16.1.1 Protocol and Amendments

Protocol Amendment 3, dated 07 March 2018 was generated and approved. Shortly thereafter, a decision was made to terminate the study program, the amendment was not implemented. The last version of the protocol, under which the study was active, was Amendment 2, dated 2014 March 20.

CLINICAL STUDY PROTOCOL

Protocol Title:	Phase 1b Multicenter Study of Oprozomib, Pomalidomide, and Dexamethasone in Primary Refractory or Relapsed and Refractory Multiple Myeloma Subjects
Protocol Number:	OPZ007
Name of Investigational Product:	Oprozomib ER Tablets
IND Number:	117,851
NCT Number:	**NCT01999335**
Sponsor:	Onyx Therapeutics**, Inc.** **One Amgen Center Drive** **Thousand Oaks,** CA 9**1320, USA** **Phone: (805) 447-1000**
Study Medical Monitor:	[redacted] MD **Medical Director, Early Development** **1120 Veterans Blvd** South San Francisco, CA 94080 **USA** **Phone**: [redacted] Email: [redacted]
Investigator(s):	[redacted] MD Assistant Professor Department of Lymphoma/Myeloma MD Anderson Cancer Center 1515 Holcombe Blvd., Unit 429 Houston, Texas 77030 Office: [redacted] Cell: [redacted] Email: [redacted]
Date of Original Protocol:	15 August 2013
Date of Amendment 1.0:	21 March 2014
Date of Amendment 2.0:	08 July 2014
Date of Amendment 3.0:	**07 March 2018**
Confidentiality Statement:	This material is the property of Onyx Therapeutics (a wholly owned subsidiary of Onyx Pharmaceuticals, an Amgen subsidiary). The material is highly confidential and is to be used only in connection with matters

Compliance Statement:

This study will be conducted in accordance with Protocol OPZ007, the International **Council for** Harmonisation (ICH), Good Clinical Practice (GCP) guidelines, and the applicable country and regional regulatory requirements.

PROTOCOL ACCEPTANCE PAGE

Issue/Date: OPZ007 (07 March 2018)

I have read this protocol for Study OPZ007 entitled:

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

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) while conducting this clinical investigation. Once signed, the original of this form should be detached from the protocol and returned to Onyx Therapeutics or its designee (please retain a copy for your files).

1 SYNOPSIS

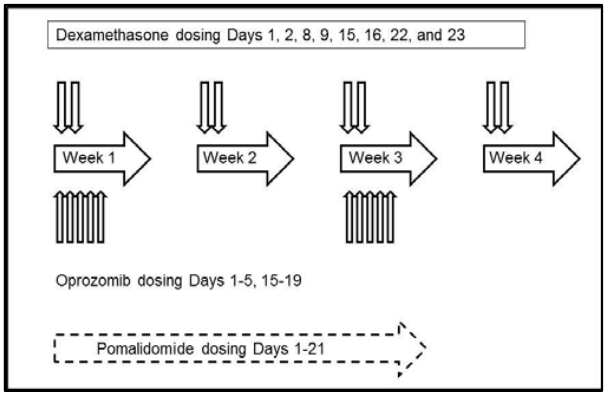
Name of sponsor/company:	Onyx Therapeutics
Name of product:	Oprozomib
Title of study and protocol number and phase:	Protocol Number: OPZ007 Phase 1b Multicenter Study of Oprozomib, Pomalidomide, and Dexamethasone in Primary Refractory or Relapsed and Refractory Multiple Myeloma Subjects
Study objective(s):	Primary Objectives • To determine the maximum tolerated dose (MTD) and identify the recommended Phase 3 dose (RP3D) and schedule of oprozomib in combination with pomalidomide and dexamethasone (OPomd) in subjects with primary refractory or relapsed and refractory multiple myeloma • To evaluate the safety and tolerability of the OPomd combination in subjects with primary refractory or relapsed and refractory multiple myeloma Secondary Objectives • To estimate the overall response rate (ORR) of OPomd, defined as the proportion of subjects with an overall response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) as determined by investigator according to the International Myeloma Working Group - Uniform Response Criteria (IMWG-URC) • To estimate the clinical benefit rate (CBR) of OPomd, defined as the proportion of subjects with an overall response of minimal response (MR) or better as determined by investigator according to the IMWG-URC and modified European Group for Blood and Marrow Transplantation (EBMT) criteria • To characterize the pharmacokinetics (PK) of oprozomib in the OPomd regimen Exploratory Objectives • To evaluate the pharmacodynamic (PDn) biomarkers that may correlate with antitumor activity • To evaluate genomic biomarkers that may correlate with antitumor activity and resistance following treatment with proteasome inhibitors • To evaluate (in the dose-expansion portion only) the patient-reported outcomes (PRO) using the tools listed below: o Bone pain and the impact of bone pain measured with the Brief Pain Inventory - Short Form (BPI-SF) o Health-related quality of life (HRQoL) measured by the global health status/QoL scale of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Module (QLQ-C30) questionnaire o Health status assessed by the EQ-5D-5L o Disease symptoms as measured by the disease symptoms subscale of the EORTC Multiple Myeloma Module (QLQ-MY20) questionnaire o Neurotoxicity symptoms as measured by the neurotoxicity subscale of the Functional Assessment of Cancer Therapy / Gynecological Oncology Group - Neurotoxicity (FACT/GOG-Ntx4 [(Version 4]) questionnaire

Study design: This is a Phase 1b study of oprozomib in combination with pomalidomide and dexamethasone in subjects with primary refractory or relapsed and refractory multiple myeloma. **This study** includes an open-label, Phase 1b, dose-escalation and dose-expansion portion (equivalent to a small Phase 2), during which the RP3D will be identified. Further evaluation of safety and activity will be assessed during the dose-expansion portion. During th**is** study, subjects will receive Oprozomib extended release (ER) Tablets according to their assigned dose cohort.

This study will include subjects with primary refractory or relapsed and refractory multiple myeloma, ie, those who have demonstrated disease progression on or within 60 days of their last therapy, and who have received at least 2 prior lines of therapy (including bortezomib and lenalidomide and/or thalidomide, and in the dose-expansion portion of the study only, been treated with adequate alkylator therapy). Subjects whose last therapy was bortezomib and who were not refractory but developed bortezomib intolerance, as defined by the development of Grade 2 peripheral neuropathy with pain or ≥ Grade 3 peripheral neuropathy after ≥ 2 consecutive cycles, are eligible.

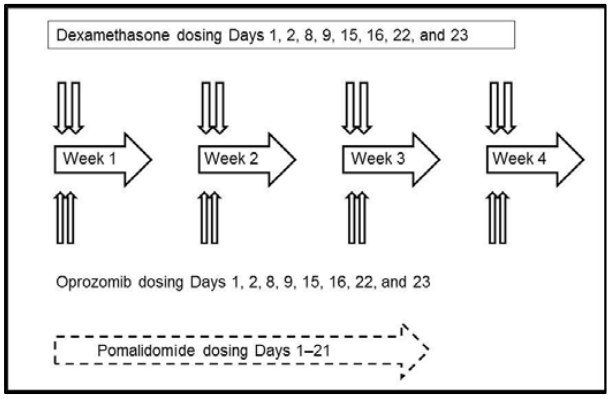
Treatment cycles are 28 days in duration. Two (2) oprozomib dosing schedules will be assessed during dose escalation. All study subjects will receive oprozomib once daily either on Days 1–5 and 15–19, referred to hereafter as the 5/14 schedule, or an alternate schedule of once daily on Days 1, 2, 8,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

5/14 Schedule Study Dosing Schema



Study design (cont'd):

2/7 Schedule Study Dosing Schema



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

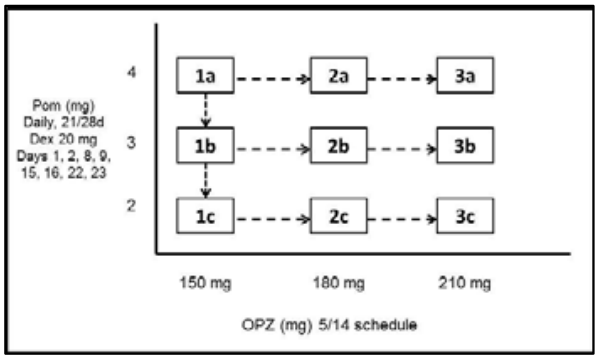
There is no planned maximum dose of oprozomib to be studied as it is being added to the FDA-approved regimen of pomalidomide/dexamethasone, however, this could be imposed at any time during the course of the study, based on Sponsor discretion. The starting dose of oprozomib for the 5/14 schedule is 150 mg, 3 dose levels below the established 5/14 single-agent MTD of 240 mg. The starting dose of oprozomib for the 2/7 schedule is 210 mg, 3 dose levels below the established 2/7 single-agent MTD of 300 mg. Following dose escalation, the sponsor has the option of expanding 1 or both schedules in order to establish the RP3D and schedule.

Study design (cont'd):

Dose-Escalation Schema for the 5/14 Oprozomib Dosing Schedule

The starting dose for the 5/14 schedule will be 150 mg of oprozomib and 4 mg of pomalidomide. The 5/14 primary and alternate paths are summarized below; these are examples, and are not inclusive of all possible dose-escalation paths.

5/14 Schedule Primary Study Dose-Escalation Paths[a]



5/14 = Dosing on Days 1–5 and 15–19; Dex = dexamethasone; OPZ = oprozomib; Pom = pomalidomide.

[a] There is no predefined maximum dose level of oprozomib being studied.

Study design (cont'd):

Primary Dose-Escalation Path for Oprozomib on 5/14 Schedule with Pomalidomide 4mg in Phase 1b

Cohort	Oprozomib Dose (mg/day)	Pomalidomide Dose (mg/day)
1a (initial cohort)	150	4
2a	180	4
3a	210	4

5/14 = Dosing on Days 1–5 and 15–19; MTD = maximum tolerated dose.

Note: This is an example of the primary dose-escalation cohort. Dose escalation will continue in 30-mg increments of oprozomib at sponsor discretion or until the MTD has been identified.

Alternative Dose-Escalation Path 1 for Oprozomib on 5/14 Schedule with Pomalidomide in Phase 1b if Cohort 1a Exceeds the MTD, or at Sponsor Discretion

Cohort	Oprozomib Dose (mg/day)	Pomalidomide Dose (mg/day)
1b	150	3
2b	180	3
3b	210	3

5/14 = Dosing on Days 1–5 and 15–19; MTD = maximum tolerated dose.

Alternative Dose-Escalation Path 2 for Oprozomib on 5/14 Schedule with Pomalidomide in Phase 1b if Cohort 1b Exceeds the MTD, or at Sponsor Discretion

Cohort	Oprozomib Dose (mg/day)	Pomalidomide Dose (mg/day)
1c	150	2
2c	180	2
3c	210	2

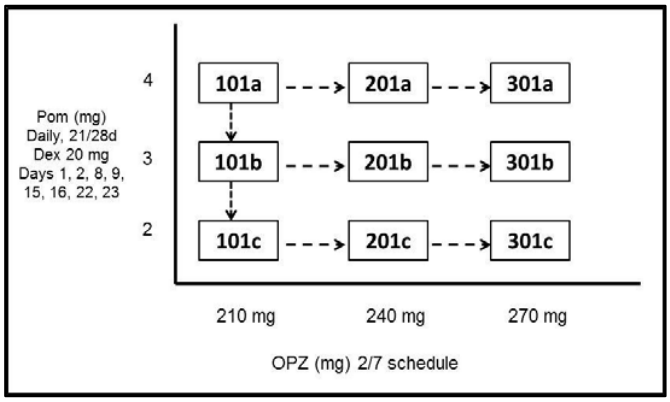
5/14 = Dosing on Days 1–5 and 15–19; MTD = maximum tolerated dose.

Study design (cont'd):

Dose-Escalation Schema for the 2/7 Oprozomib Dosing Schedule

The starting doses for the 2/7 oprozomib dosing schedule will be 210 mg of oprozomib and 4 mg of pomalidomide. The 2/7 primary and alternate paths are summarized below; these are examples, and are not inclusive of all possible dose-escalation paths.

2/7 Schedule Primary Study Dose-Escalation Paths[a]



2/7 = Dosing on Days 1, 2, 8, 9, 15, 16, 22, and 23; Dex = dexamethasone; OPZ = oprozomib; Pom = pomalidomide.

[a] There is no predefined maximum dose level of oprozomib being studied.

Primary Dose-Escalation Path for Oprozomib on 2/7 Schedule with Pomalidomide 4 mg in Phase 1b

Cohort	Oprozomib Dose (mg/day)	Pomalidomide Dose (mg/day)
101a (initial cohort)	210	4
201a	240	4
301a	270	4

2/7 = Dosing on Days 1, 2, 8, 9, 15, 16, 22, and 23; MTD = maximum tolerated dose.

Note: This is an example of the primary dose-escalation cohort. Dose escalation will continue in 30-mg increments of oprozomib at sponsor discretion or until the MTD has been identified.

Study design (cont'd):

Alternative Dose-Escalation Path 1 for Oprozomib on 2/7 Schedule with Pomalidomide in Phase 1b if Cohort 101a Exceeds the MTD, or at Sponsor Discretion

Cohort	Oprozomib Dose (mg/day)	Pomalidomide Dose (mg/day)
101b	210	3
201b	240	3
301b	270	3

2/7 = Dosing on Days 1, 2, 8, 9, 15, 16, 22, and 23; MTD = maximum tolerated dose

Alternative Dose-Escalation Path 2 for Oprozomib on 2/7 Schedule with Pomalidomide in Phase 1b if Cohort 101b Exceeds the MTD, or at Sponsor Discretion

Cohort	Oprozomib Dose (mg/day)	Pomalidomide Dose (mg/day)
101c	210	2
201c	240	2
301c	270	2

2/7 = Dosing on Days 1, 2, 8, 9, 15, 16, 22, and 23; MTD = maximum tolerated dose

At the sponsor's discretion, once the MTD for oprozomib is reached on 1 or both schedules, or if the initial cohort exceeds the MTD, additional dose escalation with oprozomib may continue with lower doses of pomalidomide down to the 2-mg dose level.

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

Dose-Limiting Toxicities

During th**is** study, assessment of DLTs will occur during the 28-day period of Cycle 1 combination therapy. For the purposes of this study, a DLT is defined as any of the study drug-related events listed below occurring within the 4 weeks after the first dose of combination therapy. Study drug is defined as the combination of oprozomib, pomalidomide, and dexamethasone. Study drug-related is defined as a reasonable likelihood of clinical causality based on time of event, biology, dechallenge improvement, and that the adverse event (AE) was not likely explained by the subject's clinical state, underlying disease, concomitant medication, or study/nonstudy procedure.

- Any toxicity requiring a dose reduction or requiring that a dose of oprozomib or pomalidomide be held in Cycle 1 that does not meet the criteria for DLT will be discussed by the CSRC to determine whether the subject should be considered evaluable for DLT determination. If it is determined that the subject is not evaluable for DLT, the subject will be replaced.
- A delay in ability to receive Day 1 dose of Cycle 2 due to a hematologic or nonhematologic drug-related toxicity persisting beyond 14 days from Cycle 1 Day 28 will be considered a DLT

Study design (cont'd):

- For a nonhematologic DLT, any ≥ Grade 3 toxicity will be considered a DLT with exceptions as described below:
  - Grade 3 asymptomatic electrolyte abnormalities will not be considered a DLT
  - Asymptomatic Grade 3 hypophosphatemia lasting less than 24 hours will not be considered a DLT
  - Grade 3 nausea and vomiting will not be considered a DLT unless persisting longer than 3 days despite optimal supportive care, which at a minimum must include a 5-hydroxytryptamine type-3 ($5\text{-}HT_3$) antagonist and aprepitant
  - Grade 3 diarrhea will not be considered a DLT unless persisting longer than 3 days despite optimal supportive care, which at a minimum must include loperamide (Imodium) and atropine diphenoxylate (Lomotil)
  - Grade 3 fatigue lasting < 14 days is not considered a DLT
  - ≥ Grade 3 hyperglycemia or toxicity attributed to dexamethasone is not considered a DLT
  - ≥ Grade 3 rash attributed specifically to pomalidomide is not considered a DLT
- Hematologic DLTs consist of the following:
  - Grade 4 neutropenia:
    - Absolute neutrophil count (ANC) < 0.5×10^9/L lasting ≥ 7 days despite adequate growth factor support (eg, granulocyte-colony stimulating factor [G-CSF])
    - Febrile neutropenia: Any single temperature ≥ 38.3°C or a sustained temperature of ≥ 38.0°C for over 1 hour with ≥ Grade 3 neutropenia (ANC < 1.0×10^9/L)
  - Thrombocytopenia:
    - Grade 4 lasting ≥ 7 days, or
    - Grade 4 lasting < 7 days with Grade 2 clinically significant bleeding or < 10,000 platelets requiring platelet transfusion, or
    - Grade 3 with clinically significant bleeding or requiring platelet transfusion

  Note: Grade 4 anemia is not considered a DLT

Subject Replacement

Subjects must meet the following criteria to be considered evaluable for MTD determination during the 4-week DLT evaluation period unless a DLT occurs before the subject receives all planned doses of oprozomib for both the 5/14 and 2/7 dosing schedules:

- A minimum of 17 of 21 planned doses of pomalidomide must be received
- A minimum of 6 of 8 planned doses of dexamethasone must be received
- All planned doses of oprozomib must be received

Subjects not meeting all of the above criteria or assessed as unevaluable by the CSRC will be replaced. Each subject in the cohort under review will be discussed and assessed. Once all data have been presented, the CSRC will decide on the most appropriate course of action regarding dose escalation based on guidance in Section 5.1.

Study design (cont'd):	**Dose Expansion** The criteria for selecting the RP3D for 1 or both schedules of oprozomib at the sponsor's discretion will include assessment of the safety, tolerability, and preliminary activity observed across multiple cycles of therapy. In addition, both PK and PDn assessments to demonstrate adequate exposure and proteasome inhibition will be a key factor. Therefore, the RP3D may differ from the MTD. Once the MTD(s) has been determined and the recommended dose for the expansion phase has been selected, a minimum of 20 additional subjects for 1 or both schedules of oprozomib at the sponsor's discretion will be enrolled in the dose-expansion portion **of the study** in order to continue the evaluation of the safety and efficacy of the regimen. The safety of subjects in the Dose Expansion will be monitored on an ongoing basis by the CSRC during regularly scheduled calls. This information will inform the selection of a RP3D and schedule by the sponsor and CSRC.
Number of investigational sites:	Approximately 35 study sites will participate in **this** study (15 sites for the dose-escalation and 20 additional sites for the dose-expansion portions of the study).
Planned number of subjects:	A total enrollment of approximately 82 subjects is planned for th**is** study. During the Dose-Escalation portion, approximately 21 subjects will be enrolled for each schedule. The estimate assumes the need to enroll up to 6 subjects in 3 different dose cohorts and the need for replacement of 1 in 6 subjects in order to enable MTD determination. The RP3D may differ from the MTD depending on observed safety and activity data during dose escalation. A minimum of 20 additional subjects are planned for enrollment for each schedule at the sponsor's discretion and treatment at the RP3D during the Dose-Expansion portion of the study.
Sample size justification:	The estimated sample size for the dose-escalation part of the study is based on standard 3 + 3 dose-escalation rules, with the expectation that 2–3 dosing cohorts of 3–6 subjects per cohort will be required to establish the MTD. A minimum of 20 additional subjects will be enrolled for each schedule at the sponsor's discretion during the dose expansion to acquire additional safety and efficacy experience for the RP3D in the population before initiation of the Phase 3 portion of the study. In the dose-expansion portion of the study, if the true ORR $\geq$ 40% then the probability of seeing at least 7 responses among the 26 subjects (6 treated at the MTD during escalation + 20 in the expansion) in either schedule is approximately 94%.
Study populatio n:	The study population will consist of subjects with primary refractory or relapsed and refractory, multiple myeloma, ie, those who have demonstrated disease progression on or within 60 days of their last therapy, and who have received at least 2 prior lines of therapy (including bortezomib and lenalidomide and/or thalidomide, and in the dose-expansion portion of the study only, been treated with adequate alkylator), and who are considered to be appropriate for this clinical study by their treating physicians.
Test product, dose, and mode of administration:	Oprozomib ER Tablet in strengths of 150, 180, 210, 240, and 270 mg Oral pomalidomide with capsule strengths of 1, 2, 3, and 4 mg Oral dexamethasone with tablet strengths of 4 and 6 mg
Reference therapy, dose, and mode of administration:	**Active control** Oral pomalidomide with capsule strengths of 1, 2, 3, and 4 mg Oral dexamethasone with tablet strengths of 4 and 6 mg

Treatment regimen(s):	Oral oprozomib taken Days 1–5 and 15–19 or Days 1, 2, 8, 9, 15, 16, 22, and 23, pomalidomide taken on 21 of 28 days, and oral dexamethasone taken on Days 1, 2, 8, 9, 15, 16, 22, and 23
Inclusion criteria:	**Disease Related** 1. Multiple myeloma that is primary refractory, relapsed and refractory, or intolerant after at least 2 lines of standard therapy for multiple myeloma including: a. ≥ 2 consecutive cycles of both bortezomib and lenalidomide or thalidomide (alone or in combination) b. In the dose-expansion portion of the study only: In addition to the above, treatment with adequate alkylator therapy, defined as: i. High-dose melphalan or other alkylating agent as conditioning for autologous or allogeneic stem cell transplant (SCT), or ii. ≥ 6 cycles of induction therapy, or iii. Progressive disease after ≥ 2 cycles 2. Measurable disease as indicated by 1 or more of the following: a. Serum M-protein ≥ 500 mg/dL b. Urine M-protein ≥ 200 mg/24 h c. Only for subjects without measurable M-protein by serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP), involved free light chain (FLC) concentration ≥ 10 mg/dL provided serum free light chain (SFLC) ratio is abnormal 3. Disease progression on or within 60 days of completion of the last therapy, or intolerance to bortezomib if received as their last therapy a. Patients who received bortezomib as their last therapy who were not refractory but developed bortezomib intolerance, as defined by the development of Grade 2 peripheral neuropathy with pain or ≥ Grade 3 peripheral neuropathy after ≥ 2 consecutive cycles, are eligible 4. Prior carfilzomib is allowed if a subject was not removed from carfilzomib therapy due to toxicity, unless approved by the **Sponsor's** study medical monitor. **Demographic** 5. Males and females ≥ 18 years old 6. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0–2 **Laboratory** 7. Adequate hepatic function, with bilirubin ≤ 1.5 times the upper limit of normal (ULN) in the absence of Gilbert's disease or hemolysis, and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 times ULN 8. ANC ≥ 1500/mm^3. Screening ANC should be independent of myeloid growth factor support for at least 1 week or 2 weeks for pegylated growth factors. 9. Hemoglobin ≥ 8.0 g/dL. Patients may receive red blood cell (RBC) transfusions or receive erythropoietin or darbepoetin alfa in accordance with institutional guidelines up to 1 week before Screening. 10. Platelet count ≥ 75,000 mm^3. Patients should not have received platelet transfusions for at least 1 week before Screening. 11. Uric acid, if elevated, must be correct to within laboratory normal range before dosing 12. Calculated or measured creatinine clearance (CrCl) ≥ 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.

