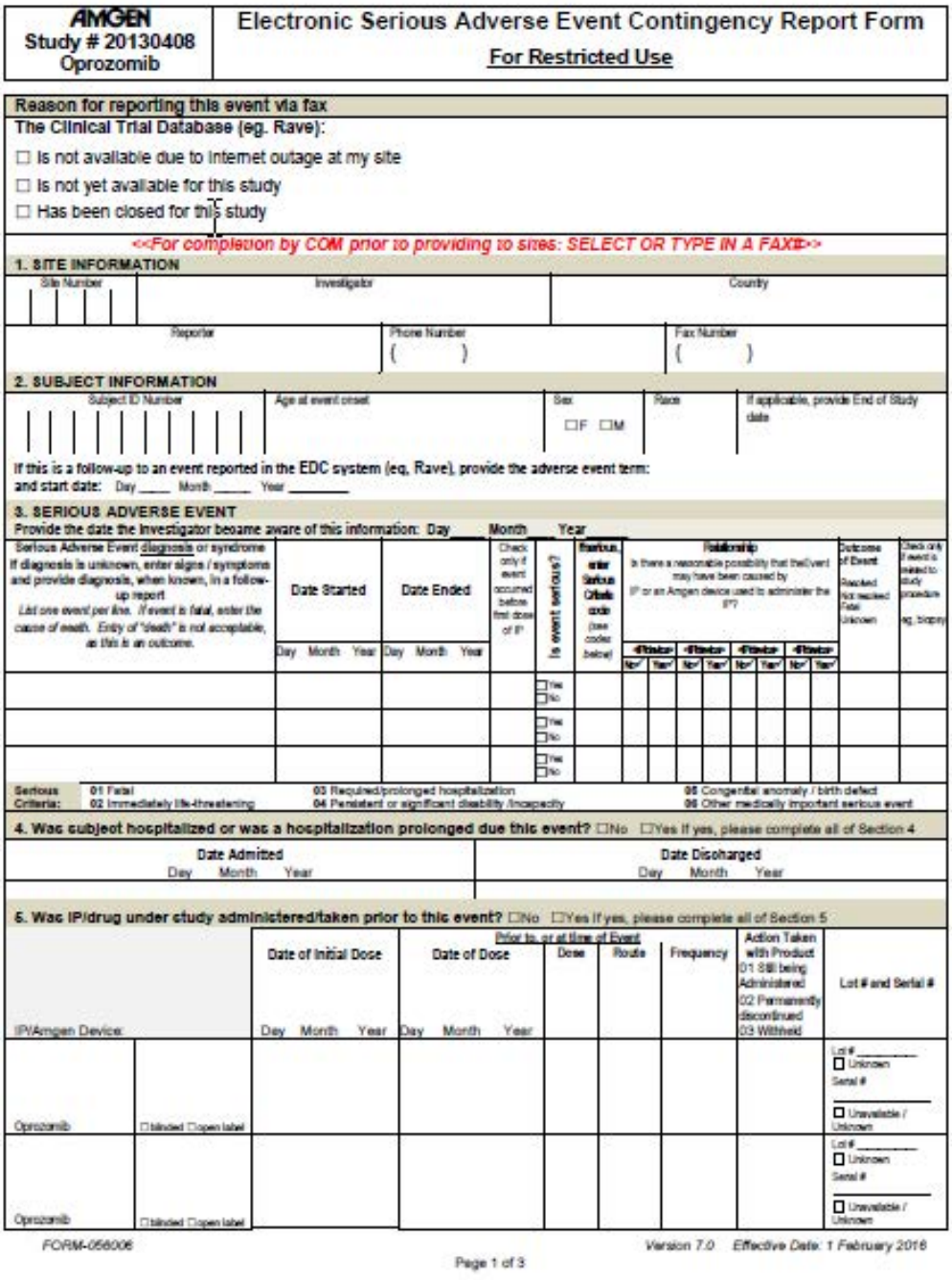
Ankle Reflexes Score

- 0 = absent
- 1 = hypoactive
- 2 = normal deep tendon reflexes
- 3 = hyperactive
- 4 = clonus
- 8 = unable to or did not assess

R	L

Source: NIAID Adult AIDS Clinical Trials Group: From Peripheral Neuropathy**, Primary Care of Veterans with HIV,** Office of Clinical Public Health Programs, Veterans Health Administration, 2009

Appendix K EXAMPLE ELECTRONIC SERIOUS ADVERSE EVENT CONTINGENCY REPORT FORM



AMGEN
Study # 20130408
Oprozomib

Electronic Serious Adverse Event Contingency Report Form
For Restricted Use

Reason for reporting this event via fax
The Clinical Trial Database (eg. Rave):
☐ Is not available due to Internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION
Site Number | Investigator | Country
Reporter | Phone Number ( ) | Fax Number ( )

2. SUBJECT INFORMATION
Subject ID Number | Age at event onset | Sex ☐F ☐M | Race | If applicable, provide End of Study date
If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term:
and start date: Day ____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT
Provide the date the Investigator became aware of this information: Day ___ Month ___ Year

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP?								Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year | Date Discharged Day Month Year

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Amgen Device		Date of Initial Dose Day Month Year	Date of Dose Day Month Year	Prior to, or at time of Event: Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
Oprozomib	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Oprozomib	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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AMGEN Study # 20130408 Oprozomib	Electronic Serious Adverse Event Contingency Report Form **For Restricted Use**

Site Number	Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete.