Inclusion criteria (cont'd):	**Ethical/Other** 13. Patient must sign a written informed consent form in accordance with federal, local, and institutional guidelines 14. Female patients of childbearing potential must have a negative pregnancy test (with a sensitivity of at least 50 mIU/mL) within 1 day of the first dose of study drug, and agree to use 2 effective methods of contraception during the study and for 28 days following the last dose of study drug. Postmenopausal females (> 45 years old and without menses for ≥ 2 years) and surgically sterilized females are exempt from these requirements. 15. Male patients, including those with prior vasectomy, 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. Additionally, they must agree not to donate sperm while being treated and for up to 3 months after discontinuing treatment.
Exclusion criteria:	**Disease Related** 1. Systemic chemotherapy with approved or investigational anticancer therapeutics, intended to treat underlying malignancy, within 3 weeks before the first dose of study treatment or 6 weeks for antibody therapy 2. Dexamethasone at cumulative doses greater than 160 mg or equivalent within 21 days prior to the first dose of study treatment is not allowed. Use of topical or inhaled steroids is acceptable. 3. Radiation therapy within 3 weeks before first dose of study drug. Radioimmunotherapy within 8 weeks before first dose of study drug. 4. Plasmapheresis is not permitted at any time during the Screening period or while the subject is receiving study treatment. If a subject has started Screening procedures requiring plasmapheresis, or is anticipated to require plasmapheresis during or after the Screening period, this patient will be considered ineligible and should not be enrolled. 5. Autologous SCT within 8 weeks and allogeneic SCT within 16 weeks prior to initiation of study treatment. Patients with prior allogeneic SCT should not have evidence of moderate-to-severe graft-versus-host disease (as defined in Filipovich 2005) and must be approved by the **Sponsor's** study medical monitor. 6. Known hypersensitivity to any immunomodulatory drugs (IMiDs), including rash 7. Prior pomalidomide exposure a. For the Dose-Escalation portion of the study: Subjects requiring pomalidomide dose reduction or removal due to toxicity b. For the Dose-Expansion portion of the study: Prior pomalidomide treatment of any duration 8. Known hypersensitivity/toxicity or intolerance to dexamethasone 9. Prior exposure to oprozomib 10. Hypersensitivity, intolerance, or inability to take antithrombotic prophylaxis **Concurrent Conditions** 11. Major surgery within 3 weeks before first dose of study drug 12. Congestive heart failure (New York Heart Association Class III to IV), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, or myocardial infarction within 6 months before first dose of study drug 13. Acute active infection requiring systemic antibiotics, antivirals, or antifungals within 2 weeks before first dose of study drug 14. History of previous clinically significant gastrointestinal (GI) bleed in the 6 months prior to first dose of study drug

Exclusion criteria (cont'd):	15. Known or suspected human immunodeficiency virus (HIV) infection or patients who are HIV seropositive 16. Active hepatitis A, B, or C infection 17. Significant neuropathy (Grade 2 with pain or ≥ Grade 3) at the time of the first dose of study drug 18. Other malignancy within the past 3 years, except those considered cured by surgical resection; examples include some cases of: a. Adequately treated basal or squamous cell carcinoma of the skin b. Thyroid cancer c. Carcinoma in situ of the cervix or breast d. Prostate cancer with Gleason Score of 6 or less with stable prostate-specific antigen levels 19. Plasma cell leukemia 20. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) 21. Known amyloidosis 22. Female patients who are pregnant or nursing 23. Uncontrolled diabetes or hypertension 24. Inability to swallow medication, inability or unwillingness to comply with the drug administration requirements, or gastrointestinal condition that could interfere with the oral absorption or tolerance of treatment 25. Any contraindication to oral hydration (e.g., preexisting cardiac impairment or fluid restriction) 26. Any clinically significant psychiatric, social, or medical condition that, in the opinion of the investigator, could increase patient risk, interfere with protocol adherence, or affect a patient's ability to give informed consent
Overview of treatment and assessments:	Treatment cycles will last 28 days. Disease response assessments will be performed at the end of every 4-week cycle for the first 18 months on study, and at the end of every other cycle (every 8 weeks) thereafter, beginning with Month 20. Details are provided in Appendices A1, A2, B1, and B2 (Schedule of Assessments).
Criteria for evaluation:	
Efficacy variables:	Disease response assessments will be performed at the end of every 4-week cycle for the first 18 months of study treatment, and at the end of every other cycle (every 8 weeks) thereafter, beginning with Month 20, according to the IMWG-URC and modified EBMT criteria.
Safety variables:	Safety assessments will include monitoring and assessment of all AEs, clinical laboratory parameters, electrocardiograms (ECGs), and vital signs. Safety assessments will begin after the subject has signed the informed consent form and will continue until 30 days after the End of Study Treatment. The safety and tolerability of the study treatment will be assessed through documentation of AEs graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events ([NCI-CTCAE] Version 4.03).

Other:	**Pharmacokinetics** In the Dose-Escalation and Dose-Expansion portions of the study, blood samples will be collected from all subjects for determination of plasma concentrations of oprozomib at 1 predose time point and up to 7 postdose time points on Day 1 of Cycle 1 and Cycle 2 (0.25, 0.5, 1, 2, 3, 4, and 6 hours postdose) and 1 predose time point on Day 2 of Cycle 1 for both schedules. Population PK parameter estimates and variability in these estimates will be determined using a population-based analysis method. **Pharmacodynamics** Blood samples for quantitation of proteasome inhibition by oprozomib will be collected from all subjects in th**is** study. **Genomics** Analysis of genomic biomarkers that may predict response and resistance following treatment with proteasome inhibitors will be conducted for all subjects receiving oprozomib who consent to optional genomic biomarker analysis. These analyses will be performed on the required bone marrow aspirate obtained at Baseline (within 45 days prior to Cycle 1 Day 1 dosing; a portion of the bone marrow aspirate sample obtained at Baseline will be used; no additional sample is required), as well as a sample of blood and saliva also collected at Baseline. Bone marrow aspirate or biopsy collection does not need to be repeated if previously completed within 45 days prior to Cycle 1 Day 1 dosing. Additional bone marrow samples for biomarkers may be collected at disease progression (End of Study Treatment due to progressive disease [PD]) from all subjects who consent.
Statistical methods and analyses:	**Safety Population (All Subjects)** **T**he safety population includes all subjects receiving any amount of study treatment (oprozomib, pomalidomide, or dexamethasone). **Efficacy Population** For th**is** study, the efficacy population is equivalent to the safety population. **Endpoints** **Primary Endpoints** • DLTs • Adverse events and laboratory abnormalities graded according to NCI-CTCAE, Version 4.03 • Vital signs and clinical laboratory results during and following study drug administration **Secondary Endpoints** • Overall response, defined as the best response of sCR, CR, VGPR, or PR, as determined by investigator according to the IMWG-URC • Clinical benefit, defined as the best response of MR or better, as determined by the investigator, according to the IMWG-URC and modified EBMT criteria • Pharmacokinetic parameters, including maximum plasma concentration (C_{max}), time to maximum concentration (T_{max}), area under the plasma concentration time curve from time 0 to last time point ($AUC_{0-\tau}$), and area under the plasma concentration time curve from time 0 to time infinity ($AUC_{0-\infty}$) using noncompartmental methods

Statistical methods and analyses (cont'd):	**Exploratory Endpoints** • Pharmacodynamic biomarkers that may be correlated with antitumor activity • Genomic biomarkers that may be correlated with antitumor activity and resistance following treatment with proteasome inhibitors • Change over time in bone pain and the impact of bone pain measured with the BPI-SF (Dose Expansion only) • Change over time in the global health status/QoL scale of the EORTC QLQ-C30 (Dose Expansion only) • Change over time in health status assessed by EQ-5D-5L (Dose Expansion only) • Change over time in the disease symptoms subscale of the EORTC QLQ-MY20 (Dose Expansion only) • Change over time in neurotoxicity symptoms measured by the FACT/GOG-Ntx4 score (Version 4) (Dose Expansion only) **Efficacy Analyses** Progression-free survival and duration of response will be listed for all subjects by dose level and schedule. Overall response rate and clinical benefit rate will be estimated for all subjects treated at the RP3D along with the associated 95% exact binomial confidence intervals (CIs). **Safety Analyses** For th**is** study, safety will be assessed through summaries of DLTs, AEs, changes in laboratory test results, ECGs, vital signs, and oprozomib, pomalidomide, and dexamethasone exposure. All AE data collected will be listed by study site, cohort, subject number, and study day.

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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-HT_3	5-hydroxytryptamine type-3
ADCC	antibody-dependent cytotoxic T-cell activity
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
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0-\infty}$	area under the plasma concentration time curve from time 0 to time infinity
AUC_{0-t}	area under the curve at the last measurable time point
BPI-SF	Brief Pain Inventory – Short Form
C	Cycle
CBC	complete blood count
CBR	clinical benefit rate
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum plasma concentration
CPomd	carfilzomib + pomalidomide + dexamethasone
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CSRC	Cohort Safety Review Committee
CTCAE	Common Terminology Criteria for Adverse Events
CT-L	chymotrypsin-like
CYP1A2	cytochrome P450, 1A2 (enzyme)
CYP3A	cytochrome P450 3A (enzyme)
D	Day
D/C	discontinue
DLT	dose-limiting toxicity
DOR	duration of response
DVT	deep vein thrombosis
EBMT	European Group for Blood and Marrow Transplantation
ECG	electrocardiogram

Abbreviation	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immmunosorbent assay
EORTC	European Organization for Research and Treatment of Cancer
ER	Extended Release
EU	European Union
EQ-5D-5L	European Quality of Life – Descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression)
FACT/GOG-Ntx	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity subscale questionnaire
FCBP	females of childbearing potential
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FLC	free light chain
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GFR	glomerular filtration rate
GI	gastrointestinal
GLP	Good Laboratory Practices
H_2	histamine 2 blocker
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International **Council for** Harmonisation
IEC	Independent Ethics Committee
IMiDs	immunomodulatory drug(s)
IMWG-URC	International Myeloma Working Group-Uniform Response Criteria
IND	Investigational New Drug
IP	investigational product
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous(ly)
K/λ	kappa lambda
MAD	maximum administered dose

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MR	minimal response
MTD	maximum tolerated dose
NA	not applicable or not available
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NF-Kappa B	nuclear factor kappa light chain enhancer of activated B cells
NHL	non-Hodgkin lymphoma
OPomd	oprozomib + pomalidomide + dexamethasone
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PDn	pharmacodynamic(s)
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PN	peripheral neuropathy
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes
Pomd	pomalidomide + dexamethasone
PR	partial response
PRO	patient-reported outcomes
QLQ-C30	Quality of Life Core Module
QOL	quality of life
QT_c	corrected QT interval
RBC	red blood cell
RP3D	recommended Phase 3 dose
SAE	serious adverse event
SAH	subachnoid hemorrhage
SAP	Statistical Analysis Plan
sCR	stringent complete response
SCT	stem cell transplant
SD	stable disease
SFLC	serum free light chain
SPEP	serum protein electrophoresis
TLS	tumor lysis syndrome
T_{max}	time to maximum plasma concentration
ULN	upper limit of normal

Abbreviation	Definition
UPEP	urine protein electrophoresis
US	United States
VGPR	very good partial response
WBC	white blood cell
WES	whole exome sequencing
WGS	whole genome sequencing
WM	Waldenström macroglobulinemia

3 BACKGROUND INFORMATION

3.1 INTRODUCTION

This is a Phase 1b clinical trial of the oral proteasome inhibitor, oprozomib, in subjects with primary refractory or relapsed and refractory multiple myeloma. See Section 5 for a complete description of the study design.

The protocol has been amended with changes to the study design as new data became available from other ongoing oprozomib studies, and based on review of safety results from these studies. A summary of changes for each amendment is included in the appendix of each version of the protocol. The main purposes for each amendment are summarized below.

Amendment 1:

1. Added an alternative oprozomib dosing schedule consisting of 2 consecutive days every 7 days (2/7), as preliminary data suggest that a 2/7 schedule has single-agent activity, and may be better tolerated than the existing schedule of 5 consecutive days every 14 days (5/14 schedule).
2. Clarified that plasmapheresis is not permitted at any time during the study.
3. The starting dose of oprozomib was changed from 210 mg to 150 mg to provide increased margin of safety for subjects participating in this study. This dose (150 mg) is 3 dose levels below the single-agent MTD and was selected due to the overlapping toxicities of oprozomib with pomalidomide.
4. Additional dose modification text was added to the dose modification table for nonhematologic toxicities and guidance to investigators to mitigate Grade 4 gastrointestinal (GI) hemorrhage.

Amendment 2:

1. To allow subjects with prior carfilzomib exposure to be considered for inclusion in the study, if carfilzomib was not withdrawn due to toxicity.
2. To allow subjects with prior pomalidomide exposure to be considered for inclusion in the dose-escalation portion of the study, if pomalidomide was neither dose-reduced nor withdrawn due to toxicity.
3. To specify that only subjects who have been treated with adequate alkylator therapy are eligible to be considered for inclusion in the Phase 1b dose-escalation portion and Phase 3 portion of the study.
4. Additional safety guidance regarding Grade 3 or 4 GI hemorrhage (see Section 10.4.2.1.2), mandatory proton-pump inhibitors (see Section 10.6.1.5), and the addition of an exclusion criterion for patients with prior clinically significant

bleed in the 6 months prior to first dose of study treatment, because of toxicities observed in Study 2011-001.

5. Revisions in synopsis, statistical sections, objectives, and endpoints for accuracy, clarity, and consistency within the protocol.

Amendment 3:

1. **Data collection for subjects on active treatment is being pared down due to both the completion of this study's analysis and its abbreviated clinical study report.**

3.2 MULTIPLE MYELOMA BACKGROUND

Multiple myeloma, a clonal neoplastic proliferation of plasma cells, is the second most common hematologic malignancy and is responsible for approximately 11,000 deaths per year in the United States (US) and more than 19,000 deaths per year in Europe (American Cancer Society 2005; Boyle 2005). Multiple myeloma is characterized by anemia, bone destruction, monoclonal gammopathy, renal failure, hypercalcemia, and increased susceptibility to infections. The disease is systemic, and chemotherapy or novel agents are indicated for management of symptomatic myeloma. Current treatment options for relapsed/refractory myeloma commonly include single-agent or combination regimens using alkylators such as melphalan (Alkeran) or cyclophosphamide (Cytoxan), bortezomib (Velcade), carfilzomib (Kyprolis), an immunomodulatory drug (IMiD) such as thalidomide (Thalomid), lenalidomide (Revlimid), or pomalidomide (Pomalyst) with and without corticosteroids such as dexamethasone or prednisone, and other agents. Subjects aged 65 to 70 years or younger frequently undergo consolidation therapy with myeloablative chemotherapy or radiation followed by autologous stem cell transplantation (SCT). Carflizomib and pomalidomide received accelerated approval in the US to treat this patient population in 2012 and 2013, respectively. In the European Union (EU), pomalidomide has received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) for the treatment of patients with advanced myeloma and was approved in August 2013. Although improvements in progression-free survival (PFS) and overall survival (OS) have occurred in the past 5 years, even with the best available approved agents, essentially all patients eventually relapse. Median OS from diagnosis was reported at 3 years for high-risk patients, 4 to 5 years for intermediate-risk patients, and 8 to 10 years for standard-risk patients (Mikhael 2013).

3.3 PROTEASOME BACKGROUND

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

Proteasome inhibitors have been shown to have antiproliferative, proapoptotic, antiangiogenic, and antitumor activities across multiple tumor models. Treatment with oprozomib, carfilzomib, or bortezomib results in an increase in the accumulation of proapoptotic proteins, promotion of autophagy, and an increase in the stability of negative regulators of the cell cycle (Boccadoro 2005; Shen 2013; Zang 2012).

3.4 OPROZOMIB BACKGROUND

Oprozomib (formerly ONX 0912) is a tripeptide epoxyketone proteasome inhibitor and structural analogue of carfilzomib (Kyprolis) that primarily targets the CT-L activity of the 20S proteasome. Carfilzomib received accelerated approval in the US for the treatment of patients with multiple myeloma who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy (Kyprolis Prescribing Information [Onyx Pharmaceuticals 2012]). Similar to carfilzomib, oprozomib is a potent, selective, and irreversible inhibitor of the CT-L activity of the constitutive proteasome (the form of proteasome found in most cell types) and the immunoproteasome (the form of proteasome found in many hematopoietic cells) (Zhou 2009). In addition, when measured against a broad panel of proteases containing metallo-, aspartyl, cysteine, and serine proteases, oprozomib demonstrated minimal reactivity against nonproteasomal proteases.

Exposure to oprozomib is associated with potent pro-apoptotic activity across a broad panel of tumor-derived cell lines in culture. The antitumor efficacy of oprozomib has been tested in immunocompromised mice implanted with a variety of human tumor cell lines, including models of both solid (colorectal adenocarcinoma, non-small cell lung carcinoma) and

hematologic (multiple myeloma, non-Hodgkin lymphoma [NHL]) tumors, where its activity was equivalent to carfilzomib (Zhou 2009).

3.4.1 RELEVANT NONCLINICAL BACKGROUND

Oprozomib is orally bioavailable in plasma following solution administration in rodents and dogs. Pharmacodynamic (PDn) determinations demonstrate that proteasome inhibition of > 80% was readily achieved in blood and a wide variety of tissues at tolerated doses in rodents and in whole blood in dogs.

The safety of oprozomib has been established in Good Laboratory Practices (GLP)-compliant toxicity studies in rats and dogs. In 28-day repeat-dose studies, a suspension formulation of oprozomib was administered orally, once daily, for 5 consecutive days with 9 days rest (5 consecutive days bimonthly) for 2 complete 14-day cycles. Oprozomib was administered to rats at doses of 20, 30, and 40 mg/kg (120, 180, and 240 mg/m^2) and to dogs at 3, 6, and 10 mg/kg (60, 120, and 200 mg/m^2). A GLP-compliant, single-dose cardiovascular safety pharmacology study in dogs was also performed. The results of these studies show that oprozomib can be safely administered at doses that result in > 80% proteasome inhibition. This level of proteasome inhibition with carfilzomib has been shown to correlate with antitumor activity in subjects with malignancies.

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

3.4.2 RELEVANT CLINICAL BACKGROUND

3.4.2.1 Study 2009-003: Solid Tumors

Efficacy

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

Safety

The majority of adverse events (AEs) were Grade 1 and 2, manageable, and there were no apparent cumulative toxicities. The most common AEs were in the GI system organ class. This was consistent with preclinical animal studies with oprozomib. Dose-limiting toxicities for the once daily dose group in Study 2009-003 included Grade 3 dehydration/vomiting and Grade 3 hypophosphatemia in the 180 mg cohort. The maximum tolerated dose (MTD) for the once daily x5 days dose group is 150 mg. Dose-limiting toxicities for the split daily x5 days dosing group in Study 2009-003 included Grade 3 hypophosphatemia at 180 mg and Grade 5 upper GI hemorrhage and Grade 3 hallucinations at 210 mg. The MTD for the split dosing is 180 mg.

3.4.2.2 Study 2011-001: Hematologic Malignancies

Efficacy

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

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

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

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

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

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

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

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

Safety

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

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

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

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

Nineteen subjects (19) experienced serious adverse events (SAEs) across both schedules. The 11 treatment-related SAEs comprised 4 GI events (diarrhea, nausea/vomiting, fatigue/dehydration/nausea, and dehydration), 2 hematological events (anemia and neutropenia), 2 cases of TLS, 1 infection (pneumonia), and 1 general event

(fatigue/dehydration/nausea; events could be counted in more than 1 category). All of these are expected events based on the Oprozomib IB (Version 6). There were 2 cases of renal failure. There were also 2 Grade 5 GI hemorrhages at the 240 mg dose level on the 5/14 schedule.

3.4.2.3 Study 2012-001: Oprozomib in Combination with Dexamethasone in Multiple Myeloma

Efficacy

For the 2012-001 Phase 1b/2 study, as of 31 March 2014, 5 response-evaluable relapsed and/or refractory multiple myeloma subjects received Oprozomib Tablets on a 5 consecutive day bimonthly (5/14) schedule with daily dosing; 1 subject had MR and 4 subjects had SD as their best response. As of 31 March 2014, 8 response-evaluable subjects have received Oprozomib Tablets administered orally, once daily, on Days 1, 2, 8, and 9 of a 14-day cycle (2/7) in combination with 20 mg of dexamethasone; 1 subject had a VGPR (unconfirmed), 2 subjects had a partial response ([PR] confirmed or unconfirmed), 1 subject had a MR, and 4 subjects had SD as the best response.

Safety

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

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

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

3.4.2.4 Study OPZ003: Oprozomib in Combination with Lenalidomide and Dexamethasone in Multiple Myeloma

Efficacy

No efficacy data are available at this time.

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, 3 subjects have been enrolled. Two (2) subjects remain on study. One subject, a [redacted] year old [redacted] experienced a treatment-related SAE of Grade 3 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.

3.5 DOSE RATIONALE

3.5.1 OPROZOMIB

Early development of oprozomib focused on the 5 consecutive day bimonthly (either once or twice daily) (5/14) and 2 consecutive days weekly (2/7) schedules, both on 14-day treatment cycles. The MAD for Oprozomib Tablets administered once daily on a 5 consecutive day bimonthly schedule has been reached with a total daily dose of up to 270 mg in subjects with hematologic malignancies, with 1 dose-limiting toxicity (DLT) of TLS and 1 Grade 3 vomiting out of 6 subjects. At the 240-mg dose, 6 subjects were dosed with 1 DLT of TLS, therefore 240 mg was the declared as the MTD. For the 5/14 schedule, the starting dose of 150 mg of oprozomib will be added to the Food and Drug Administration (FDA)-approved

regimen of pomalidomide/dexamethasone, 3 dose levels below the MTD in the single-agent study.

For the 2/7 schedule, the MAD was reached with a total daily dose of 330 mg with 1 DLT of Grade 3 diarrhea and 1 DLT of Grade 4 thrombocytopenia. One DLT of Grade 3 orthostatic hypotension was reported in the 300-mg cohort, therefore 300 mg was declared the MTD. The starting dose for the 2/7 schedule in combination with Pomd will be 210 mg, 3 dose levels below the single agent MTD of 300 mg.

This study will assess both schedules in this study, as oprozomib has demonstrated preliminary activity in subjects with hematologic malignancies on both schedules (Kaufman, 2013).

3.5.2 DEXAMETHASONE

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 improved efficacy when administered 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 a previous study, the addition of steroids to a proteasome inhibitor reduced GI toxicity when compared with single-agent bortezomib (Jagannath, 2006). The addition of low doses of 4 mg of dexamethasone to oprozomib appears to reduce GI toxicity in Study 2011-001. Given that GI AEs have been the most frequent events observed in subjects treated with oprozomib, it is anticipated that Oprozomib ER Tablets will have even less GI toxicity in combination with antimyeloma doses of 20 to 40 mg of dexamethasone once weekly, and therefore may be safely dosed at the same level as or higher than oprozomib monotherapy.

3.5.3 POMALIDOMIDE

Pomalidomide (Pomalyst), a thalidomide analogue, is an IMiD that displays similar antiangiogenic activity but far greater antiproliferative and immunomodulatory activity compared with the parent drug (Bartlett, 2007; Payvandi, 2004). Pomalidomide has also been shown to stimulate antibody-dependent cytotoxic T-cell activity (ADCC) (Bartlett, 2007).

Pomalidomide received accelerated approval in the EU in August 2013 and in the US in February 2013. The European Commission has granted approval for pomalidomide in combination with dexamethasone, for the treatment of relapsed and refractory multiple myeloma who received at least two prior therapies and have demonstrated disease progression on the last drug taken and the US FDA granted accelerated approval for patients with multiple myeloma with 2 prior therapies including both bortezomib and lenalidomide and who are refractory to their last therapy or progressed within 60 days. The approved dose of pomalidomide is 4 mg given 21 days of a 28-day cycle until progressive disease (PD).

Approval was based on Study MM002, a randomized Phase 2 comparison of pomalidomide in combination with low-dose therapeutic dexamethasone (POM + LoDex) to pomalidomide alone (Jagannath, 2012). The overall response rate (ORR) was 34%, with a median PFS of 4.6 months and median OS of 16.5 months. Grade 3 or 4 AEs reported in > 5% of subjects were neutropenia (41%), anemia (22%), pneumonia (22%), thrombocytopenia (19%), fatigue (14%), dyspnea (13%), leukopenia (10%), back pain (10%), and urinary tract infection (9%). Grade 3 or 4 neutropenia occurred in 46% of subjects aged ≤ 65 years and in 35% of subjects aged > 65 years. Febrile neutropenia was observed in only 1 subject in each age group (2%). Overall, 78% of subjects who developed Grade 3 or 4 neutropenia were treated with granulocyte-colony stimulating factor (G-CSF) during study treatment. There was no Grade 3 or 4 peripheral neuropathy (PN) reported, although Grade 1 or 2 PN occurred in 7% of subjects treated with POM + LoDex. Deep vein thrombosis (DVT) occurred in 2 subjects (2%). Pomalidomide appears to provide an efficacious option with a manageable toxicity profile for subjects with refractory or relapsed and refractory multiple myeloma.

The MM003 randomized Phase 3 study was designed to assess relapsed and/or refractory subjects with multiple myeloma who had been previously treated with bortezomib and lenalidomide or thalidomide, and progressed on or within 60 days of the last therapy. A regimen of pomalidomide and dexamethasone was compared to high-dose dexamethasone.

Subjects were randomized 2:1 to receive 28-day cycles of pomalidomide 4 mg on Days 1-21 + dexamethasone 40 mg (20 mg for subjects more than 75 years old) weekly or dexamethasone 40 mg (20 mg for subjects more than 75 years old) on Days 1–4, 9–12, and 17–20. Treatment continued until PD or unacceptable toxicity. The primary endpoint was PFS. Secondary endpoints included OS, ORR (≥ PR), and safety. Analyses were based on intent-to-treat. A total of 455 subjects were randomized to pomalidomide + low-dose dexamethasone (n = 302) or high-dose dexamethasone (n = 153). The median number of prior therapies was 5 (range: 1−17). Seventy-two percent (72%) of subjects were refractory to lenalidomide and bortezomib. Median follow-up was 4 months. Pomalidomide + low-dose dexamethasone significantly extended median PFS (3.6 versus 1.8 months, hazard ratio [HR] = 0.45, $p < 0.001$) and OS (not reached versus 7.8 months, HR = 0.53, $p < 0.001$) compared with high-dose dexamethasone. The OS benefit was observed despite 29% of high-dose dexamethasone subjects receiving pomalidomide after PD (Jagannath, 2012). With updated data, the ORR was 21% for pomalidomide + low-dose dexamethasone versus 3% for high-dose dexamethasone ($p < 0.001$) and 24% versus 3% for subjects randomized ≥ 6 months after enrollment ($p < 0.001$). Median OS was 12.7 months for pomalidomide + low-dose dexamethasone and 8.1 months for high-dose dexamethasone; HR = 0.74 ($p = 0.28$). The most frequent Grade 3/4 AEs for pomalidomide + low-dose dexamethasone versus high-dose dexamethasone were neutropenia (42% versus 15%), anemia (27% versus 29%), and infection (24% versus 23%). Discontinuation due to AEs was infrequent (7% versus 6%) (San Miguel, 2013).

Lacy et al. (2011) conducted a study to assess efficacy and toxicity of 2- and 4-mg doses of pomalidomide. Pomalidomide was given orally on Days 1–28 of a 28-day cycle at a dose of 2 or 4 mg, with dexamethasone administered at 40 mg weekly. Thirty-five (35) subjects were enrolled in each cohort. Based on confirmed responses, the ORR was 49% in the 2-mg cohort and 43% in the 4-mg cohort. Overall survival at 6 months was 78% and 67% in

the 2- and 4-mg cohorts, respectively. Myelosuppression was the most common toxicity. Grade 3 or 4 hematologic toxicity, regardless of attribution, occurred in 83% (2-mg cohort) and 80% (4-mg cohort) of subjects, and was considered to be at least possibly related to the regimen in 71% (2-mg cohort) and 74% (4-mg cohort). Grade 3 or 4 neutropenia (regardless of attribution) was seen in 51% (2-mg cohort) and 66% (4-mg cohort) of subjects. Grade 3 or 4 nonhematologic toxicity, regardless of attribution, occurred in 69% (2-mg cohort) and 54% (4-mg cohort) of subjects, and was considered to be at least possibly related to the regimen in 26% (2-mg cohort) and 26% (4-mg cohort). These data obtained from nonrandomized subjects suggest no advantage for 4 mg over the 2 mg daily dose. This is the basis for the dose de-escalation to 2 mg of pomalidomide in the event the initial dose level of 4 mg or the first dose de-escalation to 3 mg is not tolerated (Lacy, 2011).

3.6 STUDY RATIONALE

The clinical activity of proteasome inhibition in hematologic malignancies has been demonstrated in multiple myeloma in the clinical setting. Specifically, bortezomib, which is a covalent, slowly reversible proteasome inhibitor that primarily targets the CT-L activity of the proteasome, was the first approved proteasome inhibitor. Because of the benefit of bortezomib observed in subjects with relapsed or refractory myeloma in Phase 1 and 2 trials, the drug received accelerated approval by the US FDA, and was made available to subjects 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) is an irreversible inhibitor of the epoxyketone class (proteasome) that received accelerated approval in the US for the treatment of patients with multiple myeloma who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy (Kyprolis Prescribing Information [Onyx Pharmaceuticals, 2012]). Carfilzomib 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 CT-L 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, and 16] and 12 days rest). Prolonged proteasome inhibition was believed to have greater antitumor activity and would be pursued if tolerable.

Data collected in these 2 trials 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 dose and schedule and have provided data indicating both tolerability and efficacy in advanced stage, heavily pretreated multiple myeloma subjects. Both schedules will be assessed with oprozomib to determine which schedule provides an advantage in tolerability and efficacy.

Oprozomib, a structural analogue of carfilzomib, is a synthetic small-molecule peptide that specifically functions as an irreversible and highly selective inhibitor of the CT-L 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, patient convenience, and potentially prolong treatment duration.

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

Phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone in subjects with newly diagnosed multiple myeloma has demonstrated excellent activity and tolerability, with 62% of 53 subjects achieving near complete response or better and with only Grade 1/2 peripheral neuropathy in 23% of the subjects (Jakubowiak, 2012).

Stadtmauer et al. (2013) demonstrated the activity of carfilzomib in combination with pomalidomide and dexamethasone (CPomd) in a Phase 1b/2 study. In this ongoing 82-subject trial, the primary objective is to assess the safety, tolerability, and MTD of carfilzomib in combination with pomalidomide and low-dose therapeutic dexamethasone. Secondary objectives include a preliminary assessment of efficacy as measured by best ORR, PFS, and OS. All subjects were refractory to prior lenalidomide and relapsed and refractory to their most recent therapy at the time of enrollment. The MTD of carfilzomib was determined to be 20/27 mg/m^2 in combination with 4 mg of pomalidomide per day on Days 1–21, and 40 mg/week of dexamethasone. Drug-related AEs occurring in > 20% of subjects included fatigue, anemia, thrombocytopenia, neutropenia, diarrhea, dyspnea, skin rash/pruritis, elevated creatinine, and hypocalcemia. Notable SAEs were Grade 3 pneumonia (n = 3), pulmonary embolism (n = 1), and congestive heart failure (n = 1). The ORR was 50% and the 6-month PFS was 71%. The OS at 12 months was 90%. The authors concluded that this regimen was safe and adequately tolerated and led to compelling improvements in outcome for subjects with advanced myeloma.

The rationale for this study is based on the results of the previously described study (Stadtmauer, 2013), as well as the similarities between carfilzomib and oprozomib in mechanism of action, preclinical toxicity profile, clinical profile, and the non-overlapping toxicity profile of oprozomib and pomalidomide. Subjects treated with carfilzomib have demonstrated an ORR of 23% and an OS of 15.6 months (Siegel, 2012), while subjects treated with pomalidomide in combination with dexamethasone have demonstrated an ORR of 30% and an OS of 16.5 months (Jagannath, 2012). The proposed study of oprozomib in combination with pomalidomide and dexamethasone will assess whether this triplet can confer improvements in outcome as measured by PFS when compared with pomalidomide and dexamethasone alone.

4 STUDY OBJECTIVES

4.1 PRIMARY OBJECTIVES

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

4.2 SECONDARY OBJECTIVES

- To estimate the overall response rate (ORR) of OPomd, defined as the proportion of subjects with an overall response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) as determined by investigator according to the International Myeloma Working Group- Uniform Response Criteria (IMWG-URC)
- To estimate the clinical benefit rate (CBR) of OPomd, defined as the proportion of subjects with an overall response of minimal response (MR) or better as determined by investigator according to the IMWG-URC and modified European Group for Blood and Marrow Transplantation (EBMT) criteria
- To characterize the pharmacokinetics (PK) of oprozomib in the OPomd regimen

4.3 EXPLORATORY OBJECTIVES

- To evaluate the pharmacodynamic (PDn) biomarkers that may correlate with antitumor activity
- To evaluate genomic biomarkers that may correlate with antitumor activity and resistance following treatment with proteasome inhibitors
- To evaluate (in the dose-expansion portion only) the patient-reported outcomes (PRO) using the tools listed below:
    - Bone pain and the impact of bone pain measured with the Brief Pain Inventory- Short Form (BPI-SF)
    - Health-related quality of life (HRQoL) measured by the global health status/QoL scale of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Module (QLQ-C30) questionnaire
    - Health status assessed by the EQ-5D-5L
    - Disease symptoms as measured by the disease symptoms subscale of the EORTC Multiple Myeloma Module (QLQ-MY20) questionnaire
    - Neurotoxicity symptoms as measured by the neurotoxicity subscale of the Functional Assessment of Cancer Therapy /Gynecological Oncology Group-Neurotoxicity (FACT/GOG-Ntx4 [Version 4]) questionnaire

5 STUDY DESIGN

This is a Phase 1b study of oprozomib in combination with pomalidomide and dexamethasone in subjects with primary refractory or relapsed and refractory multiple myeloma. **T**his study includes an open-label, Phase 1b, dose-escalation and dose-expansion portion (the equivalent of a small Phase 2) during which the RP3D will be identified. Further evaluation of safety and efficacy will be assessed during the dose-expansion portion. During th**is** study, subjects will receive Oprozomib ER Tablets according to their assigned dose cohort.

This study will include subjects with primary refractory or relapsed and refractory multiple myeloma, ie, those who have demonstrated disease progression on or within 60 days of their last therapy, and who have received at least 2 prior lines of therapy (including bortezomib and lenalidomide and/or thalidomide, and in the dose-expansion portion of the study only, been treated with adequate alkylator therapy). Subjects whose last therapy was bortezomib and who were not refractory but developed bortezomib intolerance, as defined by the development of Grade 2 peripheral neuropathy with pain or ≥ Grade 3 peripheral neuropathy after ≥ 2 consecutive cycles, are eligible.

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

Approximately 35 study sites will participate in **this** study (15 sites for the dose-escalation and 20 additional sites for the dose-expansion portions of the study).

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

5.1 DOSE-ESCALATION AND DOSE-EXPANSION PORTIONS OF THE STUDY

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

There is no planned maximum dose of oprozomib to be evaluated as it is being added to the FDA-approved regimen of pomalidomide/dexamethasone, however, this could be imposed at any time during the course of the study, based on sponsor discretion. The starting dose of oprozomib for the 5/14 schedule is 150 mg, 3 dose levels below the established single-agent MTD of 240 mg. The starting dose of oprozomib for the 2/7 schedule is 210 mg, 3 dose levels below the established 2/7 single-agent MTD of 300 mg. The MTD will be determined as outlined in the protocol for each schedule. Following dose escalation, the sponsor has the option of expanding 1 or both schedules in order to establish the RP3D and schedule.

The sponsor, with input from the Cohort Safety Review Committee ([CSRC] consisting of investigators, sponsor's medical monitor, and sponsor's drug safety representative), will determine which dose and schedule of oprozomib in combination with Pomd to use for the dose-expansion (ie, the RP3D) portion of the study. The sponsor has the option of expanding

1 or both schedules in order to establish the RP3D and schedule. The RP3D may differ from the MTD, but will not be higher than the MTD, and will be selected based upon the assessment of the safety, tolerability, PK, PDn, preliminary activity, and other variables to be observed across multiple cycles of combination therapy.

5.1.1 DOSE-ESCALATION SCHEMA FOR THE 5/14 OPROZOMIB DOSING SCHEDULE

The study dosing schema for the 5/14 schedule is displayed in Figure 1. The potential doses to be evaluated on the 5/14 dosing schedule are displayed in Figure 2. The primary and alternative pathways for dose escalation of oprozomib and pomalidomide for the 5/14 Schedule are summarized in Table 3 through Table 5; these are examples, and are not inclusive of all possible dose-escalation paths.

Figure 1 Study Dosing Schema for the 5/14 Dosing Schedule

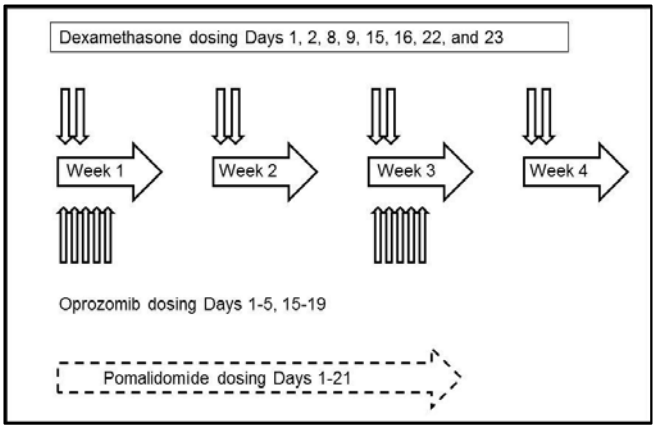
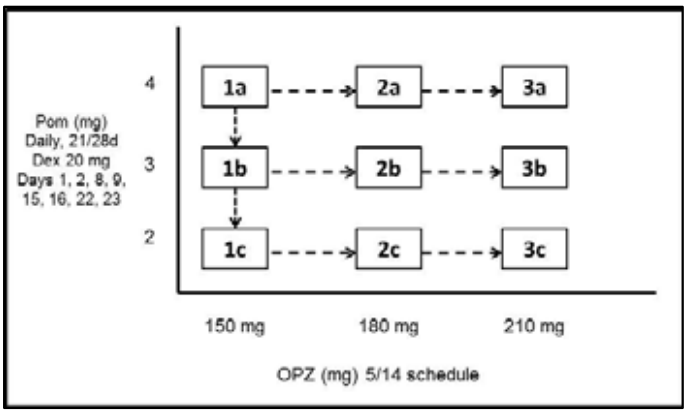


Figure 2 5/14 Schedule Primary Study Dose-Escalation Paths[a]



5/14 = Dosing on Days 1–5 and 15–19; Dex = Dexamethasone;
OPZ = oprozomib; Pom = pomalidomide
[a] There is no predefined maximum dose level of oprozomib being studied.

Table 3 Primary Dose-Escalation Path for Oprozomib on 5/14 Schedule with Pomalidomide 4 mg in Phase 1b

Cohort 5/14 Schedule	Oprozomib Dose (mg/day)	Pomalidomide Dose (mg/day)
1a (initial cohort)	150	4
2a	180	4
3a	210	4

5/14 = Dosing on Days 1–5 and 15–19; MTD = maximum tolerated dose.
Note: This is an example of the primary dose-escalation cohort. Dose escalation will continue in 30-mg increments of oprozomib until the MTD is identified.

If Cohort 1a exceeds the MTD, or at the sponsor's discretion, the alternative path 1 described in Table 4 may be followed.

Table 4 Alternative Dose-Escalation Path 1 for Oprozomib on 5/14 Schedule with Pomalidomide in Phase 1b if Cohort 1a Exceeds the MTD or at Sponsor Discretion

Cohort 5/14 Schedule	Oprozomib Dose (mg/day)	Pomalidomide Dose (mg/day)
1b	150	3
2b	180	3
3b	210	3

5/14 = Dosing on Days 1–5 and 15–19; MTD = maximum tolerated dose.

If Cohort 1b exceeds the MTD, or at the sponsor's discretion, the alternative path 2 described in Table 5 may be followed.

Table 5 Alternative Dose-Escalation Path 2 for Oprozomib on 5/14 Schedule with Pomalidomide in Phase 1b if Cohort 1b Exceeds the MTD or at Sponsor Discretion

Cohort 5/14 Schedule	Oprozomib Dose (mg/day)	Pomalidomide Dose (mg/day)
1c	150	2
2c	180	2
3c	210	2

5/14 = Dosing on Days 1–5 and 15–19; MTD = maximum tolerated dose.

5.1.2 DOSE-ESCALATION SCHEMA FOR THE 2/7 OPROZOMIB DOSING SCHEDULE

The study dosing schema for the 2/7 schedule is displayed in Figure 3. The potential doses to be evaluated on the 2/7 dosing schedule are displayed in Figure 4. The primary and alternative pathways for dose escalation of oprozomib and pomalidomide in the Phase 1b portion of the study for the 2/7 schedule are summarized in Table 6 through Table 8; these are examples, and are not inclusive of all possible dose-escalation paths.

Figure 3 Study Dosing Schema for the 2/7 Dosing Schedule

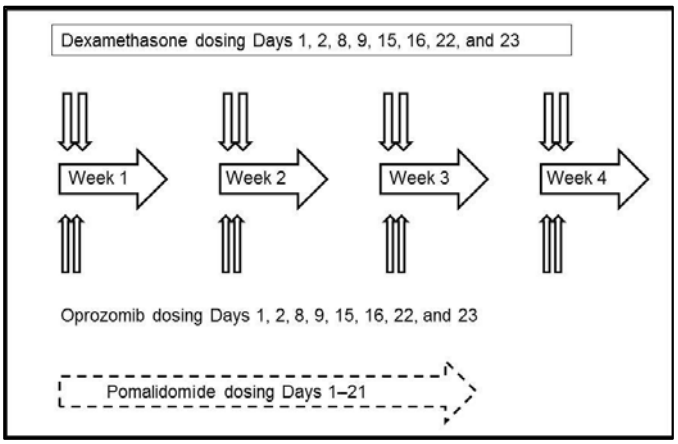
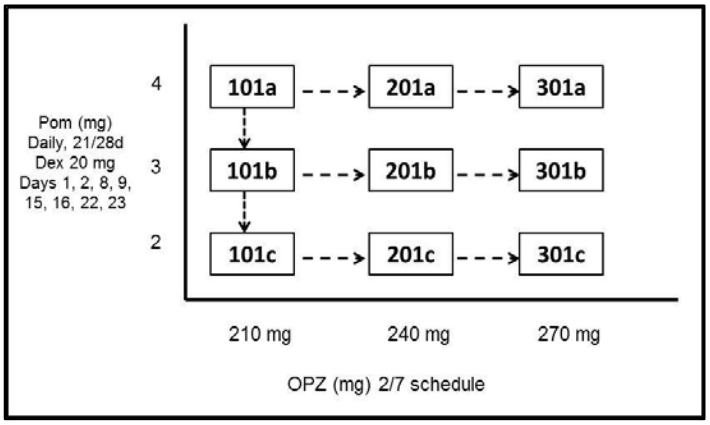


Figure 4 2/7 Schedule Primary Study Dose-Escalation Paths[a]



2/7 = Dosing on Days 1, 2, 8, 9, 15, 16, 22, and 23; Dex = Dexamethasone; OPZ = oprozomib; Pom = pomalidomide

[a] There is no predefined maximum dose level of oprozomib being studied.

Table 6 Primary Dose-Escalation Path for Oprozomib on the 2/7 Schedule with Pomalidomide 4 mg in Phase 1b

Cohort 2/7 Schedule	Oprozomib Dose (mg/day)	Pomalidomide Dose (mg/day)
101a (initial cohort)	210	4
201a	240	4
301a	270	4

2/7 = Dosing on Days 1, 2, 8, 9, 15, 16, 22, and 23; MTD = maximum tolerated dose.
Note: This is an example of the primary dose-escalation cohort. Dose escalation will continue in 30-mg increments of oprozomib until the MTD is identified.

If Cohort 101a exceeds the MTD, or at the sponsor's discretion, the alternative path 1 described in Table 7 may be followed.

Table 7 Alternative Dose-Escalation Path 1 for Oprozomib on 2/7 Schedule with Pomalidomide in Phase 1b if Cohort 101a Exceeds the MTD or at Sponsor Discretion

Cohort 2/7 Schedule	Oprozomib Dose (mg/day)	Pomalidomide Dose (mg/day)
101b	210	3
201b	240	3
301b	270	3

2/7 = Dosing on Days 1, 2, 8, 9, 15, 16, 22, and 23; MTD = maximum tolerated dose.

If Cohort 101b exceeds the MTD, or at the sponsor's discretion, the alternative path 2 described in Table 8 may be followed.

Table 8 Alternative Dose-Escalation Path 2 for Oprozomib on 2/7 Schedule with Pomalidomide in Phase 1b if Cohort 101b Exceeds the MTD or at Sponsor Discretion

Cohort 2/7 Schedule	Oprozomib Dose (mg/day)	Pomalidomide Dose (mg/day)
101c	210	2
201c	240	2
301c	270	2

2/7 = Dosing on Days 1, 2, 8, 9, 15, 16, 22, and 23; MTD = maximum tolerated dose.

5.1.3 DOSE-LIMITING TOXICITIES

Subjects in both dosing schedules will be evaluated for DLTs according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03 during the 28-day period of Cycle 1 combination therapy. Intrasubject dose escalation to the RP3D may be permitted once that dose has been determined and after a discussion has occurred between the treating physician and **the Sponsor's** study medical monitor. The decision to escalate to the next higher dose of oprozomib in th**is** study will be based on an assessment of study drug-related DLTs during Cycle 1 by the CSRC. The CSRC consists of investigators, the **Sponsor's study** medical monitor, and **the Sponsor's d**rug **s**afety representative. Each subject in the cohort under review will be discussed and assessed. Once all data have been presented, the CSRC will decide on the most appropriate course of action regarding dose escalation based on guidance in Section 5.1.

Study drug is defined as the combination of oprozomib, pomalidomide, and dexamethasone. Study drug-related is defined as a reasonable likelihood of clinical causality based on time of event, biology, dechallenge improvement and that the AE was not likely explained by the subject's clinical state, underlying disease, concomitant medication, or study/nonstudy procedure. Definition of DLTs and additional details are provided in Section 10.5.

5.1.4 SUBJECT REPLACEMENT

Subjects must meet the following criteria to be considered evaluable for MTD determination during the 4-week DLT evaluation period unless a DLT occurs before the subject receives all planned doses of oprozomib for both the 5/14 and 2/7 dosing schedules:

- A minimum of 17 of 21 planned doses of pomalidomide must be received
- A minimum of 6 of 8 planned doses of dexamethasone must be received
- All planned doses of oprozomib must be received

Subjects not meeting all of the above criteria or assessed as unevaluable by the CSRC will be replaced.

5.1.5 DOSE EXPANSION

The criteria for selecting the RP3D for 1 or both schedules of oprozomib at the sponsor's discretion will include assessment of the safety, tolerability, and preliminary activity

observed across multiple cycles of therapy. In addition, both PK and PDn assessments to demonstrate adequate exposure and proteasome inhibition will be a key factor. Therefore, the RP3D may differ from the MTD. Once the MTD and the recommended dose for the expansion phase have been determined, a minimum of 20 additional subjects at 1 or both schedules of oprozomib at the sponsor's discretion will be enrolled in the dose-expansion portion **of the study** in order to continue the evaluation of the safety and efficacy of the regimen. The safety of subjects in the Dose Expansion will be monitored on an ongoing basis by the CSRC during regularly scheduled calls.