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect (No✓)	Co-suspect (Yes✓)	Continuing (No✓)	Continuing (Yes✓)	Dose	Route	Freq.	Treatment Med (No✓)	Treatment Med (Yes✓)

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete.

Date (Day Month Year)	Test											
	Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete.

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20130408 Oprozomib	Electronic Serious Adverse Event Contingency Report Form **For Restricted Use**

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee - *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the Investigator for this study, or by a Qualified Medical Person authorized by the Investigator for this study.*	Title	Date

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Appendix L EXAMPLE AMGEN PREGNANCY NOTIFICATION WORKSHEET

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20130408

Study Design: ■ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (___) _____ Fax (___) _____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject DOB: mm ▼ / dd ▼ / yyyy

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
Oprozomib				mm ▼ /dd ▼ /yyyy

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ▼ /dd ▼ /yyyy

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm ▼ / dd ▼ / yyyy ☐ Unknown

Estimated date of delivery mm ▼ / dd ▼ / yyyy ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm ▼ / dd ▼ / yyyy

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm ▼ / dd ▼ / yyyy

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details: _____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: March 27, 2011

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Appendix M EXAMPLE AMGEN LACTATION NOTIFICATION WORKSHEET

Print Form

AMGEN™ Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: 20130408

Study Design: ☑ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm____ / dd____ / yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
Oprozomib				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details: _____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2

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Appendix N SUMMARY OF CHANGES IN PROTOCOL 2012-001 AMENDMENT 4

Study 2012-001 was amended due to the following

- Study visits are less frequent with data collection (eg labs, vitals, ECGs), and are being pared down to instances of clinical need for subjects on active treatment. This amendment is based on the completion of the primary analysis of the study and abbreviated clinical study report.

In addition, 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.

SUMMARY OF CHANGES

Deletions of text are presented in strikethrough format. Added text is presented in bold format.

Section(s)	Changed from	Changed to	Rationale
Global	International Conference on Harmonisation (ICH)	International **Council for** Harmonisation (ICH)	Change in regulatory body name
Global	Onyx	The **Sponsor**	New sponsor protocol SOP
Global	Onyx Drug Safety	**Sponsor Global Patient** Safety	New sponsor protocol SOP
Title page	*New text added*	**NCT Number: NCT01832727**	New protocol SOP
Title page	Onyx Therapeutics 249 East Grand Avenue South San Francisco, CA 94080 USA Phone: (650) 266-0000	Onyx Therapeutics **One Amgen Center Drive** **Thousand Oaks**, CA shou**91320** USA **(805) 447-1000**	Change in sponsor title and contact information
Title page	Medical monitor: [redacted], MD Medical Director, Clinical Development Onyx Pharmaceuticals 249 East Grand Avenue South San Francisco, CA 94080 USA Phone: [redacted] Email: [redacted]	Medical monitor: [redacted], MD Medical Director, Clinical Development **1120 Veterans Blvd** South San Francisco, CA 94080 USA Phone: [redacted] Email: [redacted]	Change in responsibilities
Title page	*New text added*	**Amendment 4 / 08 February 2018**	New amendment identifiers
Clinical Study Protocol Approval Signature Page	Protocol Approval Signature Page	[Approval section removed]	New sponsor protocol SOP
Protocol Acceptance Page	Amendment 3 / 26 June 2014	Amendment **4** / **08 February 2018**	New amendment identifiers
Synopsis (Study Design)	*New text added*	The 240 mg dose is 2 dose levels below the single agent MTD, which was found to be 300 mg in Study 2011-001. **Subjects on active treatment will continue with Oprozomib ER Tablets under protocol Amendment 4. No changes in drug product, dosage, or treatment**	Provide clarity for patients remaining on-study regarding study drug