5.2 ESTIMATED STUDY DURATION AND STUDY CLOSURE

The total study duration is expected to be approximately **12-13** months.

- The Phase 1b portion of the study will take approximately 7–8 months to complete
- Approximately 5 months will be required to enroll and evaluate response status of subjects in the dose-expansion portion of the study

5.3 MINIMIZING BIAS

5.3.1 BLINDING

Both the dose-escalation and dose-expansion portions of **this study** are open-label.

6 SUBJECT SELECTION

6.1 INCLUSION CRITERIA

Disease Related

2. Multiple myeloma that is primary refractory, relapsed and refractory, or intolerant after at least 2 lines of standard therapy for multiple myeloma, including:
    a. ≥ 2 consecutive cycles of both bortezomib and lenalidomide or thalidomide (alone or in combination)
    b. In the dose-expansion portion of the study only: In addition to the above, treatment with adequate alkylator therapy, defined as:
        i. High-dose melphalan or other alkylating agent as conditioning for autologous or allogeneic SCT, or
        ii. ≥ 6 cycles of induction therapy, or
        iii. Progressive disease after ≥ 2 cycles

3. Measurable disease as indicated by 1 or more of the following:
    a. Serum M-protein ≥ 500 mg/dL
    b. Urine M-protein ≥ 200 mg/24 h
    c. Only for subjects without measurable M-protein by serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP), involved free light chain (FLC) concentration ≥ 10 mg/dL provided serum free light chain (SFLC) ratio is abnormal
4. Disease progression on or within 60 days of completion of the last therapy, or intolerance to bortezomib if received as their last therapy
    a. Patients who received bortezomib as their last therapy who were not refractory but developed bortezomib intolerance, as defined by the development of Grade 2 peripheral neuropathy with pain or ≥ Grade 3 peripheral neuropathy after ≥ 2 consecutive cycles, are eligible
5. Prior carfilzomib is allowed if a subject was not removed from carflizomib therapy due to toxicity, unless approved by the **Sponsor's** study medical monitor.

Demographic

6. Males and females ≥ 18 years old
7. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0–2 (Appendix H)

Laboratory

8. Adequate hepatic function, with bilirubin ≤ 1.5 times the upper limit of normal (ULN) in the absence of Gilbert's disease or hemolysis, and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 times ULN
9. Absolute neutrophil count (ANC) ≥ 1500/mm^3. Screening ANC should be independent of myeloid growth factor support for at least 1 week or 2 weeks for pegylated growth factors.
10. Hemoglobin ≥ 8.0 g/dL. Patients may receive red blood cell (RBC) transfusions or receive erythropoietin or darbepoetin alfa in accordance with institutional guidelines up to 1 week before screening.
11. Platelet count ≥ 75,000 mm^3. Patients should not have received platelet transfusions for at least 1 week before screening.
12. Uric acid, if elevated, must be corrected to within laboratory normal range before dosing.
13. Calculated or measured creatinine clearance (CrCl) ≥ 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.

Ethical/Other

14. Patient must sign a written informed consent form in accordance with federal, local, and institutional guidelines.
15. Female patients of childbearing potential must have a negative pregnancy test (with a sensitivity of at least 50 mIU/mL) within 1 day of the first dose of study drug and agree to use 2 effective methods of contraception during the study and for 28 days following the last dose of study drug. Postmenopausal females (> 45 years old and without menses for ≥2 years) and surgically sterilized females are exempt from these requirements.
16. Male patients, including those with prior vasectomy, 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. Additionally, they must agree not to donate sperm while being treated and for up to 3 months after discontinuing treatment.

6.2 EXCLUSION CRITERIA

Disease Related

1. Systemic chemotherapy with approved or investigational anticancer therapeutics, intended to treat underlying malignancy, within 3 weeks before the first dose of study treatment or 6 weeks for antibody therapy.
2. Dexamethasone at cumulative doses of greater than 160 mg or equivalent within 21 days prior to the first dose of study treatment is not allowed. Use of topical or inhaled steroids is acceptable.
3. Radiation therapy within 3 weeks before first dose of study drug. Radioimmunotherapy within 8 weeks before first dose of study drug.
4. Plasmapheresis is not permitted at any time during the Screening period or while the subject is receiving study treatment. If a subject has started Screening procedures requiring plasmapheresis, or is anticipated to require plasmapheresis during or after the Screening period, this patient will be considered ineligible and should not be enrolled.
5. Autologous SCT within the prior 8 weeks or allogeneic SCT within 16 weeks prior to initiation of study treatment. Patients with prior allogeneic SCT should not have evidence of moderate-to-severe graft-versus-host disease (as defined in Filipovich 2005) and must be approved by the **Sponsor's** study medical monitor.
6. Known hypersensitivity to any IMiDs, including rash

7. Prior pomalidomide exposure
    a. For the dose-escalation portion of the study: Subjects requiring pomalidomide dose reduction or removal due to toxicity
    b. For the dose-expansion portion of the study: Prior pomalidomide treatment of any duration
8. Known hypersensitivity/toxicity or intolerance to dexamethasone
9. Prior exposure to oprozomib
10. Hypersensitivity, intolerance, or inability to take antithrombotic prophylaxis

Concurrent Conditions

11. Major surgery within 3 weeks before first dose of study drug
12. Congestive heart failure (New York Heart Association Class III to IV), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, or myocardial infarction within 6 months before first dose of study drug
13. Acute active infection requiring systemic antibiotics, antivirals, or antifungals within 2 weeks before first dose of study drug
14. History of previous clinically significant GI bleed in the 6 months prior to first dose of study drug
15. Known or suspected human immunodeficiency virus (HIV) infection or patients who are HIV seropositive
16. Active hepatitis A, B, or C infection
17. Significant neuropathy (Grade 2 with pain or ≥ Grade 3) at the time of the first dose of study drug
18. Other malignancy within the past 3 years except those considered cured by surgical resection; examples include some cases of:
    a. Adequately treated basal or squamous cell carcinoma of the skin
    b. Thyroid cancer
    c. Carcinoma in situ of the cervix or breast
    d. Prostate cancer with Gleason Score of 6 or less with stable prostate-specific antigen levels
19. Plasma cell leukemia
20. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
21. Known amyloidosis

22. Female patients who are pregnant or nursing
23. Uncontrolled diabetes or hypertension
24. 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
25. Any contraindication to oral hydration (eg, preexisting cardiac impairment or fluid restriction)
26. Any clinically significant psychiatric, social, or medical condition that, in the opinion of the investigator, could increase patient risk, interfere with protocol adherence, or affect a patient's ability to give informed consent

7 SUBJECT SCREENING

A signed and dated informed consent form will be obtained before any screening procedures are performed. Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the study-specific evaluations, provided they meet the time windows described below. Subjects will acknowledge and agree to the possible use of this information for the study by giving informed consent. The screening period for a particular subject commences at the point, after informed consent is signed, at which the subject undergoes the first study-specific screening assessment, and must be completed within 28 days of receiving the first dose of study drug.

8 SUBJECT ENROLLMENT

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

9 STUDY DRUG

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

9.1 OPROZOMIB

9.1.1 OPROZOMIB PHYSICAL 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 CT-L activity of the 20S proteasome, which leads to the accumulation of protein substrates within the cell and induction of apoptosis.

9.1.2 OPROZOMIB FORMULATION

Oprozomib will be provided as a tablet for oral administration. 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 ER Tablets are white to off-white tablets manufactured at 5 dosage strengths:

- Oprozomib 150 mg oval shape tablets are debossed with “H” on one side and contain 150 mg of oprozomib
- Oprozomib 180 mg oval shape tablets are debossed with “I” on one side and contain 180 mg of oprozomib
- Oprozomib 210 mg oval shape tablets are debossed with “J” on one side and contain 210 mg of oprozomib
- Oprozomib 240 mg oval shape tablets are debossed with “K” on one side and contain 240 mg of oprozomib
- Oprozomib 270 mg oval shape 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 5 dosage strengths.

9.1.3 OPROZOMIB PACKAGING AND LABELING

The Oprozomib ER Tablets will be available in 150, 180, 210, 240, and 270 mg of oprozomib. Details are provided in the Pharmacy Manual.

9.1.4 OPROZOMIB STORAGE

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

9.2 POMALIDOMIDE

Pomalidomide is available as a capsule containing 1, 2, 3, and 4 mg of pomalidomide drug substance for oral administration. Additional product information is provided in the Pomalidomide Prescribing Information (Celgene Corporation, 2013).

9.2.1 POMALIDOMIDE PHYSICAL DESCRIPTION

POMALYST is available in 1-mg, 2-mg, 3-mg, and 4-mg capsules for oral administration. Each capsule contains pomalidomide as the active ingredient and the following inactive ingredients: mannitol, pregelatinized starch, and sodium stearyl fumarate. The 1-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, white ink, and black ink. The 2-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, FD&C red 3, and white ink. The 3-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, and white ink. The 4-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 1, FD&C blue 2, and white ink.

9.2.2 POMALIDOMIDE PACKAGING AND LABELING

Pomalidomide is commercially available as capsules for oral administration.

9.2.3 POMALIDOMIDE STORAGE

Store at 20°C–25°C (68°F–77°F); excursions permitted to 15°C–30°C (59°F–86°F). See USP Controlled Room Temperature.

9.3 DEXAMETHASONE

Dexamethasone, a synthetic adrenocortical steroid, is available as tablets containing 4 or 6 mg of dexamethasone drug substance for oral administration.

9.3.1 DEXAMETHASONE PACKAGING AND LABELING

Dexamethasone is commercially available both as tablets for oral administration and as various sterile formulations for parenteral administration. Additional information is provided in the Dexamethasone Prescribing Information (Pfizer Laboratories, 2012).

9.3.2 DEXAMETHASONE STORAGE

Dexamethasone is not to be stored above 30°C (86°F). Additional storage and usage instructions are provided in the Dexamethasone Prescribing Information (Pfizer Laboratories, 2012).

9.4 STUDY DRUG ACCOUNTABILITY

The Sponsor (or designee) and the investigator will maintain records of each shipment of investigational product (IP). Upon receipt of IP, the designated recipient at the study site will inspect the shipment, verify the number and condition of the bottles or blister packs, and prepare an inventory or drug accountability record. The records will document shipment dates, method of shipment, batch numbers, product presentation, quantity of bottles or blister packs contained in the shipment, and dispensation to individual subjects using the subject identification number.

Sites will be required to record and document subject compliance with oprozomib, pomalidomide, and dexamethasone dosing.

Additional details for oprozomib are provided in the Pharmacy Manual.

10 OPROZOMIB TREATMENT ADMINISTRATION

It is recommended that oprozomib not be taken on an empty stomach. Subjects will be instructed to take the oprozomib doses after eating with approximately 8 ounces of water. On the PK collection days, dosing of oprozomib in relation to the meal intake (within 2 hours before and 1 hour after dose) will be recorded.

10.1 OPROZOMIB TREATMENT ADMINISTRATION

Oprozomib ER Tablets will be administered in single daily doses. Oprozomib will be administered orally, once daily for 5 consecutive days every other week ([5/14 schedule] ie, on Days 1–5 and 15–19) or once daily for 2 consecutive days of every week ([2/7 schedule] ie, on Days 1, 2, 8, 9, 15, 16, 22, and 23) of each 28-day treatment cycle. Treatment with oprozomib will continue until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason. On days on which oprozomib and dexamethasone are administered concurrently, dexamethasone should be taken at least 30 minutes before oprozomib. Subjects are to be informed not to break, chew, or crush the Oprozomib ER Tablets.

In the dose-escalation and dose-expansion portions of the study, subjects who permanently discontinue pomalidomide or oprozomib may continue on study. If both pomalidomide and oprozomib are permanently discontinued, study treatment will be discontinued but the subject will be followed until disease progression.

10.2 POMALIDOMIDE TREATMENT ADMINISTRATION

Pomalidomide will be administered at 4 mg, orally, in the fasted condition (2 hours before or after meals) according to the Prescribing Information (Celgene Corporation, 2013) on Days 1–21. Pomalidomide may be taken with water. Subjects are to be informed not to break, chew, or open the capsules.

The starting dose of pomalidomide for this study is 4 mg once daily, orally, on Days 1–21 of repeated 28-day cycles until disease progression. Pomalidomide may be given at the same time as dexamethasone; however, dexamethasone must be given at least 30 minutes prior to oprozomib.

10.3 DEXAMETHASONE TREATMENT ADMINISTRATION

Dexamethasone will be administered at 20 mg, orally, on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day cycle. On days of concurrent oprozomib and dexamethasone administration, dexamethasone should be taken at least 30 minutes prior to oprozomib. Subjects may take dexamethasone with or without food. Dexamethasone may be given at the same time as pomalidomide; however, dexamethasone must be given at least 30 minutes prior to oprozomib.

Dexamethasone may be administered intravenously (IV), if needed, at the investigator's discretion, but IV dexamethasone will not be provided by the sponsor.

10.4 DOSE MODIFICATION GUIDELINES

This section provides dose reduction and other modification guidelines for oprozomib, pomalidomide, and dexamethasone to manage possible toxicity. Administration of oprozomib or pomalidomide will be discontinued in the event of a treatment-related toxicity that, in the opinion of the investigator, warrants permanent discontinuation.

Monotherapy with dexamethasone is not allowed in the dose-escalation and dose-expansion portions of the study.

Exceptions to the dose modification guidelines are permitted with written approval from the **Sponsor's** study medical monitor.

10.4.1 DOSE REDUCTIONS

For th**is** study, the initial cohort will start at an oprozomib dose level of 150 mg for the 5/14 schedule and 210 mg for the 2/7 schedule. For these subjects, oprozomib or pomalidomide or dexamethasone dose reductions are discouraged during the DLT assessments. Subjects requiring dose reductions in Cycle 1 will be referred to the CSRC for determination if the subject is considered evaluable and for DLT assessment per Section 5.1.4. Dose reduction levels for oprozomib subsequent to Cycle 1 for the 5/14 and 2/7 dosing schedules are provided in Table 9 and Table 10, respectively. Modifications of the dose of oprozomib will occur in up to three 30-mg decrements down to a minimum dose of 150 mg. Additional reductions will be managed by schedule change.

Table 9 Dose Decrements for Oprozomib – 5/14 Schedule

Nominal Dose Level	Reduced Oprozomib Doses		
	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
150 mg	Continue 150 mg AND change to 3/14[a] schedule (Days 1, 2, 3, 15, 16, 17 of 28-day schedule)	D/C oprozomib	NA
180 mg	Dose − 30 mg	Dose − 30 mg AND change to 3/14 schedule (Days 1, 2, 3, 15, 16, 17 of 28-day schedule)	D/C oprozomib
210 mg	Dose − 30 mg	Dose − 60 mg	Dose − 60 mg AND change to 3/14 schedule (Days 1, 2, 3, 15, 16, 17 of 28-day schedule)
≥ 240 mg	Dose − 30 mg	Dose − 60 mg	Dose − 90 mg

5/14 = Dosing on Days 1–5 and 15–19; D/C = discontinue; NA = not applicable.

[a] The minimum oprozomib dose is 150 mg; thus, additional reductions will be managed by schedule change to the 3/14 schedule where doses of oprozomib will be skipped on Days 4, 5, 18, and 19.

Table 10 Dose Decrements for Oprozomib – 2/7 Schedule

Nominal Dose Level	Reduced Oprozomib Doses		
	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
210 mg	Dose − 30 mg	Dose − 60 mg	Dose − 60 mg AND change to 1/7[a] schedule (Days 1, 8, 15, 22 of 28-day schedule)
≥ 240 mg	Dose − 30 mg	Dose − 30 mg	Dose − 90 mg

2/7 = Dosing on Days 1, 2, 8, 9, 15, 16, 22, and 23.

[a] The minimum oprozomib dose is 150 mg; thus, additional reductions will be managed by schedule change to the 1/7 schedule where doses of oprozomib will be skipped on Days 2, 9, 16, and 23.

The dose reduction levels for pomalidomide are provided in Table 11. Dose adjustments should, in general, follow the instructions provided in the Pomalidomide Prescribing Information 2013 (Celgene Corporation, 2013).

Table 11 Dose Decrements for Pomalidomide

Dose	Reduced Pomalidomide Doses		
	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
4 mg	3 mg	2 mg	1 mg

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

Treatment guidelines for specific hematologic toxicities are outlined in Section 10.4.2.1.1 and nonhematologic toxicities in Section 10.4.2.1.2. In addition to dose reductions, administration of oprozomib, pomalidomide**,** and dexamethasone may be temporarily interrupted for a maximum of 4 weeks in the event of a treatment-related toxicity. If the dose delay because of toxicity is longer than 4 weeks, the subject will be discontinued from study treatment. If a subject misses more than 4 consecutive weeks for reasons other than toxicity after completing Cycle 1, the subject will be discontinued from study treatment unless it is determined that the subject was benefiting from therapy and the **Sponsor's** study medical monitor permits the subject to resume therapy.

Dose reduction levels for dexamethasone are provided in Table 12.

Table 12 Dose Decrements for Dexamethasone

Nominal Dose	Reduced Dexamethasone Doses	
	Dose -1	Dose -2
20 mg	12 mg	8 mg
Cycle 2 +: Age > 75 yrs per investigator discretion 10 mg	8 mg	4 mg

For subjects over 75 years old, after the first cycle and at the investigator's discretion, dexamethasone can be reduced to 10 mg. Dexamethasone will be permanently discontinued after 2 dose reductions for either nominal dose in the event of additional dexamethasone-related toxicity. At the investigator's discretion, dexamethasone may be

tapered prior to complete discontinuation according to institutional practice. If the dexamethasone dose is reduced during the previous cycle, the reduced 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 with the dose level prior to the reduction at the start of the next cycle.

If dexamethasone dosing is permanently stopped due to toxicity in accordance with the dose modification guidelines described in Table 15, the subject should stay on oprozomib and/or pomalidomide, depending on the arm to which they are randomized, and continue to follow protocol required therapy, procedures, and assessments. Subjects may continue to take antiemetic doses of dexamethasone (4 mg) on days of oprozomib dosing, if tolerated, at the investigator's discretion.

10.4.2 DOSE MODIFICATION GUIDELINES

10.4.2.1 Oprozomib Dose Modification Guidelines

10.4.2.1.1 Hematologic Toxicities

Dose modification guidelines for oprozomib/placebo and pomalidomide for hematologic toxicities are summarized in Table 13.

Table 13 Guidelines for Dose Modification of Oprozomib/Placebo and Pomalidomide for Hematologic Toxicities

Findings	Oprozomib	Pomalidomide
Findings on Day 1 of Cycle	**Recommended Action**	
Platelets < 25×10^9/L	Hold dose[a] until recovery ≥ 25×10^9/L; restart at previous dose.	Not applicable.
Platelets < 30 x 10^9/L	Not Applicable.	Hold dose[a], follow CBCs. Hold prophylactic anticoagulation until platelets return to ≥ 30×10^9/L[a], then resume at 1 dose decrement.
ANC < 0.5×10^9/L or febrile neutropenia (fever ≥ 38.5°C and ANC < 1.0×10^9/L)	Hold dose[a]. Add colony stimulating factor[b] With resolution to ≥ 1.0×10^9/L, restart at previous dose.	Hold dose[a]. Add colony stimulating factor[b] With resolution to ≥ 0.5×10^9/L, restart at 1 dose decrement.
Findings on Subsequent Days of Cycle	**Recommended Action**	
Platelets 25 to < 50×10^9/L without ≥ Grade 2 bleeding/hemorrhage	Full dose.	Full dose.
Platelets 25 to < 50×10^9/L with ≥ Grade 2 bleeding/hemorrhage	Hold dose[a] until platelets return to ≥ 50×10^9/L and/or bleeding is controlled, then resume at 1 dose decrement.	Hold dose[a] until platelets return to ≥ 50×10^9/L and/or bleeding is controlled, then resume at 1 dose decrement.
Platelets < 25×10^9/L or thrombocytopenia with ≥ Grade 2 bleeding/hemorrhage	Hold dose[a] until recovery to ≥ 25×10^9/L; restart at 1 dose decrement.	Hold dose[a]. Hold prophylactic anticoagulation until platelets return to ≥ 30×10^9/L[a], then resume at 1 dose decrement.
Neutropenic fever (ANC < 1.0×10^9/L and single temperature > 38.3°C or temperature > 38.0°C sustained for more than 1 hour)	Hold dose[a]; follow CBC at least 3 times per week. Add colony stimulating factor.[b] With resolution of fever and ANC ≥ 1.0×10^9/L, restart at 1 dose decrement.	Hold dose[a]; follow CBCs. Add colony stimulating factor[b]. With resolution of fever and ANC ≥ 1.0×10^9/L, restart at 1 dose decrement.
ANC < 0.5×10^9/L	Hold dose[a]; follow CBC at least 3 times per week; administration of colony stimulating factor[b] is permitted. Resume at full dose if ANC ≥ 0.5×10^9/L within < 7 days. Resume at 1 dose decrement if ANC returns to ≥ 0.5×10^9/L ≥ 7 days.	Hold dose[a] until ANC increases to ≥ 0.5×10^9/L. Administer colony stimulating growth factor[b]. Resume at 1 dose decrement each subsequent decrease to < 0.5×10^9/L).

ANC = absolute neutrophil count; CBC = complete blood count.
[a] The maximum allowed dose interruption is 4 weeks for treatment-related toxicity.
[b] Colony stimulating factors such as filgrastim or sargramostim as examples.

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

- To initiate a new cycle of pomalidomide, the neutrophil count must be at least 500 per **µ**L and the platelet count must be at least 50,000 per **µ**L. If toxicities continue to occur after dose reductions down to 1 mg, then discontinue pomalidomide.
- Nontreatment-related events: If the toxicity resolves to ≤ Grade 1 or baseline and the toxicity is not treatment-related, oprozomib may be restarted at the same dose level
- If required by continued or recurrent toxicity, a second or third dose reduction of oprozomib may be permitted after discussion with the **Sponsor's** study medical monitor. No more than 3 dose reductions down to a minimum of 150 mg will be permitted for an individual subject on study and additional reductions will be managed by schedule change. If toxicity continues, oprozomib should be discontinued.

10.4.2.1.2 Nonhematologic Toxicities

Table 14 provides oprozomib dosing actions that should be taken for nonhematologic toxicities.

Table 14 Guidelines for Dose Modification of Oprozomib/Placebo and Pomalidomide for Nonhematologic Toxicities

Symptom	Findings	Recommended Action[a]	
		Oprozomib	Pomalidomide
Tumor Lysis Syndrome	Generally recognized in at least 3 or more of the following categories: (1) Increase in creatinine, uric acid, or phosphate of ≥ 50% (2) Increase in potassium of ≥ 30% (3) Decrease in calcium of ≥ 20%, or (4) Increase in LDH ≥ 2-fold from baseline	Hold both oprozomib and pomalidomide until all abnormalities in serum chemistries have resolved to baseline; resume at full doses.	
Neuropathy	Grade 2 neuropathy with pain or ≥ Grade 3 neuropathy	Hold dose until toxicity resolves to ≤ Grade 1 or has returned to baseline. Resume study drug at 1 dose decrement.	Hold dose until toxicity resolves to ≤ Grade 1 or has returned to baseline. Resume study drug 1 dose decrement from previous dose.
Infection	Grade 3 or 4	Hold both oprozomib and pomalidomide until systemic treatment for infection complete. If ANC ≥ 1.0×10^9/L, resume both drugs at full dose. If ANC < 1.0×10^9/L, follow hematologic toxicities dose reduction guidelines (Table 13).	
Nausea, vomiting, diarrhea, or constipation	≥ Grade 3 without optimal supportive care as defined by use of both a 5-HT_3 antagonist and aprepitant	Oprozomib-related: Full dose oprozomib but institute optimal supportive care.	Pomalidomide-related: Hold dose until toxicity resolves to ≤ Grade 1 or has returned to baseline. Resume study drug at 1 dose decrement from previous dose.
	≥ Grade 3 with optimal supportive care as defined by use of both a 5-HT_3 antagonist and aprepitant	Oprozomib-related: Hold dose until toxicity resolves to ≤ Grade 1 or has returned to baseline. Resume study drug at 1 dose decrement.	
Fatigue	Grade 3 fatigue lasting < 14 days	Full dose.	Hold dose until toxicity resolves to ≤ Grade 1 or has returned to baseline. Resume study drug at 1 dose decrement from previous dose.
	Grade 3 fatigue lasting ≥ 14 days	Hold dose until toxicity resolves to ≤ Grade 1 or has returned to baseline. Resume study drug at 1 dose decrement.	

Table 14 Guidelines for Dose Modification of Oprozomib/Placebo and Pomalidomide for Nonhematologic Toxicities (cont'd)

Symptom	Findings	Recommended Action[a]	
		Oprozomib	Pomalidomide
Renal Dysfunction	CrCl 30 to < 50 mL/min (Grade 2)	Full dose.	Full dose.
	CrCl 15 to < 30 mL/min (Grade 3)	Hold dose. When CrCl recovers to ≤ Grade 2, resume at 1 dose decrement.	Hold dose. When CrCl recovers to ≤ Grade 2, resume dose at 1 dose decrement. If Grade 3 CrCl reappears, then hold dose until CrCl recovers to ≤ Grade 2 and reduce dose an additional 1 dose decrement.
	CrCl 0 to < 15 mL/min (Grade 4)	Discontinue.	Discontinue.
Elevation in Liver Function Tests	≥ Grade 3 (AST, ALT, or total bilirubin)[b]	Hold until resolves to baseline. Resume at 1 dose decrement.	Hold pomalidomide and restart treatment at 1 dose decrement less than the previous dose when toxicity has resolved to ≤ Grade 2 at physician discretion.
Other Nonhematologic Toxicity	Assessed as oprozomib-related and ≥ Grade 3[c]	Hold oprozomib dose until toxicity resolves to ≤ Grade 1 or baseline; restart at 1 dose decrement.	Full dose.
Other Nonhematologic Toxicity	Assessed as pomalidomide-related and ≥ Grade 3[c,d]	Full dose.	Hold pomalidomide and restart treatment at 1 dose decrement less than the previous dose when toxicity has resolved to ≤ Grade 2 at physician discretion.
Grade 1 or 2 GI hemorrhage	Assessed as oprozomib-related	DELAY until Grade 0 DECREASE one dose level for Grade 2	Full dose at physician discretion
Grade 3 or 4 GI Hemorrhage	Assessed as oprozomib-related	Discontinue.	Full dose when AE resolves to ≤ Grade 2 at physician discretion.

5-HT_3 = 5-hydroxytryptamine type-3; AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CrCl = creatinine clearance; eCRF = electronic case report form; GI = gastrointestinal; LDH = lactate dehydrogenase; ULN = upper limit of normal.

[a] The maximum allowed dose interruption is 4 weeks for treatment-related toxicity.

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

[c] If cardiac or pulmonary treatment-emergent toxicities occur, the "cardiopulmonary AE" eCRF should be completed.

[d] See Celgene Corporation, 2013.

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

- Nontreatment-related events: If the toxicity resolves to ≤ Grade 1 or baseline and the toxicity is not treatment-related, oprozomib may be restarted at the same dose level
- If the subject tolerates the reduced dose for 1 cycle, the subject's dose may be re-escalated to the dose being taken prior to the dose reduction
- If required by continued or recurrent toxicity, a second or third dose reduction of oprozomib may be permitted after discussion with the **Sponsor's** study medical monitor. No more than 3 dose reductions down to a minimum of 150 mg will be permitted for an individual subject on study and additional reductions will be managed by schedule change. If toxicity continues, oprozomib should be discontinued.
- Subjects who develop Grade 3 or 4 GI hemorrhage should not be rechallenged with oprozomib. Oprozomib should be permanently discontinued. Endoscopy should be strongly considered for any subject with GI hemorrhage.

10.4.2.2 Dexamethasone Dose Modification Guidelines

Guidelines for dexamethasone dose modifications and treatment are summarized in Table 15.

Table 15 Treatment Guidelines for Dexamethasone-Related Toxicity

Body System	Symptom	Recommended Action
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, or gastritis Grade 1 or 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 antiulcer 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 activities of daily living)	Hold dexamethasone until symptoms return to baseline. Administer 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 activities of daily living)	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 activities of daily living)	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 felt related to dexamethasone	Hold dexamethasone dose. Resume at 1 dose decrement when toxicity has resolved to Grade 2 or less or to baseline. If toxicity recurs, hold dexamethasone dose until toxicity has resolved to Grade 2 or less or to baseline and resume dexamethasone dose by 1 more dose decrements. If toxicity recurs despite 2 dose decrements, discontinue dexamethasone permanently.

H_2 = histamine 2 blocker.

10.5 DEFINITION OF DOSE-LIMITING TOXICITY

During this study, assessment of DLTs will occur during the 28-day period of Cycle 1 combination therapy. For the purposes of this study, a DLT is defined as any of the study drug-related events listed below occurring within the 4 weeks after the first dose of combination therapy. Study drug-related is defined as a reasonable likelihood of clinical causality based on time of event, biology, dechallenge improvement and that the AE was not likely explained by the subject's clinical state, underlying disease, concomitant medication, or study/nonstudy procedure.

- Any toxicity requiring a dose reduction or requiring that a dose of oprozomib or pomalidomide be held in Cycle 1 that does not meet the criteria for DLT will be discussed by the CSRC to determine whether the subject should be considered evaluable for DLT determination. If it is determined that the subject is not evaluable for DLT, the subject will be replaced.
- A delay in ability to receive Day 1 dose of Cycle 2 due to a hematologic or nonhematologic drug-related toxicity persisting beyond 14 days from Cycle 1 Day 28 will be considered a DLT
- For a nonhematologic DLT, any ≥ Grade 3 toxicity will be considered a DLT with exceptions as described below:
    - Grade 3 asymptomatic electrolyte abnormalities will not be considered a DLT
    - Asymptomatic Grade 3 hypophosphatemia lasting less than 24 hours will not be considered a DLT
    - Grade 3 nausea and vomiting will not be considered a DLT unless persisting longer than 3 days despite optimal supportive care, which at a minimum must include a 5-hydroxytryptamine type-3 (5-HT_3) antagonist and aprepitant
    - Grade 3 diarrhea will not be considered a DLT unless persisting longer than 3 days despite optimal supportive care, which at a minimum must include loperamide (Imodium) and atropine diphenoxylate (Lomotil)
    - Grade 3 fatigue lasting < 14 days is not considered a DLT
    - ≥ Grade 3 hyperglycemia or toxicity attributed to dexamethasone is not considered a DLT (see dose reduction guidelines for dexamethasone in Section 10.4.1)
    - ≥ Grade 3 rash attributed specifically to pomalidomide is not to be considered a DLT

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

Note: Grade 4 anemia is not considered a DLT

10.6 CONCOMITANT MEDICATIONS

A concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. All concomitant medications from 30 days before Day 1 until 30 days after the subject's last dose of study drug or before start of subsequent anticancer treatment (whichever occurs first) must be recorded on the electronic case report form (eCRF). Blood or blood products are not considered concomitant medications and must be recorded on the appropriate eCRF.

10.6.1 REQUIRED CONCOMITANT MEDICATIONS

10.6.1.1 Contraception

Females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of effective contraception simultaneously (1 highly effective form of contraception—tubal ligation, intrauterine device [IUD], hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] or partner's vasectomy and 1 additional effective contraceptive method—male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin 4 weeks prior to initiating treatment and continue during therapy, dose interruptions, and for 28 days after discontinuation of therapy. Reliable contraception is indicated even where there has been

a history of infertility, unless this is due to hysterectomy. Females of reproductive potential should be referred to a qualified provider of contraceptive methods, if needed. Additional details are provided in Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods (Appendix J), Pomalidomide Education and Counseling Guidance Document (Appendix K), and Pomalidomide Information Sheet for Subjects Enrolled in Clinical Research Studies (Appendix L).

Females of reproductive potential must have 2 negative pregnancy tests before initiating study treatment. The first test should be performed within 10–14 days of study treatment and the second test should be performed within 24 hours before study treatment. Once treatment has started and during dose interruptions, pregnancy testing for female subjects of reproductive potential should occur weekly during the first 4 weeks of treatment. Pregnancy testing should be repeated every 4 weeks thereafter for female subjects with regular menstrual cycles. For female subjects with irregular menstrual cycles (± 7 days of a 28-day cycle), pregnancy testing should be performed every 2 weeks. Pregnancy testing and counseling should be performed if a subject misses her period or if there is any abnormality in her menstrual bleeding. Study treatment must be discontinued during this evaluation.

Postmenopausal females (> 45 years old and without menses for > 2 years) and surgically sterilized females are exempt.

Male subjects 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.

Because pomalidomide is present in the semen of male subjects who receive it, they must always use a latex or synthetic condom during any sexual contact with females of reproductive potential and for up to 3 months after discontinuation of study treatment, even if they have undergone a successful vasectomy. Male subjects must agree not to donate sperm while being treated and for up to 3 months after discontinuing treatment.

10.6.1.2 Antinausea and Antiemetics

It is strongly recommended that subjects be premedicated with a 5-HT_3 inhibitor, such as ondansetron or granisetron, prior to administration of the first dose of oprozomib each day

and throughout the day as needed to prevent nausea and vomiting. If nausea/vomiting at any grade persists, aprepitant or fosaprepitant is recommended. Additional antiemetics may be used per investigator discretion.

10.6.1.3 Antidiarrheals

For subjects developing any grade of diarrhea, loperamide (Imodium) is strongly recommended at the first onset of symptoms. For subjects with persistent diarrhea despite the use of Imodium, the use of diphonoxylate/atropine (Lomotil) is strongly recommended. Other antidiarrheal agents may be used if necessary; a work-up for other etiologies is suggested if diarrhea continues despite the prior 2 agents.

10.6.1.4 Antivirals

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

10.6.1.5 Acid-related Medications

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

10.6.1.6 Thrombo-prophylaxis

Aspirin (or other anticoagulant or antiplatelet medication such as clopixisdogrel bisulfate, low-molecular-weight heparin, or warfarin based on subject risk factors for deep vein thrombosis) while taking pomalidomide is required to prevent thrombosis (refer to the Pomalidomide Prescribing Information [Celgene Corporation, 2013] for more information).

10.6.1.7 Tumor Lysis Syndrome

Monitoring and Prophylaxis Guidelines: Oral hydration of 1.5–2 liters per 24 hours must be instituted in all subjects 24–48 hours prior to initiation of therapy for every cycle and continued throughout every day 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: Durie-Salmon or 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.

Tumor Lysis Syndrome Laboratory Abnormalities

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

Tumor Lysis Syndrome Treatment Guidelines

If TLS occurs as defined by the laboratory abnormalities described above, cardiac rhythm, fluid, and serial laboratory monitoring 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 abnormalities consistent with TLS. Once TLS has resolved, the subject can resume treatment at the initial dose level. The **Sponsor's** study medical monitor should be consulted if there is a treatment delay > 4 weeks.

All cases of TLS must be reported to **the Sponsor** as an SAE as outlined in Section 13.5.

10.6.1.8 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. An etiology should be sought for the orthostatic hypotension to determine if its cause is neurogenic, non-neurogenic or iatrogenic. Dose modifications should be taken in accordance with Table 13 and Table 14.

- For those subjects with orthostatic hypotension who are taking antihypertensives, 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 6–8 eight ounce glasses of fluids in the 24−48 hours prior to dosing and on every day 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 per investigator discretion, such as increased oral intake, florinef or midodrine, others depending on the etiology. Holding the dose and dose reduction upon resolution may be a consideration.
- 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 (Appendices A1, A2, B1, and B2)

10.6.2 OPTIONAL AND ALLOWED CONCOMITANT MEDICATIONS

The following medications are optional and are allowed during the study:

- Mycostatin or oral fluconazole to prevent oral thrush is optional and may be given at the investigator's discretion
- Additional antiemetics, antidiarrheal agents, and/or laxatives as necessary
- Myeloid growth factors (eg, G-CSF) may be used if neutropenia occurs, in accordance with American Society of Clinical Oncology (ASCO) Guidelines (Smith, 2006), but are not to be given prophylactically.
- Red blood cell transfusions, erythropoietic stimulating agents, or platelet transfusions, if clinically indicated in accordance with institutional guidelines
- Bisphosphonates
- Palliative radiation for pain management is permitted with the written approval of the **Sponsor's** study medical monitor

10.6.3 EXCLUDED CONCOMITANT MEDICATIONS

In vitro tests indicate that the time-dependent inhibitory effect of oprozomib on human cytochrome P450 3A (CYP3A) is weak (Kinact to KI was only 1.4 mL/min/μmol). 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 are 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 are provided in Appendix I. Investigators should consider switching to an alternative drug, or be alert to the need for dose adjustment.

In accordance with the Pomalidomide Prescribing Information, use of concomitant medications including CYP3A, cytochrome P450 1A2 (CYP1A2) and P-glycoprotein (P-gp) inhibitors and inducers are to be carefully monitored and substituted for others if necessary (Appendix I).

Glucocorticoid therapy that exceeds a cumulative dose of 160 mg of dexamethasone is not permitted within 21 days prior to randomization. During the study, glucocorticoid therapy (in addition to dexamethasone) is only permitted at the discretion of the **Sponsor's** study medical monitor to treat a concurrent medical condition (eg, asthma, inflammatory bowel disease, emesis, etc.).

Other antimyeloma or investigational agents are not permitted prior to the subject developing confirmed progressive disease.

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 requires plasmapheresis, or is anticipated to require plasmapheresis during or after the screening period, this patient will be considered ineligible and should not be enrolled. Subjects requiring plasmapheresis while on study treatment should have every attempt made to document progressive disease by IMWG criteria first, and then will discontinue study treatment and will enter Long Term Follow-up for survival. Subjects requiring plasmapheresis must have 2 serum samples (for SPEP and immunofixation) and at least one 24-hour urine sample (for UPEP and immunofixation) obtained prior to the procedure.

11 STUDY PROCEDURES

All protocol-required tests and observations, along with their chronology, are outlined in the Schedules of Assessments (Appendices A1, A2, B1, and B2). A general summary of on-treatment tests and observations is provided below.

11.1 STUDY-SPECIFIC PROCEDURES

11.1.1 VITAL SIGNS

All vital sign assessments will include measurement of orthostatic blood pressure, pulse rate, respiration rate, and temperature. Subjects should lie down for 5 minutes and then have blood pressure and pulse measured consistently in either arm. Following the supine blood pressure/pulse reading, the subject should stand and the blood pressure and pulse should be repeated after 1 and 3 minutes. Any drop of 20 mmHg systolic, 10 mmHg diastolic or lightheadedness/dizziness between supine and standing blood pressures would indicate orthostatic hypotension. Usually an increase in pulse of 10 beats/min is associated with but not required for identification of orthostatic hypotension. For time points where PK and vital signs are to be done together, vital signs should be obtained first as the act of phlebotomy may impact vital sign measurement results.

11.1.2 COMPLETE PHYSICAL EXAMINATION

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

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

11.1.3 ELECTROCARDIOGRAM

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

11.2 LABORATORY EVALUATIONS FOR SAFETY

Laboratory tests, including hematology, blood chemistries, and coagulation tests during scheduled visits, will be performed locally. Unscheduled or additional laboratory samples may be collected and analyzed by local laboratories if results are necessary for management of treatment-emergent AEs or dose modification.

The schedule for laboratory evaluations for safety is outlined in Appendices A1, A2, B1, and B2. The laboratory tests included in the full chemistry panel are defined in Table 16.

11.2.1 CHEMISTRY

Table 16 Full Chemistry Panel

Full Chemistry Panel	
Alanine aminotransferase	Glucose
Albumin	Lactate dehydrogenase
Alkaline phosphatase	Magnesium
Aspartate aminotransferase	Phosphorous
Bicarbonate	Potassium
Blood urea nitrogen	Sodium
Calcium	Total bilirubin
Chloride	Total protein
Creatinine	Uric acid
Creatinine clearance (calculated or measured)	

11.2.2 HEMATOLOGY

The complete blood count (CBC) with differential includes the following:

- Hemoglobin
- Hematocrit
- White blood cell (WBC) count with complete manual or automated differential (reported as absolute counts)
    - Total neutrophils
    - Lymphocytes
    - Monocytes
    - Eosinophils
    - Basophils
- Red blood cell count
- Platelet count

11.2.3 COAGULATION

- Prothrombin time
- Activated partial thromboplastin time
- International normalized ratio

11.2.4 PREGNANCY

For females of childbearing potential (FCBP), both a serum pregnancy test that is confirmed negative at Screening and a serum pregnancy test that is confirmed negative within 24 hours prior to Day 1 of each cycle is required prior to dosing. For the first cycle, negative pregnancy tests are required weekly. Starting with the second cycle, a negative pregnancy test monthly is required. For FBCP subjects with irregular menses (ie, other than 28 ± 7 days) or whose menses are not present, a negative pregnancy test every other week is required. More frequent pregnancy tests may be conducted if required according to local regulations.

11.3 DISEASE RESPONSE ASSESSMENTS

The schedule of disease assessments for treated subjects is provided in Appendices A1, A2, B1, and B2. Disease response will be assessed by the investigator. Beginning with Cycle 1, assessments are to be completed at the end of every 4-week cycle for the first 18 months of study treatment, and then at the end of every other cycle (every 8 weeks), beginning with Month 20, for the remainder of study treatment. Response assessment will be according to the IMWG-URC and modified EBMT guidelines (Appendix C). Disease response and progression assessments include:

- Serum protein electrophoresis (SPEP)
- Urine protein electrophoresis (UPEP)
- Serum immunofixation, serum free light chain (SFLC)
- Urine immunofixation
- Serum calcium
- Bone marrow sample as clinically indicated to confirm CR
- Radiographic assessments including plasmacytoma evaluation if baseline assessments were positive and as clinically indicated per the response criteria

- Skeletal survey if baseline assessments were positive and as clinically indicated per the response criteria

Serum protein electrophoresis and immunofixation assessments will be conducted according to the schedule outlined in Appendices A1, A2, B1, and B2, Schedule of Assessments. Immunofixation will only be required after Screening, Baseline (Day -7 to 1), and End of Study Treatment, if results of the previous SPEP are zero/undetectable.

Urine protein electrophoresis and immunofixation will be performed on a 24-hour urine specimen collected from all subjects during the Screening period, Baseline (Day -7 to 1), and at the End of Study Treatment visit. The UPEP with 24-hour urine collection will be conducted according to the schedule outlined in Appendices A1, A2, B1, and B2, Schedule of Assessments, and is required: 1) only if Baseline UPEP was ≥ 200 mg/24 hours, and 2) to confirm a disease response or disease progression. If the Baseline UPEP was negative, spot urine is required at each time point. If positive for paraprotein, a 24-hour urine collection with UPEP must be done at the next assessment and at each subsequent assessment unless the UPEP shows an absence of paraprotein.

Serum free light chain assay and kappa:lambda (K/λ) ratio will be conducted according to the schedule outlined in the Schedule of Assessments, Appendices A1, A2, B1, and B2. Only in subjects without measurable serum and urine M-protein levels (serum M-protein < 0.5 g/dL or urine M-protein < 200 mg/24 hours) at Baseline will SFLC assays be used to determine eligibility and response. In subjects with measurable SPEP and/or UPEP, SFLC may be used in conjunction with those assessments to determine response per disease response criteria but only SPEP and/or UPEP will be used to determine eligibility.

All response categories (CR, sCR, VGPR, PR, MR, PD) require 2 consecutive assessments made at any time before the institution of any new therapy. All subjects will be followed until disease progression (confirmed by 2 consecutive measurements that are also verified by the **Sponsor's** medical monitor prior to treatment discontinuation), unacceptable toxicity, or withdrawal of consent, whichever occurs first.

Disease progression will be determined and confirmed with the medical monitor by two consecutive assessments using the IMWG-URC (Appendices A1, A2, B1, and B2).

Serum M component increases of ≥ 1.0 g/dL are sufficient to define progression if the starting component is ≥ 0.5 g/dL according to these criteria. However, it is understood from these criteria that a single measurement is adequate in cases of clear increased bone marrow plasma cell percentage, development of new or worsened bone lesions from a skeletal survey, or development of new or worsened soft tissue plasmacytomas.

11.4 CORRELATIVE STUDIES

11.4.1 PHARMACOKINETIC MEASUREMENTS

In the dose-escalation and dose-expansion portions of the study, blood samples will be collected from all subjects from both schedules to measure plasma concentrations of oprozomib at 1 predose time point and up to 7 postdose time points on Day 1 of Cycle 1 and Cycle 2 (0.25, 0.5, 1, 2, 3, 4, and 6 hours postdose) and 1 predose time point on Day 2 of Cycle 1. Estimates of oprozomib PK parameters will be determined when possible.

11.4.2 PHARMACODYNAMIC MEASUREMENTS

In the dose-escalation and dose-expansion portions of the study, blood samples for the quantitation of proteasome inhibition by oprozomib will be collected from all subjects for both schedules at 1 predose time point, up to 2 postdose time points (4 and 6 hours postdose) on Day 1 of Cycle 1 and Cycle 2, and 1 predose timepoint on Day 2 of Cycle 1. These timepoints are also specified in the Laboratory Manual. Details about collection times and volumes, and processing and shipping of PDn samples, are provided in the Laboratory Manual. Measurement of proteasome activity in whole blood and peripheral blood mononuclear cells (PBMCs) will be performed using a fluorogenic substrate assay and/or enzyme-linked immunosorbent assay.

11.4.3 GENOMIC MEASUREMENTS

Analysis of genomic biomarkers that may predict for response and resistance following treatment with proteasome inhibitors will be conducted for all subjects **in** the study who consent to optional genomic biomarker analysis. These analyses will be performed on the required bone marrow aspirate obtained at Baseline (within 45 days prior to Cycle 1 Day 1 dosing; a portion of the bone marrow aspirate sample obtained at Baseline will be used; no

additional sample is required), as well as a sample of blood and saliva, also collected at Baseline. Bone marrow aspirate or biopsy collection does not need to be repeated if previously completed within 45 days prior to Cycle 1 Day 1 dosing. Additional bone marrow samples for biomarkers may be collected at disease progression (End of Study Treatment due to PD) from all subjects who consent.

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 (eg, saliva or peripheral blood) in order to determine the presence of somatic mutations in tumor cell samples. Data will be analyzed to examine specific hypotheses about whether drug response is related to alterations in genes regulated by or involved in activation of nuclear factor kappa light chain enhancer of activated B cell (NF-κB) transcription factors as well as genes involved in immunoglobulin production and plasma cell protein homeostasis. Immunoglobulin levels in tumor cells will be quantified by enzyme-linked immmunosorbent assay (ELISA) and/or other protein quantification methods. These data will also be used to derive new hypotheses about mechanisms of drug response, resistance, and safety.

The schedule for genomic sampling is provided in the Laboratory Manual and in the Schedule of Assessments (Appendices A1, A2, B1, and B2).