Section(s)	Changed from	Changed to	Rationale
		regimen occurred in this protocol amendment from the previous version.	
Synopsis (Duration of study/treatment periods)	Note: For subjects who discontinue treatment for reasons other than progression in either study phase, disease assessments must be performed every 8 weeks until progression or until a new multiple myeloma therapy is started.	Note: For subjects who discontinue treatment for reasons other than progression in either study phase, disease assessments **will no longer be required under protocol Amendment 4**.	Provide convenience for those on study treatment as study has completed its abbreviated report
Section 1 (Introduction)	The main purpose of the current amendment (Amendment 3) is to: 1. Introduce the Oprozomib ER tablet broadly in the study. 2. Introduce step-up dosing in the dose escalation to determine if tolerability and safety are improved. This approach is based on preclinical data suggesting this schedule may be better tolerated than continuous dosing (see Section 1.3). 3. Include the use of the results of the safety and tolerability of step-up dosing in the determination of the recommended Phase 2 dose. 4. Provide additional safety guidance and exclusion criteria regarding GI hemorrhage as toxicities were observed in subjects treated with oprozomib on the 5/14 schedule (5 consecutive days every 14 days bimonthly) at 240 mg.	The main purpose of the current amendment (Amendment **4**) is to: **Pare down data collection for subjects on active treatment due to the completion of this study's analysis and abbreviated clinical study report.**	Update text to reflect the rationale for Amendment 4
Section 1.5.1 (Dose Rationale)	*New text added*	**Protocol Amendment 4** **No changes in drug product, dosage, or treatment regimen occurred in this protocol amendment from the previous version.**	Added text to maintain continuity within the section to explain no changes to dose in Amendment 4
Section 3.4 (Estimated Study Duration)	For subjects who discontinue treatment for reasons other than progression, disease assessments must be performed every 8	For subjects who discontinue treatment for reasons other than progression, disease assessments **will no longer be required under protocol amendment 4**.	Provide convenience for those on study treatment

Section(s)	Changed from	Changed to	Rationale
	weeks, or until a new multiple myeloma therapy is started or disease progresses.		as study has completed its abbreviated report
Section 7 (Study Tests and Observations)	For subjects with SD or better after at least 12 cycles of therapy who are on a steady dose for ≥ 2 cycles and are tolerating oprozomib, study assessments may be performed every 2 cycles, and 2 cycles of study medication may be dispensed from the study site at a time starting with Cycle 13	For subjects with SD or better after at least 12 cycles of therapy who are on a steady dose for ≥ 2 cycles and are tolerating oprozomib, study assessments may be performed every **4** cycles, and **4** cycles of study medication may be dispensed from the study site at a time starting with Cycle 13	
Section 7.7 (Assessments At End Of Study Treatment Or Early Discontinuation)	For subjects who discontinue treatment for reasons other than progression, disease assessments will be performed every 8 weeks or until a new multiple myeloma therapy is started or disease progresses. The same methods of disease assessment must be used throughout the study. If disease assessments show confirmed disease progression, assessments do not need to be repeated with End-of-Study Assessments.	For subjects who discontinue treatment for reasons other than progression, disease assessments **will no longer be required under protocol Amendment 4**.	Provide convenience for those on study treatment as study has completed its abbreviated report
Appendix E (Schedule of Assessments: Disease Response Evaluations, footnote a)	For subjects who discontinue treatment for reasons other than progression, disease assessments must be performed every 8 weeks or until a new multiple myeloma therapy is started or disease progresses. The same methods of disease assessment must be used throughout the study. If disease assessments show confirmed disease progression, assessments do not need to be repeated with End-of-Study Assessments.	For subjects who discontinue treatment for reasons other than progression, disease assessments **will no longer be required under Amendment 4**.	Provide convenience for those on study treatment as study has completed its abbreviated report
Section 9.1 (Adverse Events Definitions)	*New text added*	**The National Cancer Institute Common Terminology Criteria for Adverse Events does not use to the term "intermittent" and this term must not be used to describe AEs.**	Update safety reporting language with latest template.

Section(s)	Changed from	Changed to	Rationale
Section 9.2 (Causality)	A suspected adverse reaction means any AE for which there is a reasonable possibility that the study drug caused the AE. "Reasonable possibility" means 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:	~~A suspected adverse reaction means any AE for which there is a reasonable possibility that the study drug caused the AE. "Reasonable possibility" means 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:	Update safety reporting language with latest template.
Section 9.3.2 (Disease Progression)	All deaths that occur from the time that ICF is signed until 30 days after the last dose of study drug is administered are to be reported as SAEs (see Section 9.4). Disease progression-related deaths must be reported on the AE eCRF using the verbatim term "Disease Progression" rather than the specific sign or symptom that may have been the immediate cause of death. Additional details of the event (such as the primary and contributory causes of death) should be reported on the Death eCRF.	All deaths that occur from the time that ICF is signed until 30 days after the last dose of study drug is administered are to be reported as SAEs (see Section 9.4). **Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, metastatic, pancreatic cancer). Note: The term "disease progression" should not be used to describe the disease related event or adverse event.** Additional details of the event (such as the primary and contributory causes of death) should be reported on the Death eCRF.	Update safety reporting language with latest template.
Section 9.5 (Serious Adverse Event Reporting and Documentation Requirements)	Onyx Drug Safety must be notified within 24 hours of the investigator, designee, or site personnel knowledge of the event. To report an 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.	**Amgen Global Patient** Safety must be notified within 24 hours of the investigator, designee, or site personnel knowledge of the event. To report an SAE to **Amgen Global Patient** Safety, please refer to the SAE reporting guidelines **below**. **The primary mechanism for reporting serious adverse events will be the electronic data capture system (EDC) via the Safety Report Form. If the EDC system is unavailable for more than 24 hours, then the site will**	Update safety reporting language with latest template.