11.5 PATIENT-REPORTED OUTCOMES ASSESSMENTS

Beginning with Cycle 1, HRQoL/PRO assessments are to be completed at the beginning of every cycle prior to drug administration through End of Study Treatment/Early Discontinuation visit during the dose-expansion portion of the trial, and at the beginning of every cycle prior to drug administration through End of Study Treatment/Early Discontinuation visit. The HRQoL/PRO assessments include:

- BPI-SF (See Appendix M for a sample Brief Pain Inventory – Short Form)
- EORTC QLQ-C30 (Appendix D)
- EORTC QLQ-MY20 (Appendix D)

- Neurotoxicity subscale of the FACT/GOG-Ntx4 (Version 4; Appendix E)
- EQ-5D-5L (Appendix F)

12 STUDY AND STUDY TREATMENT DISCONTINUATION

Early discontinuation and End of Study Treatment assessments must be performed within 30 days following the subject's last dose of study drug and prior to initiation of any other treatment.

All subjects must complete a visit approximately 4 weeks after the last cycle of treatment to allow for safety follow-up 30 days after the last dose of oprozomib. An individual subject who discontinues study treatment for PD will be followed for OS in long-term follow-up. Any subject who withdraws without PD will **no longer** be followed with long-term assessments every 4 weeks through 18 months on study, and then every 8 weeks thereafter, beginning with Month 20, until progression or initiation of next therapy **under Amendment 3**. The study will be completed once the last subject completes the last required follow-up visit. The same methods of disease assessment must be used throughout the study. If 2 prior disease assessments show disease progression, assessments do not need to be repeated with End of Study Treatment assessments.

12.1 STUDY TREATMENT DISCONTINUATION

For th**is** study, subjects may withdraw from study treatment at any time.

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

- Disease progression
- 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
- Suspected pregnancy

The primary reason for treatment discontinuation will be documented in the eCRF.

If the reason for treatment discontinuation is the occurrence of an AE, the subject will be followed by the investigator until such event(s) resolve, stabilize, or, according to the investigator's judgment, there is no need of further follow-up.

Subjects who discontinue from study treatment will be monitored for AEs for 30 days after the last dose of oprozomib or immediately before the start of subsequent anticancer treatment (whichever occurs first). Treatment discontinuation due to progression should be recorded on the Study Drug Completion/Discontinuation eCRF as "Disease Progression." Verbatim terms such as "disease progression," "progressive disease," etc. should not be reported as AEs or SAEs as outlined in Section 13.3.2 unless the investigator considers the progression to be atypical, accelerated, or caused by the study drug, in which case it should also be recorded as an SAE in the AE eCRF.

The Sponsor, or designee must be notified within 24 hours if a subject is withdrawn from treatment for any reason (ie, disease progression, toxicity, etc.). Disease progression with 2 consecutive disease assessments must be confirmed by the medical monitor before any subject is discontinued from study treatment.

For dose escalation and expansion, subjects who withdraw from treatment before completing adequate safety or efficacy evaluations, or Cycle 1 dosing, will be considered unevaluable and may be replaced. Additional subjects may be enrolled to account for subjects who have not had adequate safety or efficacy evaluations.

12.2 STUDY DISCONTINUATION

Each subject will be followed until death or study closure. The reason for discontinuation from the study will be documented on the eCRF.

Reasons for complete withdrawal from the study (treatment and all follow-up) before documentation of subject death include:

- Withdrawal of consent
- Lost to follow-up
- Sponsor decision

12.3 LONG-TERM FOLLOW-UP

After completion of the End of Study Treatment visit, subjects will be followed for OS. Subjects will be followed based on their disease progression status at End of Study Treatment.

Progression and Overall Survival

- For subjects who have not progressed at end of study treatment, disease response assessments will **no longer** be performed every 4 weeks through 18 months on study, and then every 8 weeks thereafter, beginning with Month 20, until progression or initiation of next therapy **under Amendment 3**
- Subjects who have progressed at end of study treatment or long-term follow-up will be followed for survival status approximately every 3 months, or as needed

Long-term follow-up will continue until the subject has withdrawn consent for further participation, is lost to follow-up, has died, or the sponsor makes a decision to close the study. For any subject who is lost to follow-up, the study site will attempt to ascertain survival information via public database search.

12.4 STUDY TERMINATION

The Sponsor has the right to terminate this study, either schedule, or a study site from participating in a study at any time. Reasons for terminating the study overall or at a specific study site may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Data recording is inaccurate or incomplete
- Investigator does not adhere to the protocol or applicable regulatory requirements in conducting the study

13 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

13.1 ADVERSE EVENT REPORTING

13.1.1 DEFINITIONS

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

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

Whenever possible, the NCI-CTCAE Version 4.03 should be used to describe the event and for assessing the severity of AEs. For AEs not adequately addressed in the NCI-CTCAE Version 4.03, Table 17 below should be used.

Table 17 Toxicity Grading for Adverse Events Not Covered in the NCI-CTCAE (Version 4.03)

Severity	Description
GRADE 1 - Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
GRADE 2 – Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (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

NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events

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

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

13.2 CAUSALITY

A suspected adverse event means any AE for which there is reasonable possibility that the study drug caused the AE. "Reasonable possibility" means that there is evidence to suggest a causal relationship between the drug and the AE.

The relationship of the AE to the study drug should be assessed using the following criteria:

YES; the event is suspected to be related if:

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

NO; the event is not suspected to be related if:

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

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

13.3 ADVERSE EVENTS REPORTING PROCEDURES

13.3.1 GENERAL

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

All AEs will be collected from the time the subject signs informed consent through 30 days after receiving the last dose of study drug or before start of subsequent anticancer treatment (whichever occurs first). If initiation of new anticancer therapy occurs following the last dose of study drug(s), the date of new anticancer therapy will be recorded on the appropriate eCRF. In addition, the investigator should report any AEs that may occur after this time period that are assessed to have a reasonable possibility of being associated with study drug. If the subject is randomized but discontinues participation in the study prior to receiving study drug, AEs must be reported through the End of Study Treatment visit.

All AE severity changes will be recorded on the AE case report form (CRF) as separate events. All AEs that are considered related to study drug and all SAEs regardless of relationship to study drug must be followed to resolution or to stabilization if improvement is not expected. Adverse events that completely resolve and then recur should be recorded as a new AE. For subjects who complete the End of Study Treatment visit less than 30 days following the last dose of study drug, a follow-up of ongoing AEs should be attempted by telephone and documented in the subject's source file. Adverse events continuing at 30 days after the last dose of study treatment should have a comment in the source file by the investigator that the event has stabilized or is not expected to improve.

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

13.3.2 DISEASE PROGRESSION

Disease progression will be documented on an eCRF intended to capture PD information and will be analyzed as a study endpoint. Signs and symptoms related to disease progression (eg, pathologic fracture in a subject with progressive multiple myeloma) should be reported in the appropriate case report form as an AE or as a SAE (if the event in question meets the criteria for seriousness) while the cause of study treatment discontinuation should be reported as progression of disease. Verbatim terms such as "disease progression," "progressive disease," etc. should not be reported as AEs or SAEs unless the investigator considers the progression to be atypical, accelerated, or caused by the study drug. Similarly, deaths occurring as a result of disease progression should be reported on the eCRF intended to capture death information and should not be reported as SAEs.

13.4 SERIOUS ADVERSE EVENTS DEFINITIONS

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

- Death
- Life-threatening experience, defined as any adverse experience that places the subject, in the view of the sponsor or investigator, at immediate risk of death at the time of occurrence; ie, it does not include a reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of an existing hospitalization (except scheduled hospitalizations for a nonacute, unrelated cause such as elective surgery)
- Results in persistent or significant disability/incapacity (ie, substantial disruption in a subject's ability to conduct normal activities of daily living)
- Is a congenital anomaly/ birth defect in the offspring of an exposed female subject or offspring of a female partner of a male subject

- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, the event jeopardizes the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition

13.5 SERIOUS ADVERSE EVENT REPORTING AND DOCUMENTATION REQUIREMENTS

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

The primary mechanism for reporting serious adverse events will be the 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 Contingency Report Form (see Appendix N) 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 off line 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 off line, then the site can report this information on a paper Serious Adverse Event Report Form (see Appendix N).

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

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

13.6 PREGNANCY REPORTING

Pregnancy occurring in a female subject, or in a male subject's partner, while enrolled in this clinical trial through 30 days after the subject's last dose of study drug, although not considered an SAE, must be reported to **Amgen Global Patient** Safety on a**n Amgen** Pregnancy **Notification Worksheet (Appendix O)** within 24 hours of the investigator, designee, or site personnel learning of the event. If the subject is pregnant, all study treatment must be discontinued immediately and the pregnancy must be reported to the investigator and sponsor within 24 hours. **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 O). 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 13.5. 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 O). 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.**

Collection of Lactation Information

- **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 P) 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 22.**

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.

14 STATISTICS

This section outlines the statistical analysis strategy and procedures for the study. Specific details of the primary and key secondary analyses will be provided in the Statistical Analysis Plan (SAP). If, after the study has begun but prior to the final analysis, important changes are made to the protocol that affect principal features of the primary and/or key secondary analyses, then the protocol and/or SAP will be amended, as appropriate. 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.

14.1 STUDY ENDPOINTS

14.1.1 PRIMARY ENDPOINTS

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

14.1.2 SECONDARY ENDPOINTS

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

14.1.3 EXPLORATORY ENDPOINTS

- Pharmacodynamic biomarkers that may be correlated with antitumor activity
- Genomic biomarkers that may be correlated with antitumor activity and resistance following treatment with proteasome inhibitors
- Change over time in bone pain and the impact of bone pain measured with the BPI-SF (Dose Expansion only)
- Change over time in the global health status/QoL scale of the EORTC QLQ-C30 (Dose Expansion only)
- Change over time in health status assessed by EQ-5D-5L (Dose Expansion only)
- Change over time in the disease symptoms subscale of the EORTC QLQ-MY20 (Dose Expansion only)
- Change over time in neurotoxicity symptoms measured by the FACT/GOG-Ntx4 score (Version 4) (Dose Expansion only)

14.2 ANALYSIS OF THE CONDUCT OF THE STUDY

Enrollment, subject disposition, study treatment administration, and discontinuation from the study will be summarized. Eligibility exceptions and important protocol deviations will be summarized.

14.3 DATA MONITORING COMMITTEE

In this study, safety will be monitored by a CSRC for both the dose-escalation and dose-expansion portions of the study.

14.4 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Descriptive statistics will be used to summarize baseline subject characteristics. Summaries of discrete data will include number of subjects and incidence as a frequency and as a percentage. Summaries of continuous data will include mean, standard deviation, median, minimum, maximum, and sample size.

14.4.1 TREATMENT EXPOSURE AND MEDICATION COMPLIANCE

Extent of exposure to all study treatments (oprozomib, pomalidomide, and dexamethasone) will be evaluated by summary statistics (N, mean, standard deviation, median, and range). Percentage of subjects and cycles with dose delays and reductions will be calculated by treatment group.

The dose intensity of oprozomib, pomalidomide, and dexamethasone (ie, the amount of drug delivered to a subject per week of treatment) will be calculated according to standard methodology (Hryniuk, 1990; Longo, 1991) that accounts for treatment delays on the calculated dose intensity result. For each subject, the relative dose intensity (actual versus planned) of each treatment will be calculated. The average relative dose intensity for each treatment group will be calculated by summarizing the average relative dose intensity for individual subjects. The results for pomalidomide and dexamethasone will be provided to determine the presence of any major differences between the treatment groups for the planned versus actual dose and schedule of these two (2) study medications.

14.5 STATISTICAL METHODS

14.5.1 ANALYSIS POPULATIONS

14.5.1.1 Safety Population

All subjects receiving any amount of study treatment (oprozomib, pomalidomide, or dexamethasone) will be included in safety analyses. A baseline measurement and at least 1 laboratory, vital sign, or ECG measurement obtained after any amount of study treatment is required for inclusion in the analysis of a specific safety parameter when applicable.

14.5.1.2 Efficacy Population

For th**is** study, the efficacy population is equivalent to the safety population.

14.5.1.3 PK-Evaluable Population

Subjects evaluable for PK are defined as those who have adequate oprozomib plasma concentration-versus-time data to allow proper estimation of PK parameters.

14.5.2 EFFICACY ANALYSES

Overall response rate is defined as the proportion of subjects with a best response of sCR, CR, VGPR, or PR as determined by investigator according to the IMWG-URC.

Clinical benefit rate is defined as the proportion of subjects with a best response of PR or better according to IMWG-URC or a best response of MR according to the EBMT criteria, as determined by the investigator. A point estimate and 95% exact binomial confidence interval (CI) will be calculated for both ORR and CBR for all subjects treated at the RP3D (during dose escalation and expansion for each schedule). A descriptive summary of ORR and responses will also be provided by dose cohort.

Progression-free survival and **duration of response (**DOR**)** will be listed for all subjects in the efficacy population by dose cohort level and schedule.

14.5.3 SAFETY ANALYSIS

The safety population will be used in all safety analyses (see Section 14.5.1.1).

For this study, safety data will be summarized for each cohort and for the pooled cohorts. Safety will be assessed through summaries of DLTs, AEs, changes in laboratory test results, ECGs, vital signs, and oprozomib, pomalidomide, and dexamethasone exposure. Subgroup Analyses and Effects of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the estimate of the hazard ratio (or odds ratio) for treatment group (with 95% CI) will be provided for the primary and selected secondary efficacy endpoints and plotted within each of the following baseline variables, provided there is a reasonable sample size in the subgroups of interest:

- Number of prior therapies: 2 versus 3 or more (stratification factor)
- Age (< 75 years versus ≥ 75 years) (stratification factor)
- Prior carfilzomib (naïve/sensitive versus refractory) (stratification factor)
- Refractory status: Primary refractory versus relapsed-refractory versus bortezomib-intolerant
- Refractory to lenalidomide
- Refractory to bortezomib
- Double refractory (refractory to lenalidomide and bortezomib)
- FISH risk status: High-risk group versus standard-risk group.
- No prior transplant versus prior transplant
- Bone marrow infiltration by plasma cells ≤ 50% versus > 50% at baseline
- Renal function ≤ 60 mL/min versus > 60 mL/min at baseline
- Age (< 65 years versus ≥ 65 years)
- Race (Caucasian versus all others)
- Sex (male versus female)

14.5.4 PHARMACOKINETIC ANALYSES

In the Dose-Escalation and Dose-Expansion portions of the study, blood samples will be collected from all subjects for determination of plasma concentrations of oprozomib at

1 predose time point and up to 7 postdose time points on Day 1 of Cycle 1 and Cycle 2 (0.25, 0.5, 1, 2, 3, 4, and 6 hours postdose) and 1 predose time point on Day 2 of Cycle 1 for both schedules. Individual and mean plasma-concentration-versus time data will be tabulated and plotted by dose level.

The PK parameter estimates for oprozomib will be summarized, including total plasma exposure (AUC), maximum plasma concentration (C_{max}), time to maximum concentration (T_{max}), total plasma clearance, and plasma terminal half-life ($t_{1/2}$, as appropriate for data collected). Estimates for these parameters will be tabulated and summarized (mean, standard deviation).

Unless otherwise specified, the PK parameter will be estimated based on noncompartmental methods. These estimates will be summarized descriptively by dose cohort. Exploratory analyses may be performed to evaluate the relationship between the estimate PK parameters and selected safety, biomarker, or clinical effect endpoints.

14.6 HANDLING OF MISSING DATA

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

14.7 DETERMINATION OF SAMPLE SIZE

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

The actual number of required subjects will depend on both the total number of cohorts, and the need to expand a given cohort from 3 to 6 subjects in order to identify the MTD. Properties of the dose-escalation rules for different underlying DLT rates are provided in Table 18.

Table 18 Properties of the Dose-Escalation Rules for Different Underlying DLT Rates

Underlying Rate of DLT	Probability of Enrolling 3 Additional Subjects	Probability that Dose is Determined to be Tolerated
0.10	0.24	0.91
0.20	0.38	0.71
0.33	0.44	0.43
0.40	0.43	0.31
0.50	0.38	0.17
0.60	0.29	0.08

DLT = dose-limiting toxicity.

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

15 ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

15.1 COMPLIANCE STATEMENT

This study will be conducted in accordance with the protocol and with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, as well as all applicable country and regional legal and regulatory requirements. The investigator is responsible for ensuring that this protocol, the site's informed consent form, and any other information that will be presented to potential subjects are reviewed and approved by the appropriate IRB or IEC prior to the enrollment of any study subjects.

15.2 INSTITUTIONAL REVIEW BOARD OR INDEPENDENT ETHICS COMMITTEE

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

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

15.3 INFORMED CONSENT AND HUMAN SUBJECT PROTECTION

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

The Sponsor or its designated representative will provide the investigator with a sample consent form. Local and/or institutional requirements may require disclosure of additional information in the ICF. Any changes to the consent form must be submitted to the sponsor or its designated representative for approval, prior to submission to the IRB/IEC. The IRB/IEC will review the consent form for approval. A copy of the approved form must be submitted to the sponsor or its designated representative for its approval prior to initiation of the study. Before implementing any study procedure on a particular subject, informed consent shall be documented in such subject's case histories and by the use of a written consent form approved by **the Sponsor** and the IRB/IEC and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy of the signed informed consent will be given to the subject or subject's legally authorized representative. The original signed consent must be maintained by the investigator and available for inspection by **the Sponsor**, its designated representative, or regulatory authority at any time.

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

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

15.5 DATA COLLECTION AND HANDLING

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

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

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

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

All data collected in the context of this study will be stored and evaluated according to regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to assure subject confidentiality in accordance with the legal and regulatory requirements applying to protected health information. Study records (eg, copies of eCRFs, regulatory documents) will be retained at the study site, along with adequate source documentation. The study file and all source data should be retained for the time period required by applicable regulatory requirements and will not be destroyed until written notification is given by the sponsor or designee for destruction.

15.6 CONFIDENTIALITY

All records identifying the subject will be kept confidential and, in accordance with the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded on the CRF. If the subject name appears on any other document or study materials, then that information must be redacted before a copy of the document is supplied to the sponsor. Study data stored on a computer will be stored in accordance with local data protection laws and regulations. Subjects will be informed in writing that representatives of the sponsor,

IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws and regulations.

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

The investigator will maintain a list to enable subjects' records to be identified in accordance with applicable laws and regulations and according to the terms agreed upon in such subjects' signed consent forms.

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APPENDIX A1 SCHEDULE OF STUDY ASSESSMENTS – PHASE 1B DOSE ESCALATION 5/14 SCHEDULE

Visit	Screening	Baseline	Cycle 1										Cycle 2					Cycle 3 +		End of Study Treatment/ Early Discon.[a]	Long-term Follow-up
	Day -28 to -1	(Pre-C1D1 dose)	Day 1	Day 2	Day 3–4	Day 5	Day 6–7	Day 8	Day 9–14	Day 15	Day 16–21	Day 22–28	Day 1	Day 2–14	Day 15	Day 16–21	Day 22–28	Day 1	Day 22–28		
Written Informed Consent	X																				
Inclusion/Exclusion Criteria	X																				
Medical History	X																				
Previous Treatment History	X																				
Physical Examination[b]	X		X										X					X		X	
Height	X																				
Weight	X		X										X					X		X	
Neurological Assessment (BPNS and NCI-CTCAE Grading)[c]	X												X					X		X	
Vital Signs[d,e,f]	X		X	X	X	X		X		X	X		X	X	X	X		X		X	
12-lead ECG[g] (Local)	X		X										X					X		X	
Urinalysis[h]	X																			X	
Serum Chemistry[i,j]	X		X		X	X		X		X	X		X	X	X	X		X		X	
CBC with Diff and Platelets[j,k]	X		X		X	X		X		X	X		X	X	X	X		X		X	
Coagulation Tests[l]	X																				
Pregnancy Test[m]	X		X					X		X		X	X		X			X		X	
SPEP/UPEP/Serum FLC Immunofixation[n]	X	X Day -7 to 1								X sFLC only			X					X		X	

Footnotes are defined on next page

APPENDIX A1 SCHEDULE OF STUDY ASSESSMENTS – PHASE 1B DOSE ESCALATION 5/14 SCHEDULE (CONT'D)

Visit	Screening	Baseline	Cycle 1										Cycle 2					Cycle 3 +		End of Study Treatment/ Early Discon.[a]	Long-term Follow-up
	Day -28 to -1	(Pre-C1D1 dose)	Day 1	Day 2	Day 3–4	Day 5	Day 6–7	Day 8	Day 9–14	Day 15	Day 16–21	Day 22–28	Day 1	Day 2–14	Day 15	Day 16–21	Day 22–28	Day 1	Day 22–28		
β2 Microglobulin	X																				
Skeletal Survey[o]		X																		X	
Plasmacytoma Evaluation[p]		X																		X	
Bone Marrow Aspirate and FISH Analyses[q,]		X																		X	
Optional – Genomic Biomarker Assessment: Blood[r]		X																			
Optional – Genomic Biomarker Assessment: Saliva[r]		X																			
Blood for PK[s]			X	X									X								
Blood for PDn Assay[s]			X	X									X								
Oprozomib Dosing[t]			X	X	X	X				X	X		X	X	X	X		X			
Dexamethasone Dosing[u]			X	X				X	X	X	X	X	X	X	X	X	X	X	X		
Pomalidomide Dosing[v]			X	X	X	X	X	X	X	X	X		X	X	X	X		X			
AEs and Concomitant Medications[w]			→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Telephone or other contact for disease and survival status[x]																					X

Footnotes are defined on next page

APPENDIX A1 SCHEDULE OF STUDY ASSESSMENTS – PHASE 1B DOSE ESCALATION 5/14 SCHEDULE (CONT'D)

AE = adverse event; BPNS = Brief Peripheral Neuropathy Screen; C = Cycle; CBC = complete blood count; D = Day; Discon. = discontinuation; EBMT = European Group for Blood and Marrow Transplantation; ECG = electrocardiogram; FISH = fluorescence in situ hybridization; FLC = free light chain; IMWG-URC = International Myeloma Working Group-Uniform Response Criteria; NCI-CTCAE = National Cancer Institute – Common Terminology Criteria for Adverse Events; PDn = pharmacodynamic(s); PK = pharmacokinetic(s); SFLC = serum free light chain; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis

[a] All End of Study Treatment/Early Discontinuation Assessments must be performed within 30 days following the subject's last administration of study drug and prior to initiation of any other treatment, whichever comes first.

[b] Complete physical examinations will be performed during Screening and at the End of Study Treatment/Early Discontinuation visits. All other physical examinations will be limited physical examinations **only if clinically indicated**. A complete physical examination will include examination of the skin, head and neck, chest (heart and lungs), abdomen, extremities, and a brief neurological examination including an assessment for peripheral neuropathy. Rectal and pelvic examinations are optional. Eastern Cooperative Oncology Group (ECOG) performance status (assessed only at the time of the Screening and End of Study Treatment/Early Discontinuation physical examination) will be conducted. A limited physical examination will include an examination of the chest (heart and lungs) and abdomen, with additional examinations as clinically indicated or directed by AEs. Screening physicals may be used for Cycle 1 Day 1 if done within 7 days prior to Day 1. Physical exams for additional cycles can be conducted within 3 days of Day 1 of the next cycle prior to dosing.

[c] Neurological assessments (BPNS and if applicable record AEs with CTCAE grading) will be performed at Screening and on Day 1 of every cycle starting from Cycle 2 **if clinically indicated** and at the End of Study Treatment/Early Discontinuation (See Appendix M).

[d] Vital signs: On Cycle 1 Days 1–5, 8, 15, and 19. On days when oprozomib is administered, measure vitals within 1 hour prior to oprozomib dose and approximately 1 hour after each oprozomib dose. Include measurement of orthostatic blood pressure, temperature, respiration rate, and pulse on every study visit, including Screening and End of Study Treatment/Early Discontinuation. Subject should lie down for 5 minutes and then have blood pressure and pulse measured consistently in either arm. This should be followed by having the subject stand and repeating the blood pressure and pulse at 1 and 3 minutes. A drop of 20 mmHg systolic, 10 mmHg diastolic, or lightheadedness/dizziness between supine and standing blood pressures would indicate orthostatic hypotension. Usually an increase in pulse of 10 beats/min is associated but not required. Subject's dosage and use of antihypertensive agents in the setting of orthostatic hypotension should be evaluated and reassessed on an ongoing basis while on study. Fluid intake should be assessed to confirm the subject is acting in accordance with protocol requirements. Re-education should occur if subject is not adhering to protocol requirements. Fluid status should be repleted to normal levels. If protocol requirements for oral intake of fluids are being met, additional measured should be taken to increase volume status, and ongoing monitoring is warranted and can be managed per investigator discretion. For time points where PK and vital signs are to be done together, vital signs should be obtained first as the act of phlebotomy may impact vital sign measurement results.

[e] At the investigator's medical discretion, vital signs monitoring may be extended beyond the time periods specified above (d).

[f] For Cycle 2, **if clinically indicated,** vital signs are required within approximately 1 hour prior to oprozomib administration on Days 1, 5, 15, and 19. For Cycles 3 and higher, **if clinically indicated,** vital signs are required within approximately 1 hour prior to oprozomib administration on Day 1.

[g] Perform ECG approximately within 1 hour before (predose) and approximately 1 hour after (postdose) administration of oprozomib for Cycles 1, 2, 3, 4, 6, 8, 12, 18, 24 and then every 6 months **solely if clinically indicated**, until progression or unacceptable toxicity. Perform standard ECG assessment at Screening and End of Study Treatment/Early Discontinuation visit.

[h] Subjects with urine positive for protein (> than trace) will need to collect a 24-hour urine sample for creatinine and protein analyses. Urine samples and urinalysis, done locally.

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

[j] CBC and serum chemistry obtained on Days 1, 5, 15, and 19 of Cycles 1 and 2, and on Days 3 and 8 of Cycle 1. Day 1 samples for laboratory analyses can be drawn within 72 hours prior to dosing on Day 1 for all subsequent cycles after Cycle 1 **only if clinically indicated**.

[k] Complete blood count (CBC) with differential, done locally, and includes the following: Hemoglobin, hematocrit, white blood cell (WBC) count with complete manual or automated differential (total neutrophils, lymphocytes, monocytes, eosinophils, basophils; reported as absolute counts), red blood cell (RBC) count, and platelet count. Screening results may be used for Cycle 1 Day 1 if obtained within 72 hours of Cycle 1 Day 1.

APPENDIX A1 SCHEDULE OF STUDY ASSESSMENTS – PHASE 1B DOSE ESCALATION 5/14 SCHEDULE (CONT'D)

[l] Coagulation tests, done locally **if clinically indicated**, and includes the following: Prothrombin time, activated partial thromboplastin time, and international normalized ratio.

[m] Screening pregnancy testing, done locally, for females of childbearing potential (FCBP) must have a sensitivity of at least 50 mIU/mL with TWO medically supervised tests performed before pomalidomide dosing starts. One test must be obtained within 10–14 days and one test within 24 hours prior to the start of pomalidomide on Cycle 1 Day 1. A medically supervised, serum pregnancy test will be done weekly during Cycle 1 (Days 1, 8, 15, and 22). Starting with Cycle 2, serum pregnancy tests will be done within 24 hours prior to each cycle of pomalidomide dosing in FCBP only. Pregnancy tests will be repeated on Day 15 of Cycle 2 and beyond if menses are irregular (i.e., not within ± 7 days of a 28-day cycle) or menses are not present in FCBP.

[n] Results for SPEP, UPEP, and SFLC, obtained locally, during Screening must be available before starting study drug treatment. When the subject is on study drug, the disease response assessments will be performed at the end of each cycle (Day 22–28 or prior to dosing on Day 1 of the next cycle) for the first 18 months (Cycles 1–18), then every 8 weeks thereafter (starting with Cycle 20). If the subject comes off study for reasons other than progressive disease, then disease response assessments will be performed every 4 weeks through 18 months on study, and then every 8 weeks thereafter. Obtain blood for SPEP (please refer to Section 11.3 for collection times for SPEP Immunofixation, UPEP and UPEP Immunofixation with 24-hr urine, and sFLC) within 7 days prior to next Cycle study drug dosing. If a response assessment indicates PD, confirmation of PD may be obtained any time at or before the next scheduled assessment.

[o] Subjects are required to have a skeletal survey at Baseline (within 45 days prior to Cycle 1 Day 1 dosing) and at End of Study Treatment/Early Discontinuation. This does not need to be repeated if previously done within 30 days of consent. If a skeletal survey was done more than 30 days before consent, it may be acceptable with **the Sponsor's** study medical monitor approval. 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. If present at Baseline, bone lesion(s) must be monitored throughout the study only as needed to document response according to the IMWG-URC and modified EBMT criteria or if clinically indicated. For subjects who did not progress during treatment with bone lesions present at Baseline, skeletal survey will **no longer be required**. During long-term follow-up, skeletal survey evaluation **will also no longer be required**.

[p] Subjects are required to have a plasmacytoma evaluation if known or suspected clinically at Baseline (within 45 days prior to Cycle 1 Day 1 dosing) and at End of Study Treatment. This does not need to be repeated if previously done within 30 days of consent. If the assessment was done more than 30 days before consent, it may be acceptable with **the Sponsor's** study medical monitor approval. If present at Baseline, plasmacytoma evaluation is to be repeated during treatment only to document response according to the IMWG-URC and modified EBMT criteria or if clinically indicated. If clinically indicated due to history of extramedullary disease, the same technique (may include ultrasound, CT scan, MRI, PET, or other standard-of-care method) must be employed for each measurement. For subjects with plasmacytoma at Baseline and did not progress during treatment, plasmacytoma will **no longer be required**. During long-term follow-up, plasmacytoma evaluation **will also no longer be required**.

[q] Bone marrow aspirate or biopsy is required at Baseline (within 45 days prior to Cycle 1 Day 1 dosing) to quantitate percent myeloma cell involvement. Obtain bone marrow aspirate sample for fluorescence in situ hybridization (FISH) studies. A portion of the sample may be used for optional genomic biomarker analysis, for all patients who consent. If Baseline bone marrow aspirate or biopsy were previously obtained and included cytogenetics and FISH (with results available) within 45 days prior to Cycle 1 Day 1 dosing, collection does not need to be repeated unless the patient consents to the optional biomarker genomic samples, which include collection of additional bone marrow aspirate(s). Repeat bone marrow aspirate when appropriate to confirm achievement of stringent complete response (sCR) or complete response (CR) within 30 days (+ 5 days) of confirmation assessment. Bone marrow aspirate will also be collected at disease progression **if clinically indicated** (may be collected at End of Study Treatment/Early Discontinuation due to PD**; it will no longer be required** during Long-**t**erm Follow-**u**p) for subjects who consent to optional genomic biomarker analysis.

[r] Optional genomic biomarker samples- blood and saliva: For subjects who consent to participate, blood and saliva samples (in addition to a portion of the bone marrow aspirate obtained for FISH analysis; no new sample is required, as applicable) will be collected at Baseline (within 45 days prior to Cycle 1 Day 1 dosing).

[s] Sampling times are indicated in Section 11.4 of the protocol, and volumes are provided in the Laboratory Manual.

[t] Oprozomib treatment will be administered on Days 1–5 and 15–19 during 28-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason. On days on which oprozomib and dexamethasone are administered concurrently (i.e., on Days 1, 2, 15, and 16 of each cycle), dexamethasone should be taken at least 30 minutes prior to oprozomib. Oprozomib should be taken with food. On the PK collection days, dosing of oprozomib in relation to the meal intake (within 2 hours before and 1 hour after dose) will be recorded.

[u] Subjects will receive 20 mg of dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day treatment cycle.

[v] Pomalidomide will be administered Days 1–21 of each 28-day cycle up to Cycle 24. Pomalidomide should be taken in the fasted state (i.e., 2 hours before or after a meal).

APPENDIX A1 SCHEDULE OF STUDY ASSESSMENTS – PHASE 1B DOSE ESCALATION 5/14 SCHEDULE (CONT'D)

[w] Record all AEs from time of consent through 30 days after the last dose of study drug or before start of subsequent anticancer treatment (whichever occurs first). Start to record concomitant medications from 30 days prior to Day 1 until 30 days after the last dose of study drug. If there is any change in the subject's concomitant medications during the study, it must be recorded on the eCRF.

[x] All patients will be followed for survival status by telephone contact or other method approximately every 3 months (± 1 week), or as needed, until study closure.

APPENDIX A2 SCHEDULE OF STUDY ASSESSMENTS – PHASE 1B DOSE ESCALATION 2/7 SCHEDULE

Visit	Screening	Baseline	Cycle 1								Cycle 2				Cycle 3 +		End of Study Treatment/ Early Discon.[a]	Long-term Follow-up
	Day -28 to -1	(Pre-C1D1 dose)	Day 1	Day 2	Day 3–7	Day 8	Day 9–14	Day 15	Day 16–21	Day 22–28	Day 1	Day 2–14	Day 15	Day 22–28	Day 1	Day 22–28		
Written Informed Consent	X																	
Inclusion/Exclusion Criteria	X																	
Medical History	X																	
Previous Treatment History	X																	
Physical Examination[b]	X		X								X				X		X	
Height	X																	
Weight	X		X								X				X		X	
Neurological Assessment (BPNS and NCI-CTCAE Grading)[c]	X										X				X		X	
Vital Signs[d,e,f]	X		X	X		X	X	X	X	X	X	X	X		X		X	
12-lead ECG[g] (Local)	X		X								X				X		X	
Urinalysis[h]	X																X	
Serum Chemistry[i,j]	X		X	X		X	X	X	X		X	X	X		X		X	
CBC with Diff and Platelets[j,k]	X		X	X		X	X	X	X		X	X	X		X		X	
Coagulation Tests[l]	X																	
Pregnancy Test[m]	X		X			X		X		X	X		X		X		X	
SPEP/UPEP/ Serum FLC Immunofixation[n]	X	X (Day -7 to 1)						X sFLC only			X				X		X	

Footnotes are defined on next page

APPENDIX A2 SCHEDULE OF STUDY ASSESSMENTS – PHASE 1B DOSE ESCALATION 2/7 SCHEDULE (CONT'D)

Visit	Screening	Baseline	Cycle 1								Cycle 2				Cycle 3 +		End of Study Treatment/ Early Discon.[a]	Long-term Follow-up
	Day -28 to -1	(Pre-C1D1 dose)	Day 1	Day 2	Day 3–7	Day 8	Day 9–14	Day 15	Day 16–21	Day 22–28	Day 1	Day 2–14	Day 15	Day 22–28	Day 1	Day 22–28		
β2 Microglobulin	X																	
Skeletal Survey[o]		X															X	
Plasmacytoma Evaluation[p]		X															X	
Bone Marrow Aspirate and FISH Analyses[q,]		X															X	
Optional – Genomic Biomarker Assessment: Blood[r]		X																
Optional - Genomic Biomarker Assessment: Saliva[r]		X																
Blood for PK[s]			X	X							X							
Blood for PDn Assay[s]			X	X							X							
Oprozomib Dosing[t]			X	X		X	X	X	X	X	X	X	X	X	X	X		
Dexamethasone Dosing[u]			X	X		X	X	X	X	X	X	X	X	X	X	X		
Pomalidomide Dosing[v]			X	X	X	X	X	X	X		X	X	X		X			
AEs and Concomitant Medications[w]			→															
Telephone or other contact for disease and survival status[x]																		X

Footnotes are defined on next page

AE = adverse event; BPNS = Brief Peripheral Neuropathy Screen; C = Cycle; CBC = complete blood count; D = Day; s; Discon. = discontinuation; EBMT = European Group for Blood and Marrow Transplantation; ECG = electrocardiogram; FISH = fluorescence in situ hybridization; FLC = free light chain; IMWG-URC = International Myeloma Working Group-Uniform Response Criteria; NCI-CTCAE = National Cancer Institute – Common Terminology Criteria for Adverse Event; PDn = pharmacodynamic(s); PK = pharmacokinetic(s); SFLC = serum free light chain; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

[a] All End of Study Treatment/Early Discontinuation Assessments must be performed within 30 days following the subject's last administration of study drug and prior to initiation of any other treatment, whichever comes first.

[b] Complete physical examinations will be performed during Screening and at the End of Study Treatment/Early Discontinuation visits. All other physical examinations will be limited physical examinations **only if clinically indicated**. A complete physical examination will include examination of the skin, head and neck, chest (heart and lungs), abdomen, extremities, and a brief neurological examination including an assessment for peripheral neuropathy. Rectal and pelvic examinations are optional. Eastern Cooperative Oncology Group (ECOG) performance status (assessed only at the time of the Screening and End of Study Treatment/Early Discontinuation physical examination) will be conducted. A limited physical examination will include an examination of the chest (heart and lungs) and abdomen, with additional examinations as clinically indicated or directed by AEs. Screening Physicals may be used for Cycle 1 Day 1 if done within 7 days prior to Day 1. Physical exams for additional cycles can be conducted within 3 days of Day 1 of the next cycle prior to dosing.

[c] Neurological assessments (BPNS and if applicable record AEs with CTCAE grading) will be performed at Screening and on Day 1 of every cycle starting from Cycle 2 **if clinically indicated** and at the End of Study Treatment/Early Discontinuation (See Appendix M).

[d] Vital signs: On Cycle 1 Days 1, 2, 8, 9, 15, 16, 22, and 23. On days when oprozomib is administered measure vitals within 1 hour prior to oprozomib dose and approximately 1 hour after each oprozomib dose. Include measurement of orthostatic blood pressure, temperature, respiration rate, and pulse on every study visit, including Screening and End of Study Treatment/Early Discontinuation. Subject should lie down for 5 minutes and then have blood pressure and pulse measured consistently in either arm. This should be followed by having the subject stand and repeating the blood pressure and pulse at 1 and 3 minutes. A drop of 20 mmHg systolic, 10 mmHg diastolic or lightheadedness/dizziness between supine and standing blood pressures would indicate orthostatic hypotension. Usually an increase in pulse of 10 beats/min is associated but not required. Subject's dosage and use of antihypertensive agents in the setting of orthostatic hypotension should be evaluated and reassessed on an ongoing basis while on study. Fluid intake should be assessed to confirm the subject is acting in accordance with protocol requirements. Re-education should occur if subject is not adhering to protocol requirements. Fluid status should be repleted to normal levels. If protocol requirements for oral intake of fluids are being met, additional measures should be taken to increase volume status, and ongoing monitoring is warranted and can be managed per investigator discretion. For time points where PK and vital signs are to be done together, vital signs should be obtained first as the act of phlebotomy may impact vital sign measurement results.

[e] At the investigator's medical discretion, vital signs monitoring may be extended beyond the time periods specified above (d).

[f] For Cycle 2, **if clinically indicated,** vital signs are required within approximately 1 hour prior to oprozomib administration on Days 1, 2, and 15. For Cycles 3 and higher, **if clinically indicated,** vital signs are required within approximately 1 hour prior to oprozomib administration on Day 1.

[g] Perform ECG approximately within 1 hour before (predose) and approximately 1 hour after (postdose) administration of oprozomib for Cycles 1, 2, 3, 4, 6, 8, 12, 18, 24, and then every 6 months **solely if clinically indicated,** until progression or unacceptable toxicity. Perform standard ECG assessment at Screening and End of Study Treatment/Early Discontinuation visit.

[h] Subjects with urine positive for protein (> than trace) will need to collect a 24-hour urine sample for creatinine and protein analyses. Urine samples and urinalysis, done locally.

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

[j] CBC and serum chemistry obtained Days 1, 2, and 15 of Cycles 1 and 2, and on Days 8, 9, and 16 of Cycle 1. Day 1 samples for laboratory analyses can be drawn within 72 hours prior to dosing on Day 1 for all subsequent cycles after Cycle 1 **only if clinically indicated**.

[k] Complete blood count (CBC) with differential, done locally, and includes the following: Hemoglobin, hematocrit, white blood cell (WBC) count with complete manual or automated differential (total neutrophils, lymphocytes, monocytes, eosinophils, basophils; reported as absolute counts), red blood cell (RBC) count, and platelet count. Screening results may be used for Cycle 1 Day 1 if obtained within 72 hours of Cycle 1 Day 1.

[l] Coagulation tests, done locally **if clinically indicated**, and includes the following: Prothrombin time, activated partial thromboplastin time, and international normalized ratio.

[m] Screening pregnancy testing, done locally, for females of childbearing potential (FCBP) must have a sensitivity of at least 50 mIU/mL with TWO medically supervised tests performed before pomalidomide dosing starts. One test must be obtained within 10–14 days and one test within 24 hours prior to the start of pomalidomide on Cycle 1 Day 1. A medically supervised, serum pregnancy test will be done weekly during Cycle 1 (Days 1, 8, 15, and 22). Starting with Cycle 2, serum pregnancy tests will be done within 24 hours prior to each cycle of pomalidomide dosing in FCBP only. Pregnancy tests will be repeated on Day 15 of Cycle 2 and beyond if menses are irregular (i.e., not within ± 7 days of a 28-day cycle) or menses are not present in FCBP.

[n] Results for SPEP, UPEP, and SFLC, obtained locally, during Screening must be available before starting study drug treatment. When the subject is on study drug, the disease response assessments will be performed at the end of each cycle (Day 22–28 or prior to dosing on Day 1 of the next cycle) for the first 18 months (Cycles 1–18), then every 8 weeks thereafter (starting with Cycle 20). If the subject comes off study for reasons other than progressive disease, then disease response assessments will be performed every 4 weeks through 18 months on study, and then every 8 weeks thereafter. Obtain blood for SPEP (please refer to Section 11.3 for collection times for SPEP Immunofixation, UPEP and UPEP Immunofixation with 24-hr urine, and sFLC) within 7 days prior to next Cycle study drug dosing. If a response assessment indicates PD, confirmation of PD may be obtained any time at or before the next scheduled assessment.

[o] Subjects are required to have a skeletal survey at Baseline (within 45 days prior to Cycle 1 Day 1 dosing) and at End of Study Treatment/Early Discontinuation. This does not need to be repeated if previously done within 30 days of consent. If a skeletal survey was done more than 30 days before consent, it may be acceptable with **the Sponsor's** study medical monitor approval. 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. If present at Baseline, bone lesion (s) must be monitored throughout the study only as needed to document response according to the IMWG-URC and modified EBMT criteria or if clinically indicated. For subjects who did not progress during treatment with bone lesions present at Baseline, skeletal survey will **no longer be required**. During long-term follow-up, skeletal survey evaluation **will also no longer be required**.

[p] Subjects are required to have a plasmacytoma evaluation if known or suspected clinically at Baseline (within 45 days prior to Cycle 1 Day 1 dosing) and at End of Study Treatment/Early Discontinuation. This does not need to be repeated if previously done within 30 days of consent. If the assessment was done more than 30 days before consent, it may be acceptable with **the Sponsor's** study medical monitor approval. If present at Baseline, plasmacytoma evaluation is to be repeated during treatment only to document response according to the IMWG-URC and modified EBMT criteria or if clinically indicated. If clinically indicated due to history of extramedullary disease, the same technique (may include ultrasound, CT scan, MRI, PET, or other standard-of-care method) must be employed for each measurement. For subjects with plasmacytoma at Baseline and did not progress during treatment, plasmacytoma will **no longer be required**. During long-term follow-up, plasmacytoma evaluation **will also no longer be required**.

[q] Bone marrow aspirate or biopsy is required at Baseline (within 45 days prior to Cycle 1 Day 1 dosing) to quantitate percent myeloma cell involvement. Obtain bone marrow aspirate sample for fluorescence in situ hybridization (FISH) studies. A portion of the sample may be used for optional genomic biomarker analysis, for all patients who consent. If Baseline bone marrow aspirate or biopsy were previously obtained and included cytogenetics and FISH (with results available) within 45 days prior to Cycle 1 Day 1 dosing, collection does not need to be repeated unless the patient consents to the optional biomarker genomic samples, which include collection of additional bone marrow aspirate(s). Repeat bone marrow aspirate when appropriate to confirm achievement of stringent complete response (sCR) or complete response (CR) within 30 days (+ 5 days) of confirmation assessment. Bone marrow aspirate will also be collected at disease progression **if clinically indicated** (may be collected at End of Study Treatment/Early Discontinuation due to PD**; it will no longer be required** during Long-**t**erm Follow-**up**) for subjects who consent to optional genomic biomarker analysis.

[r] Optional genomic biomarker samples- blood and saliva: For subjects who consent to participate, blood and saliva samples (in addition to a portion of the bone marrow aspirate obtained for FISH analysis; no new sample is required, as applicable) will be collected at Baseline (within 45 days prior to Cycle 1 Day 1 dosing)

[s] Sampling times are indicated in Section 11.4 of the protocol, and volumes are provided in the Laboratory Manual.

[t] Oprozomib treatment will be administered on Days 1, 2, 8, 9, 15, 16, 22, and 23 during 28-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason. On days on which oprozomib and dexamethasone are administered concurrently (i.e., on Days 1, 2, 8, 9, 15, 16, 22, 23 of each cycle), dexamethasone should be taken at least 30 minutes prior to oprozomib. Oprozomib should be taken with food. On the PK collection days, dosing of oprozomib in relation to the meal intake (within 2 hours before and 1 hour after dose) will be recorded.

[u] Subjects will receive 20 mg of dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day treatment cycle.

[v] Pomalidomide will be administered Days 1–21 of each 28-day cycle up to Cycle 24. Pomalidomide should be taken in the fasted state (i.e., 2 hours before or after a meal).

[w] Record all AEs from time of consent through 30 days after the last dose of study drug or before start of subsequent anticancer treatment (whichever occurs first). Start to record concomitant medications from 30 days prior to Day 1 until 30 days after the last dose of study drug. If there is any change in the subject's concomitant medications during the study, it must be recorded on the eCRF.

[x] All patients will be followed for survival status by telephone contact or other method approximately every 3 months (± 1 week), or as needed, until study closure.