Section(s)	Changed from	Changed to	Rationale
	The investigator is responsible for notifying the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) in accordance with local regulations, of all SAEs. The sponsor may request additional source documentation pertaining to the SAE. If a subject is permanently discontinued from the study because of an SAE, this information must be included in the initial or follow-up SAE report form as well as the Study Discontinuation eCRF. All SAEs occurring from the time that the subject signs consent for study participation and through 30 days after the last administered dose of study drug will be reported, regardless of whether new chemotherapy regimens are initiated (see Section 9.2 for additional information). All SAEs, regardless of relationship to study drug, must be followed to resolution or to stabilization if improvement or resolution is not expected.	**report the information to Amgen using an electronic Serious Adverse Contintency Report Form (see Appendix K) within 24 hours of the investigator's knowledge of the event. The site will enter the serious adverse event data into the electronic system as soon as it becomes available.** **After the study is completed at a given site, the EDC system will be taken offline to prevent the entry of new data or changes to existing data.** **If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken offline, then the site can report this information on a paper Serious Adverse Event Report Form (see Appendix K).** **If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.** **New or updated information will be recorded in the originally completed Event CRF.** **The investigator will submit any updated serious adverse even data to Amgen Global Patient Safety within 24 hours of receipt of the information.** The investigator is responsible for notifying the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) in accordance with local regulations, of all SAEs. The sponsor may request additional source documentation pertaining to the SAE. If a subject is permanently discontinued from the study because of an SAE, this information must be included in the initial or	

Section(s)	Changed from	Changed to	Rationale
		follow-up SAE report form as well as the Study Discontinuation eCRF. All SAEs occurring from the time that the subject signs consent for study participation and through 30 days after the last administered dose of study drug will be reported, regardless of whether new chemotherapy regimens are initiated (see Section 9.2 for additional information). All SAEs, regardless of relationship to study drug, must be followed to resolution or to stabilization if improvement or resolution is not expected.	
Section 9.6 (Pregnancy)	Subjects will be instructed to notify the investigator as soon as possible after becoming pregnant or learning of the pregnancy of a partner. If a subject or partner of a subject becomes pregnant during treatment or up to 30 days following the last study drug administration, the investigator will notify Onyx within 24 hours of learning of the pregnancy. • If the subject becomes pregnant while taking an Onyx drug, the drug will be immediately discontinued. The investigator will discuss the risks and concerns of investigational drug exposure to a developing fetus and counsel the subject and/or pregnant partner (or ensure that such counseling is provided). • Pregnancies will be followed through the outcome of the pregnancy.	If a **patient** or **spouse or** partner of a **patient** becomes pregnant during treatment or up to 30 days following administration **of study treatment**, **Amgen Global Patient Safety and** the **medical monitor must be notified** within 24 hours of **the investigator, designee, or site personnel** learning of the pregnancy. **On notification to Amgen, the investgator must obtain a separate information release and authorization form for the use and disclosure of health information of the pregnant spouse or partner of a patient. If the patient becomes pregnant while taking oprozomib, oprozomib must be immediately discontinued. Patients, spouses, or partners will be followed through the outcome of the pregnancy. The investigator will be required to complete an Amgen Pregnancy Notification Worksheet and report the information as specified below. To report a pregnancy to Amgen Global Patient Safety, please refer to the pregnancy reporting guidelines below.**	Update safety reporting language with latest template.

Section(s)	Changed from	Changed to	Rationale
	• Newborns should be followed for a minimum of 12 weeks. The investigator will complete a Pregnancy Monitoring Form and report the information regarding the pregnancy, outcome, and status of the newborn, as appropriate. .	**<u>Collection of Pregnancy Information</u>** ***Female Subjects Who Become Pregnant*** • **Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 30 days after stopping oprozomib.** • **Information will be recorded on the Pregnancy Notification Worksheet (Appendix L). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws.** • **After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 30 days after stopping oprozomib. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).** • **Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.** • **While pregnancy itself is not considered to be an adverse event or serious adverse event, any**	

Section(s)	Changed from	Changed to	Rationale
		pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case. • **If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.** • **Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator will be reported to Amgen Global Patient Safety as described in Section 9.5. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.** • **Any female subject who becomes pregnant while participating will discontinue study treatment.** ***Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment*** • **In the event a male subject fathers a child during treatment, and for an additional 90 days after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy**	

Section(s)	Changed from	Changed to	Rationale
		Notification Worksheet (Appendix L). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws. • **The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.** • **After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.** • **Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).** • **Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.** **<u>Collection of Lactation Information</u>** • **Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 30 days after stopping oprozomib.**	

Section(s)	Changed from	Changed to	Rationale
		• **Information will be recorded on the Lactation Notification Worksheet (Appendix M) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.** • **Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 16.** **With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 30 days after discontinuing protocol-required therapies.**	
Section 11.1.2 (Formulation)	*New text added*	**No changes in drug product, dosage, or treatment regimen occurred in this protocol amendment from the previous version.**	Added text to maintain continuity within the section to explain no changes to dose in Amendment 4
Section 14 (References)	*Text deleted*	~~Kummar S, Gutierrez M, Doroshow JH, et al. Drug development in oncology: classical cytotoxics and molecularly targeted agents. Br J Clin Pharmacol. 2006;62(1):15–26.~~	Reference deleted per body of protocol
Appendix A (Schedule of Assessments – 5/14 Phase 1b, Step-up Dosing Subjects, footnote a) Appendix C (Schedule of Assessments – 2/7 Phase 1b,	*New text added*	A physical examination may be performed every 4 cycles after subjects have been on study for more than 2 months **if clinically indicated**.	Provide convenience for those on study treatment as study has completed its abbreviated report

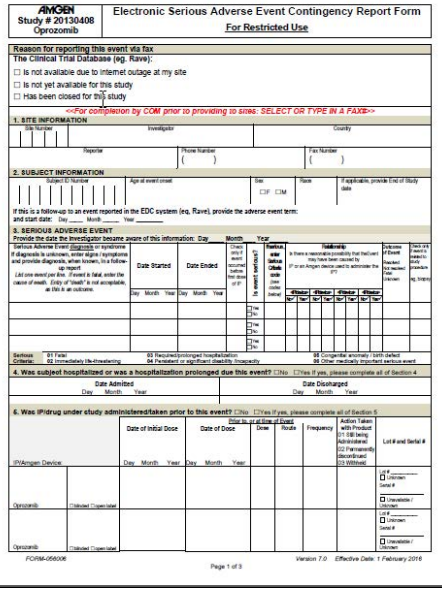
Section(s)	Changed from	Changed to	Rationale
Continuous Dosing Subjects, footnote a)			
Appendix A (Schedule of Assessments – 5/14 Phase 1b, Continuous Dosing Subjects, footnote a) Appendix C (Schedule of Assessments – 2/7 Phase 1b, Step-up Dosing Subjects, footnote a)	*New text added*	A physical examination can be performed every 4 cycles after subjects have been on study for more than 2 months **if clinically indicated**.	Provide convenience for those on study treatment as study has completed its abbreviated report
Appendix B (Schedule of Assessments – 5/14 Phase 2, footnote a)	*New text added*	A physical examination may be performed every other month after subjects have been on study for more than 2 months **if clinically indicated**	Provide convenience for those on study treatment as study has completed its abbreviated report
Appendix D (Schedule of Assessments – 2/7 Phase 2, footnote a)	*New text added*	A physical examination can be performed every other month after subjects have been on study for more than 2 months **if clinically indicated**	Provide convenience for those on study treatment as study has completed its abbreviated report
Appendix A (Schedule of Assessments – 5/14 Phase 1b, Continuous Dosing Subjects, footnotes b) Appendix A (Schedule of Assessments – 5/14 Phase 1b, Step-up	*New text added*	**Patients on active treatment under Amendment 4 will have this assessment performed only if clinically indicated and at EOS.**	Provide convenience for those on study treatment as study has completed its abbreviated report

Section(s)	Changed from	Changed to	Rationale
Dosing Subjects, footnotes b, and e) Appendix B (Schedule of Assessments – 5/14 Phase 2, footnote b) Appendix C (Schedule of Assessments – 2/7 Phase 1b, Continuous Dosing Subjects, footnote b) Appendix C (Schedule of Assessments – 2/7 Phase 1b, Step-up Dosing Subjects, footnote b Appendix D (Schedule of Assessments – 2/7 Phase 2, footnote b)			
Appendix A (Schedule of Assessments – 5/14 Phase 1b, Continuous Dosing Subjects, footnotes d an h) Appendix A (Schedule of Assessments – 5/14 Phase 1b, Step-up Dosing Subjects, footnotes d and h) Appendix B (Schedule of	*New text added*	**Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated and at EOS.**	Provide convenience for those on study treatment as study has completed its abbreviated report

Section(s)	Changed from	Changed to	Rationale
Assessments – 5/14 Phase 2 footnotes e, and i) Appendix C (Schedule of Assessments – 2/7 Phase 1b, Continuous Dosing Subjects, footnotes e, and h) Appendix C (Schedule of Assessments – 2/7 Phase 1b, Step-up Dosing Subjects, footnotes e, and h) Appendix D (Schedule of Assessments – 2/7 Phase 2, footnotes e and i)			
Appendix A (Schedule of Assessments – 5/14 Phase 1b, Continuous Dosing Subjects, footnotes c and g) Appendix A (Schedule of Assessments – 5/14 Phase 1b, Step-up Dosing Subjects, footnotes c and g)	*New text added*	**Patients on active treatment under Amendment 4 will have these assessments performed only if clinically indicated**	Provide convenience for those on study treatment as study has completed its abbreviated report

Section(s)	Changed from	Changed to	Rationale
Appendix B (Schedule of Assessments – 5/14 Phase 2, footnotes c, d, and h) Appendix C (Schedule of Assessments – 2/7 Phase 1b, Continuous Dosing Subjects, footnotes c, d, and g) Appendix C (Schedule of Assessments – 2/7 Phase 1b, Step-up Dosing Subjects, footnotes c, d, and g) Appendix D (Schedule of Assessments – 2/7 Phase 2, footnotes c, d, and h)			
Appendix A (Schedule of Assessments – 5/14 Phase 1b, Continuous Dosing Subjects, footnote r) Appendix A (Schedule of Assessments – 5/14 Phase 1b, Step-up Dosing Subjects, footnote r)	For patients with ≥ SD for at least 6 months (12 cycles), who are on a steady dose for ≥ 2 cycles, and are tolerating oprozomib, study assessments may be reduced to every 2 cycles (starting at Cycle 13, Day 1, then Cycle 15, Day 1, etc.) and 2 cycles of study medication can be provided at clinic visits. Subjects who do not meet these criteria should continue to have study assessments performed at every cycle.	For patients with ≥ SD for at least 6 months (12 cycles), who are on a steady dose for ≥ 2 cycles, and are tolerating oprozomib, study assessments may be reduced to every **4** cycles (starting at Cycle 13, Day 1, then Cycle 15, Day 1, etc.) and **4** cycles of study medication can be provided at clinic visits. Subjects who do not meet these criteria should continue to have study assessments performed at every cycle.	Provide convenience for those on study treatment as study has completed its abbreviated report

Section(s)	Changed from	Changed to	Rationale
Appendix B (Schedule of Assessments – 5/14 Phase 2, footnote r) Appendix C (Schedule of Assessments – 2/7 Phase 1b, Continuous Dosing Subjects, footnote r) Appendix C (Schedule of Assessments – 2/7 Phase 1b, Step-up Dosing Subjects, footnote r) Appendix D (Schedule of Assessments – 2/7 Phase 2, footnote r)			
Appendix K (Example Electronic Serious Adverse Event Contingency Report Form)	*New text added*		Provide updated adverse event reporting form.

Section(s)	Changed from	Changed to	Rationale
			

AMGEN
Study # 20130408
Oprozomib

Electronic Serious Adverse Event Contingency Report Form
For Restricted Use

Reason for reporting this event via fax
The Clinical Trial Database (eg, Rave):
☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION
Site Number | Investigator | Country
Reporter | Phone Number ( ) | Fax Number ( )

2. SUBJECT INFORMATION
Subject ID Number | Age at event onset | Sex ☐F ☐M | Race | If applicable, provide End of Study date

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term:
and start date: Day ____ Month ____ Year _____

3. SERIOUS ADVERSE EVENT
Provide the date the investigator became aware of this information: Day Month Year

Serious Adverse Event (diagnosis or symptoms) If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Serious and/or unexpected (SAE) (check all that apply)	Relationship Is there a reasonable possibility that the event may have been caused by IP or an Amgen device used to administer the IP?	Outcome of Event Resolved; Resolved With Sequelae; Fatal; Unknown	Check only if event is subject to study procedures (eg, biopsy)
			☐Yes ☐No				
			☐Yes ☐No				
			☐Yes ☐No				

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4
Date Admitted Day Month Year | Date Discharged Day Month Year

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

		Date of Initial Dose Day Month Year	Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
IPI/Amgen Device								
Oprozomib	☐Blinded ☐Open-label							☐ Unknown ☐ Unavailable / Withheld
Oprozomib	☐Blinded ☐Open-label							☐ Unknown ☐ Unavailable / Withheld

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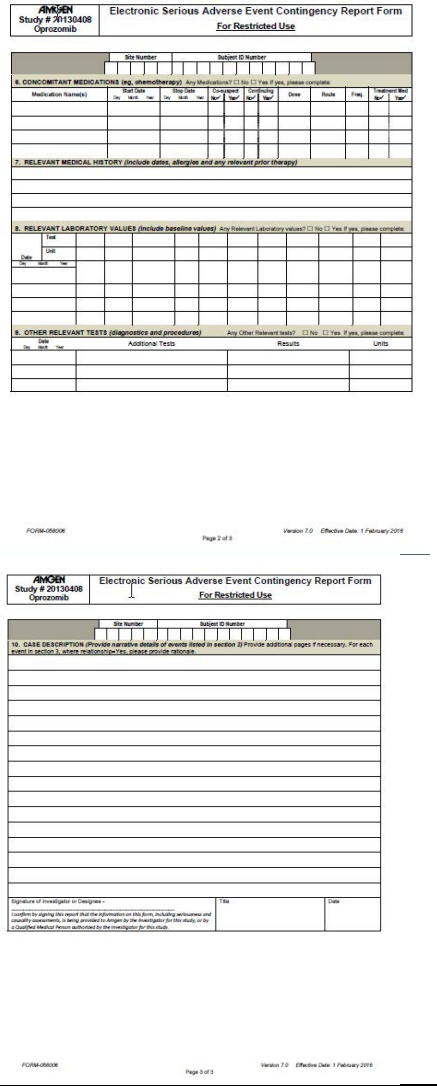
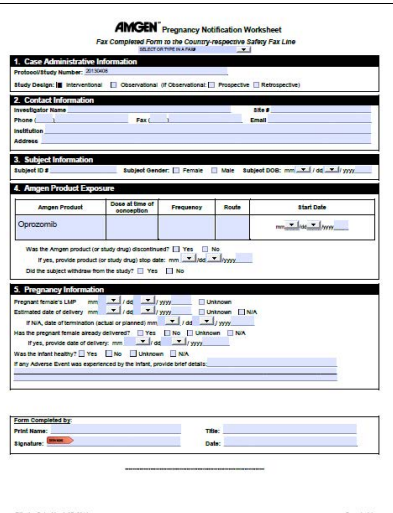
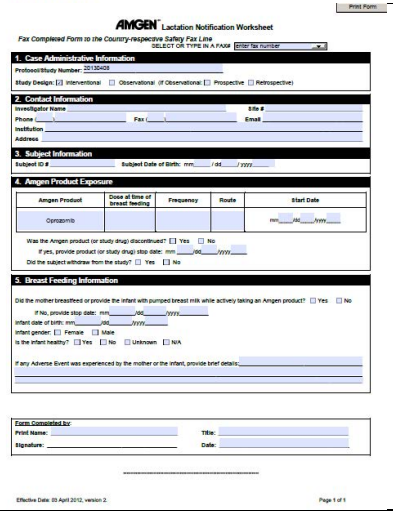
Section(s)	Changed from	Changed to	Rationale
			

Section(s)	Changed from	Changed to	Rationale
Appendix L (Example Amgen Pregnancy Notification Worksheet)	*New text added*		Provide updated pregnancy reporting worksheet.
Appendix M (Example Amgen Lactation Notification Worksheet)	*New text added*		Provide updated lactation reporting worksheet.

APPENDIX K SUMMARY OF CHANGES IN PROTOCOL 2012-001 AMENDMENT 3

The key changes in Amendment 3 are listed below:

1. Addition of the new Oprozomib ER formulation Tablets
2. Addition of the step-up dosing for dose escalation
3. Addition of additional clinic visits for safety assessments
4. Addition of PK and PD assessments based on new dosing and formulation
5. Addition of assessments of orthostatic hypotension and management
6. Updates to safety and efficacy information from oprozomib studies
7. Updates to Inclusion/Exclusion criteria
8. Updates to phototoxicity risk with oprozomib

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. Changes in the schedules of assessments have been updated to be current with the revised study plan and assessment schedule. Please see body of the protocol and the schedules of assessments for additional details. Added text is presented in bold format.

APPENDIX I: SUMMARY OF CHANGES IN PROTOCOL 2012-001 AMENDMENT 2

Study 2012-001 was amended to incorporate FDA requested changes/additions, specifically with regard to the definition of dose-limiting toxicities as applied to the Phase 1b component of the study and the incorporation of specific guidelines for the Prophylaxis and Management of Tumor Lysis Syndrome (TLS). The key changes in Amendment 2 are listed below:

1. Study Synopsis (Study Design) and Section 6.3 Dose-Limiting Toxicity: The text was edited to classify Grade ≥ 4 abnormalities in serum creatinine or electrolytes as DLTs; Grade ≥ 3 acute kidney injury defined as creatinine > 3 × baseline or > 4.0 mg/dL of any duration is to be considered a DLT; and occurrence of Grade ≥ 3 nausea, vomiting, constipation or diarrhea of > 7 days duration in spite of optimal management, including a 5-HT3 antagonist and aprepitant for nausea and vomiting, and loperamide (e.g., Imodium®) and diphenoxylate/atropine (e.g. Lomotil®) for diarrhea is to be considered a DLT.
2. Sections 6.5 and 6.6.1: Text was added to provide guidance for monitoring/prophylaxis and treatment of tumor lysis syndrome.

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. Added text is presented in bold format.

APPENDIX I: SUMMARY OF CHANGES IN PROTOCOL 2012-001 AMENDMENT 1

Study 2012-001 was amended to implement a new starting dose for Oprozomib Tablets for both dosing schedules based on dose-escalation data from ongoing Study 2011-001. This and other key changes in Amendment 1 are listed below:

1. Global change: Starting dose of 150 mg was changed to 210 mg for both oprozomib dosing schedules. This update was made based on dose-escalation data from ongoing Study 2011-001 from both tablet and product-in-capsule (PIC) formulations.
2. Global change: Changed units for absolute neutrophil count (ANC) and platelet counts from [value] $\times 10^9$/L to standard units, [value] cells/mcL.
3. Study Synopsis (Test Product, Dose, and Mode of Administration): Removed specific dexamethasone oral tablet strengths (4 mg and 6 mg). This text did not appear in the protocol body.
4. Section 1.4.1: Added dose rationale for 210 mg starting dose of Oprozomib Tablets based on preliminary safety results from Study 2011-001, PK data demonstrating comparable exposures between the tablet and capsule, and rationale for the combination of oprozomib with low-dose dexamethasone as a means to reduce gastrointestinal (GI) toxicity.
5. Section 3.4, Appendix A and Appendix B (footnote 1): Added that subjects continuing on study treatment and whose disease has not progressed 1 year after starting study treatment will reduce the frequency of their visits (on Day 1 of their next scheduled cycle) to every 4 weeks instead of every 2 weeks, with adequate drug supply for 2 cycles of treatment. Also clarified that disease response will be assessed every 8 weeks (4 cycles) after 1 year on therapy.
6. Section 4.1: Clarified in Inclusion Criterion #5 that bilirubin must be $\leq$ 1.5 times the upper limit of normal (ULN) *in the absence of Gilbert's disease or hemolysis*.
7. Section 4.2: Clarified in Exclusion Criterion #3 that glucocorticoid therapy within 14 days prior to randomization that exceeds a cumulative dose of 160 mg of dexamethasone or equivalent is not allowed.
8. Section 4.2: Added Exclusion Criterion #10, uncontrolled hypertension or uncontrolled diabetes.
9. Section 4.2: Deleted Exclusion Criteria #14, patients with pleural effusions requiring routine thoracentesis, and #15, patients with ascites requiring routine paracentesis.
10. Section 4.2: Updated Exclusion Criterion #18 to add "increased patient risk" to the criterion.

11. Section 6.1: Appendices A and B (footnote 23): Provided clarification that dexamethasone must be taken *at least 30 minutes* prior to oprozomib.
12. Section 6.1: Specified that oprozomib will be administered in combination with dexamethasone at 20 mg orally *(or intraveneously, if tablets are unavailable or subject cannot tolerate tablets).*
13. Section 6.2.2: Added that intrasubject dose escalation to the recommended Phase 2 dose may be permitted once that dose has been determined and after discussion between the treating physician and Onyx medical monitor.
14. Section 6.3: Added note that ≥ Grade 3 dexamethasone-related hyperglycemia is not considered a DLT.
15. Section 6.3: Added note that Grade 3 fatigue lasting < 14 days is not considered a DLT.
16. Section 6.6.1: Added recommended concomitant medications, valacyclovir and lansoprazole, for prevention of herpes zoster and peptic disease, respectively.
17. Sections 7.3.1–7.3.4, Appendix A and Appendix B (footnotes 15-18), and Appendix G: Updated protocol body and schedule of assessments to provide clarification and flexibility around PK and PDn sampling timepoints. For Phase 2 subjects, also provided clarity that subjects must fast before and after study drug administration on PK sampling days.
18. Section 9.3.1: Revised the text for how AEs are captured for subjects who do not receive any study drug.
19. Appendix A: Removed redundant term, cytogenetics, to clarify that FISH is the cytogenetic technique that will be used..
20. Appendix A: Added missing Cycle 2, Day 3 and 4 column that includes administration of oprozomib, administration of optional antiemetics, and recording of AEs and concomitant medications.
21. Appendices A and B (footnote 9): Added that serum chemistry and complete blood count (CBC) on Cycle 2, Day 5 will be completed for Phase 2 only (if PK or PDn sample is being collected).
22. Appendices A and B (footnote 12): Added that, if present at Baseline, bone lesions must be monitored every 2 cycles throughout the study.
23. Appendices A and B (footnote 13): Provided clarification that, in addition to Screening and End of Study assessments, subjects with plasmacytoma(s) at Baseline must also be monitored *every 2 cycles* throughout the study per IMWG response criteria.
24. Appendices A and B (footnote 14): Add clarification that bone marrow aspirate will also be collected at the time of progression (may be at time of treatment discontinuation or during long-term follow up) for subjects who have signed the separate consent.
25. Appendix B: Added missing timepoint for Cycle 2, Day 1 PDn/Proteomic analyses.

26. Appendix F (EBMT criteria): Updated criteria for minimal response based on Kyle 2009 article on response assessment in multiple myeloma.

Minor editorial changes and updates to style and formatting have been made to improve clarity and consistency throughout the document.

Detailed 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. Deleted text is presented in strikethrough format. Revised text is presented in bold format.