APPENDIX B1 SCHEDULE OF STUDY ASSESSMENTS – PHASE 1B DOSE EXPANSION 5/14 SCHEDULE

Visit	Screening	Baseline	Cycle 1										Cycle 2					Cycle 3 +		End of Study Treatment/ Early Discon.[a]	Long-term Follow-up
	Day -28 to -1	(Pre-C1D1 dose)	Day 1	Day 2	Day 3−4	Day 5	Day 6−7	Day 8	Day 9−14	Day 15	Day 16−21	Day 22−28	Day 1	Day 2−14	Day 15	Day 16−21	Day 22−28	Day 1	Day 22−28		
Written Informed Consent	X																				
Inclusion/Exclusion Criteria	X																				
Medical History	X																				
Previous Treatment History	X																				
Physical Examination[b]	X		X										X					X		X	
Height	X																				
Weight	X		X										X					X		X	
Neurological Assessment (BPNS and NCI-CTCAE Grading)[c]	X												X					X		X	
Patient Questionnaires[d]: BPI-SF EORTC QLQ-C30 EORTC QLQ-MY20 FACT/GOG-Ntx4 EQ-5D-5L			X										X					X		X	
Vital Signs[e,f]	X		X	X	X	X		X		X	X		X	X	X	X		X		X	
12-lead ECG[g] (Local)	X		X										X					X		X	
Urinalysis[h]	X																			X	
Serum Chemistry[i,j]	X		X		X	X		X		X	X		X	X	X	X		X		X	
CBC with Diff and Platelets[j,k]	X		X		X	X		X		X	X		X	X	X	X		X		X	
Coagulation Tests[l]	X																				
Pregnancy Test[m]	X		X					X		X		X	X		X			X		X	

Footnotes are defined on next page

APPENDIX B1 SCHEDULE OF STUDY ASSESSMENTS – PHASE 1B DOSE EXPANSION 5/14 SCHEDULE (CONT'D)

	Screening	Baseline	Cycle 1										Cycle 2					Cycle 3 +		End of Study Treatment/ Early Discon.[a]	Long-term Follow-up
Visit	Day -28 to -1	(Pre-C1D1 dose)	Day 1	Day 2	Day 3–4	Day 5	Day 6–7	Day 8	Day 9–14	Day 15	Day 16–21	Day 22–28	Day 1	Day 2–14	Day 15	Day 16–21	Day 22–28	Day 1	Day 22–28		
SPEP/UPEP/Serum FLC Immunofixation[n]	X	X (Day -7 to 1)								X sFLC only			X					X		X	
β2 Microglobulin	X																				
Skeletal Survey[o]		X																		X	
Plasmacytoma Evaluation[p]		X																		X	
Bone Marrow Aspirate and FISH Analyses[q,]		X																		X	
Optional – Genomic Biomarker Assessment: Blood[r]		X																			
Optional – Genomic Biomarker Assessment: Saliva[r]		X																			
Blood for PK[s]			X	X									X								
Blood for PDn Assay[s]			X	X									X								
Oprozomib Dosing[t]			X	X	X	X				X	X		X	X	X	X		X			
Dexamethasone Dosing[u]			X	X				X	X	X	X	X	X	X	X	X	X	X	X		
Pomalidomide Dosing[v]			X	X	X	X	X	X	X	X	X		X	X	X	X		X			
AEs and Concomitant Medications[w]			→																		
Telephone or other contact for disease and survival status[x]																					X

Footnotes are defined on next page

APPENDIX B1 SCHEDULE OF STUDY ASSESSMENTS – PHASE 1B DOSE EXPANSION 5/14 SCHEDULE (CONT'D)

AE = adverse event; BPI-SF = Brief Pain Inventory – Short Form; BPNS = Brief Peripheral Neuropathy Screen; C = Cycle; CBC = complete blood count; D = Day; Discon. = discontinuation; EBMT = European Group for Blood and Marrow Transplantation; ECG = electrocardiogram; EORTC = European Organization for Research and Treatment; EQ-5D-5L = a new facility for the measurement of health-related quality of life; FACT/GOG-Ntx = Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity subscale questionnaire; FISH = fluorescence in situ hybridization; FLC = free light chain; IMWG-URC = International Myeloma Working Group-Uniform Response Criteria; NCI-CTCAE = National Cancer Institute – Common Terminology Criteria for Adverse Events; PDn = pharmacodynamic(s); PK = pharmacokinetic(s); SFLC = serum free light chain; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

[a] All End of Study Treatment/Early Discontinuation Assessments must be performed within 30 days following the subject's last administration of study drug and prior to initiation of any other treatment, whichever comes first.

[b] Complete physical examinations will be performed during Screening and at the End of Study Treatment/Early Discontinuation visits. All other physical examinations will be limited physical examinations **only if clinically indicated**. A complete physical examination will include examination of the skin, head and neck, chest (heart and lungs), abdomen, extremities, and a brief neurological examination including an assessment for peripheral neuropathy. Rectal and pelvic examinations are optional. Eastern Cooperative Oncology Group (ECOG) performance status (assessed only at the time of the Screening and End of Study Treatment/Early Discontinuation physical examination) will be conducted. A limited physical examination will include an examination of the chest (heart and lungs) and abdomen, with additional examinations as clinically indicated or directed by AEs. Screening Physicals may be used for Cycle 1 Day 1 if done within 7 days prior to Day 1. Physical exams for additional cycles can be conducted within 3 days of Day 1 of the next cycle prior to dosing.

[c] Neurological assessments (BPNS and if applicable record AEs with CTCAE grading) will be performed at Screening and on Day 1 of every cycle starting from Cycle 2 **if clinically indicated** and at the End of Study Treatment/Early Discontinuation (See Appendix M).

[d] BPI-SF, EORTC QLQ-C30, EORTC QLQ-MY20, FACT/GOG-Ntx4, and EQ-5D-5L to be collected at on Day 1 of every cycle through End of Study Treatment/Early Discontinuation visit. These patient-reported outcome instruments should be administered prior to administration of any study drug.

[e] Vital signs: On Cycle 1 Days 1–5, 8, 15, and 19. On days when oprozomib is administered measure vitals within 1 hour prior to oprozomib dose and approximately 1 hour after each oprozomib dose. Include measurement of orthostatic blood pressure, pulse, respiration rate, and temperature on every study visit, including Screening and End of Study Treatment/Early Discontinuation. Subject should lie down for 5 minutes and then have blood pressure and pulse measured consistently in either arm. This should be followed by having the subject stand and repeating the blood pressure and pulse at 1 and 3 minutes. A drop of 20 mmHg systolic, 10 mmHg diastolic, or lightheadedness/dizziness between supine and standing blood pressures would indicate orthostatic hypotension. Usually an increase in pulse of 10 beats/min is associated but not required. Subject's dosage and use of antihypertensive agents in the setting of orthostatic hypotension should be evaluated and reassessed on an ongoing basis while on study. Fluid intake should be assessed to confirm the subject is acting in accordance with protocol requirements. Re-education should occur if subject is not adhering to protocol requirements. Fluid status should be repleted to normal levels. If protocol requirements for oral intake of fluids are already being met, additional measures should be taken to increase volume status, and ongoing monitoring is warranted and can be managed per investigator discretion. At the investigator's medical discretion, vital sign monitoring may be extended beyond the time periods specified above. For time points where PK and vital signs are to be done together, vital signs should be obtained first as the act of phlebotomy may impact vital sign measurement results.

[f] For Cycles 2, **if clinically indicated,** vital signs are required within approximately 1 hour prior to oprozomib administration on Days 1, 5, 15, and 19. For Cycles 3 and higher, **if clinically indicated,** vital signs are required within approximately 1 hour prior to oprozomib administration on Day 1.

[g] Perform ECG approximately within 1 hour before (predose) and approximately 1 hour after (postdose) administration of oprozomib for Cycles 1, 2, 3, 4, 6, 8, 12, 18, 24 and then every 6 months **solely if clinically indicated**, until progression or unacceptable toxicity. Perform standard ECG assessment at Screening and End of Study Treatment/Early Discontinuation visit.

[h] Subjects with urine positive for protein (> than trace) will need to collect a 24-hour urine sample for creatinine and protein analyses. Urine samples and urinalysis, done locally.

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

APPENDIX B1 SCHEDULE OF STUDY ASSESSMENTS – PHASE 1B DOSE EXPANSION 5/14 SCHEDULE (CONT'D)

[j] CBC and serum chemistry obtained Days 1, 5, 15, and 19 of Cycles 1 and 2, and on Days 3 and 8 of Cycle 1. Day 1 samples for laboratory analyses can be drawn within 72 hours prior to dosing on Day 1 for all subsequent cycles after Cycle 1 **only if clinically indicated**.

[k] Complete blood count (CBC) with differential, done locally, and includes the following: Hemoglobin, hematocrit, white blood cell (WBC) count with complete manual or automated differential (total neutrophils, lymphocytes, monocytes, eosinophils, basophils; reported as absolute counts), red blood cell (RBC) count, and platelet count. Screening results may be used for Cycle 1 Day 1 if obtained within 72 hours of Cycle 1 Day 1.

[l] Coagulation tests, done locally **if clinically indicated,** and includes the following: Prothrombin time, activated partial thromboplastin time, and international normalized ratio.

[m] Screening pregnancy testing, done locally for females of childbearing potential (FCBP) must have a sensitivity of at least 50 mIU/mL with TWO medically supervised tests performed before pomalidomide dosing starts. One test must be obtained within 10–14 days and one test within 24 hours prior to the start of pomalidomide on Cycle 1 Day 1. A medically supervised, serum pregnancy test will be done weekly during Cycle 1 (Days 1, 8, 15, and 22). Starting with Cycle 2, serum pregnancy tests will be done within 24 hours prior to each cycle of pomalidomide dosing in FCBP only. Pregnancy tests will be repeated on Day 15 of Cycle 2 and beyond if menses are irregular (i.e., not within ± 7 days of a 28-day cycle) or menses are not present in FCBP.

[n] Results for SPEP, UPEP, and SFLC, obtained locally, during Screening must be available before starting study drug treatment. When the subject is on study drug, the disease response assessments will be performed at the end of each cycle (Day 22–28 or prior to dosing on Day 1 of the next cycle) for the first 18 months (Cycles 1–18), then every 8 weeks thereafter (starting with Cycle 20). If the subject comes off study for reasons other than progressive disease, then disease response assessments will be performed every 4 weeks through 18 months on study, and then every 8 weeks thereafter. Obtain blood for SPEP (please refer to Section 11.3 for collection times for SPEP Immunofixation, UPEP and UPEP Immunofixation with 24-hr urine, and sFLC) within 7 days prior to next Cycle study drug dosing. If a response assessment indicates PD, confirmation of PD may be obtained any time at or before the next scheduled assessment.

[o] Subjects are required to have a skeletal survey at Baseline (within 45 days prior to Cycle 1 Day 1 dosing) and at End of Study Treatment/Early Discontinuation. This does not need to be repeated if previously done within 30 days of consent. If a skeletal survey was done more than 30 days before consent, it may be acceptable with **the Sponsor's** study medical monitor approval. 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. If present at Baseline, bone lesion (s) must be monitored throughout the study only as needed to document response according to the IMWG-URC and modified EBMT criteria or if clinically indicated. For subjects who did not progress during treatment with bone lesions present at Baseline, skeletal survey will **no longer be required**. During long-term follow-up, skeletal survey evaluation **will also no longer be required**.

[p] Subjects are required to have a plasmacytoma evaluation if known or suspected clinically at Baseline (within 45 days prior to Cycle 1 Day 1 dosing) and at End of Study Treatment. This does not need to be repeated if previously done within 30 days of consent. If the assessment was done more than 30 days before consent, it may be acceptable with **the Sponsor's** study medical monitor approval. If present at Baseline, plasmacytoma evaluation is to be repeated during treatment only to document response according to the IMWG-URC and modified EBMT criteria or if clinically indicated. If clinically indicated due to history of extramedullary disease, the same technique (may include ultrasound, CT scan, MRI, PET, or other standard-of-care method) must be employed for each measurement. For subjects with plasmacytoma at Baseline and did not progress during treatment, plasmacytoma will **no longer be required**. During long-term follow-up, plasmacytoma evaluation **will also no longer be required**.

[q] Bone marrow aspirate or biopsy is required at Baseline (within 45 days prior to Cycle 1 Day 1 dosing) to quantitate percent myeloma cell involvement. Obtain bone marrow aspirate sample for fluorescence in situ hybridization (FISH) studies. A portion of the sample may be used for optional genomic biomarker analysis, for all patients who consent. If Baseline bone marrow aspirate or biopsy were previously obtained and included cytogenetics and FISH (with results available) within 45 days prior to Cycle 1 Day 1 dosing, collection does not need to be repeated unless the patient consents to the optional biomarker genomic samples, which include collection of additional bone marrow aspirate(s). Repeat bone marrow aspirate when appropriate to confirm achievement of stringent complete response (sCR) or complete response (CR) within 30 days (+ 5 days) of confirmation assessment. Bone marrow aspirate will also be collected at disease progression **if clinically indicated** (may be collected at End of Study Treatment/Early Discontinuation due to PD**; it will no longer be required** during Long-**t**erm Follow-**u**p) for subjects who consent to optional genomic biomarker analysis.

[r] Optional genomic biomarker samples- blood and saliva: For subjects who consent to participate, blood and saliva samples (in addition to a portion of the bone marrow aspirate obtained for FISH analysis; no new sample is required, as applicable) will be collected at Baseline (within 45 days prior to Cycle 1 Day 1 dosing).

[s] Sampling times are indicated in Section 11.4 of the protocol, and volumes are provided in the Laboratory Manual.

APPENDIX B1 SCHEDULE OF STUDY ASSESSMENTS – PHASE 1B DOSE EXPANSION 5/14 SCHEDULE (CONT'D)

[t] Oprozomib treatment will be administered on Days 1–5 and 15–19 during 28-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason. On days on which oprozomib and dexamethasone are administered concurrently (i.e., on Days 1, 2, 15, and 16 of each cycle), dexamethasone should be taken at least 30 minutes prior to oprozomib. Oprozomib should be taken with food. On the PK collection days, dosing of oprozomib in relation to the meal intake (within 2 hours before and 1 hour after dose) will be recorded.

[u] Subjects will receive 20 mg of dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day treatment cycle.

[v] Pomalidomide will be administered Days 1–21 of each 28-day cycle up to Cycle 24. Pomalidomide should be taken in the fasted state (i.e., 2 hours before or after a meal).

[w] Record all AEs from time of consent through 30 days after the last dose of study drug or before start of subsequent anticancer treatment (whichever occurs first). Start to record concomitant medications from 30 days prior to Day 1 until 30 days after the last dose of study drug. If there is any change in the subject's concomitant medications during the study, it must be recorded on the eCRF.

[x] All patients will be followed for survival status by telephone contact or other method approximately every 3 months (± 1 week), or as needed, until study closure.

APPENDIX B2 SCHEDULE OF STUDY ASSESSMENTS – PHASE 1B DOSE EXPANSION 2/7 SCHEDULE

Visit	Screening	Baseline	Cycle 1								Cycle 2				Cycle 3 +		End of Study Treatment/ Early Discon.[a]	Long-term Follow-up
	Day -28 to -1	(Pre-C1D1 dose)	Day 1	Day 2	Day 3–7	Day 8	Day 9–14	Day 15	Day 16–21	Day 22–28	Day 1	Day 2–14	Day 15	Day 22–28	Day 1	Day 22–28		
Written Informed Consent	X																	
Inclusion/Exclusion Criteria	X																	
Medical History	X																	
Previous Treatment History	X																	
Physical Examination[b]	X		X								X				X		X	
Height	X																	
Weight	X		X								X				X		X	
Neurological Assessment (BPNS and NCI-CTCAE Grading)[c]	X										X				X		X	
Patient Questionnaires[d]: BPI-SF EORTC QLQ-C30 EORTC QLQ-MY20 FACT-COG-Ntx4 EQ-5D-5L			X								X				X		X	
Vital Signs[e,f]	X		X	X		X	X	X	X	X	X	X	X		X		X	
12-lead ECG[g] (Local)	X		X								X				X		X	
Urinalysis[h]	X																X	
Serum Chemistry[i,j]	X		X	X		X	X	X	X		X	X	X		X		X	
CBC with Diff and Platelets[j,k]	X		X	X		X	X	X	X		X	X	X		X		X	
Coagulation Tests[l]	X																	
Pregnancy Test[m]	X		X			X		X		X	X		X		X		X	

Footnotes are defined on the next page

APPENDIX B2 SCHEDULE OF STUDY ASSESSMENTS – PHASE 1B DOSE EXPANSION 2/7 SCHEDULE (CONT'D)

Visit	Screening	Baseline	Cycle 1								Cycle 2				Cycle 3 +		End of Study Treatment/ Early Discon.[a]	Long-term Follow-up
	Day -28 to -1	(Pre-C1D1 dose)	Day 1	Day 2	Day 3–7	Day 8	Day 9–14	Day 15	Day 16–21	Day 22–28	Day 1	Day 2–14	Day 15	Day 22–28	Day 1	Day 22–28		
SPEP/UPEP/ Serum FLC Immunofixation[n]	X	X (Day -7 to 1)						X sFLC only			X				X		X	
β2 Microglobulin	X																	
Skeletal Survey[o]		X															X	
Plasmacytoma Evaluation[p]		X															X	
Bone Marrow Aspirate and FISH Analyses[q,]		X															X	
Optional – Genomic Biomarker Assessment: Blood[r]		X																
Optional – Genomic Biomarker Assessment: Saliva[r]		X																
Blood for PK[s]			X	X							X							
Blood for PDn Assay[s]			X	X							X							
Oprozomib Dosing[t]			X	X		X	X	X	X	X	X	X	X	X	X	X		
Dexamethasone Dosing[u]			X	X		X	X	X	X	X	X	X	X	X	X	X		
Pomalidomide Dosing[v]			X	X	X	X	X	X	X		X	X	X		X			
AEs and Concomitant Medications[w]			→															
Telephone or other contact for disease and survival status[x]																		X

Footnotes are defined on next page

APPENDIX B2 SCHEDULE OF STUDY ASSESSMENTS – PHASE 1B DOSE EXPANSION 2/7 SCHEDULE (CONT'D)

AE = adverse event; BPI-SF = Brief Pain Inventory – Short Form; BPNS = Brief Peripheral Neuropathy Screen; C = Cycle; CBC = complete blood count; D = Day; Discon. = discontinuation; EBMT = European Group for Blood and Marrow Transplantation; ECG = electrocardiogram; EORTC = European Organization for Research and Treatment; EQ-5D-5L = a new facility for the measurement of health-related quality of life; FACT/GOG-Ntx = Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity subscale questionnaire; FISH = fluorescence in situ hybridization; FLC = free light chain; IMWG-URC = International Myeloma Working Group-Uniform Response Criteria; NCI-CTCAE = National Cancer Institute – Common Terminology Criteria for Adverse Events; PDn = pharmacodynamic(s); PK = pharmacokinetic(s); SFLC = serum free light chain; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

[a] All End of Study Treatment/Early Discontinuation Assessments must be performed within 30 days following the subject's last administration of study drug and prior to initiation of any other treatment, whichever comes first.

[b] Complete physical examinations will be performed during Screening and at the End of Study Treatment/Early Discontinuation visits. All other physical examinations will be limited physical examinations **only if clinically indicated**. A complete physical examination will include examination of the skin, head and neck, chest (heart and lungs), and abdomen, extremities, and a brief neurological examination including an assessment for peripheral neuropathy. Rectal and pelvic examinations are optional. Eastern Cooperative Oncology Group (ECOG) performance status (assessed only at the time of the Screening and End of Study Treatment/Early Discontinuation physical examination) will be conducted. A limited physical examination will include an examination of the chest (heart and lungs) and abdomen, with additional examinations as clinically indicated or directed by AEs. Screening Physicals may be used for Cycle 1 Day 1 if done within 7 days prior to Day 1. Physical exams for additional cycles can be conducted within 3 days of Day 1 of the next cycle prior to dosing.

[c] Neurological assessments (BPNS and if applicable record AEs with CTCAE grading) will be performed at Screening and on Day 1 of every cycle starting from Cycle 2 **if clinically indicated** and at the End of Study Treatment/Early Discontinuation (See Appendix M).

[d] BPI-SF, EORTC QLQ-C30, EORTC QLQ-MY20, FACT/GOG-Ntx4, and EQ-5D-5L to be collected on Day 1 of every cycle through End of Study Treatment/Early Discontinuation visit. These patient-reported outcome instruments should be administered prior to administration of any study drug.

[e] Vital signs: On Cycle 1 Days 1, 2, 8, 9, 15, 16, 22, and 23. On days when oprozomib is administered measure vitals within 1 hour prior to oprozomib dose and approximately 1 hour after each oprozomib dose. Include measurement of orthostatic blood pressure, pulse, respiration rate, and temperature on every study visit, including Screening and End of Study Treatment/Early Discontinuation. Subject should lie down for 5 minutes and then have blood pressure and pulse measured consistently in either arm. This should be followed by having the subject stand and repeating the blood pressure and pulse at 1 and 3 minutes. A drop of 20 mmHg systolic, 10 mmHg diastolic, or lightheadedness/dizziness between supine and standing blood pressure would indicate orthostatic hypotension. Usually an increase in pulse of 10 beats/min is associated but not required. Subject's dosage and use of antihypertensive agents in the setting of orthostatic hypotension should be evaluated and reassessed on an ongoing basis while on study. Fluid intake should be assessed to confirm the subject is acting in accordance with protocol requirements. Re-education should occur if subject is not adhering to protocol requirements. Fluid status should be repleted to normal levels. If protocol requirements for oral intake of fluids are already being met, additional measures should be taken to increase volume status and ongoing monitoring is warranted and can be managed per investigator discretion. At the investigator's medical discretion, vital sign monitoring may be extended beyond the time periods specified above. For time points where PK and vital signs are to be done together, vital signs should be obtained first as the act of phlebotomy may impact vital sign measurement results.

[f] For Cycle 2, **if clinically indicated,** vital signs are required within approximately 1 hour prior to oprozomib administration on Days 1, 2, and 15. For Cycles 3 and higher**, if clinically indicated,** vital signs are required within approximatley 1 hour prior to oprozomib administration on Day 1.

[g] Perform ECG approximately within 1 hour before (predose) and approximately 1 hour after (postdose) administration of oprozomib for Cycles 1, 2, 3, 4, 6, 8, 12, 18, 24 and then every 6 months **solely if clinically indicated**, until progression or unacceptable toxicity. Perform standard ECG assessment at Screening and End of Study Treatment/Early Discontinuation visit.

[h] Subjects with urine positive for protein (> than trace) will need to collect a 24-hour urine sample for creatinine and protein analyses. Urine samples and urinalysis, done locally.

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

APPENDIX B2 SCHEDULE OF STUDY ASSESSMENTS – PHASE 1B DOSE EXPANSION 2/7 SCHEDULE (CONT'D)

[j] CBC and serum chemistry obtained Days 1, 2, and 15 of Cycles 1 and 2, and on Days 8, 9, and 16 of Cycle 1. Day 1 samples for laboratory analyses can be drawn within 72 hours prior to dosing on Day 1 for all subsequent cycles after Cycle 1 **only if clinically indicated**.

[k] Complete blood count (CBC) with differential, done locally, and includes the following: Hemoglobin, hematocrit, white blood cell (WBC) count with complete manual or automated differential (total neutrophils, lymphocytes, monocytes, eosinophils, basophils; reported as absolute counts), red blood cell (RBC) count, and platelet count. Screening results may be used for Cycle 1 Day 1 if obtained within 72 hours of Cycle 1 Day 1.

[l] Coagulation tests, done locally **if clinically indicated**, and includes the following: Prothrombin time, activated partial thromboplastin time, and international normalized ratio.

[m] Screening pregnancy testing, done locally, for females of childbearing potential (FCBP) must have a sensitivity of at least 50 mIU/mL with TWO medically supervised tests performed before pomalidomide dosing starts. One test must be obtained within 10–14 days and one test within 24 hours prior to the start of pomalidomide on Cycle 1 Day 1. A medically supervised, serum pregnancy test will be done weekly during Cycle 1 (Days 1, 8, 15, and 22). Starting with Cycle 2, serum pregnancy tests will be done within 24 hours prior to each cycle of pomalidomide dosing in FCBP only. Pregnancy tests will be repeated on Day 15 of Cycle 2 and beyond if menses are irregular (i.e., not within ± 7 days of a 28-day cycle) or menses are not present in FCBP.

[n] Results for SPEP, UPEP, and SFLC, obtained locally, during Screening must be available before starting study drug treatment. When the subject is on study drug, the disease response assessments will be performed at the end of each cycle (Day 22–28 or prior to dosing on Day 1 of the next cycle) for the first 18 months (Cycles 1–18), then every 8 weeks thereafter (starting with Cycle 20). If the subject comes off study for reasons other than progressive disease, then disease response assessments will be performed every 4 weeks through 18 months on study, and then every 8 weeks thereafter. Obtain blood for SPEP (please refer to Section 11.3 for collection times for SPEP Immunofixation, UPEP and UPEP Immunofixation with 24-hr urine, and sFLC) within 7 days prior to next Cycle study drug dosing. If a response assessment indicates PD, confirmation of PD may be obtained any time at or before the next scheduled assessment.

[o] Subjects are required to have a skeletal survey at Baseline (within 45 days prior to Cycle 1 Day 1 dosing) and at End of Study Treatment/Early Discontinuation. This does not need to be repeated if previously done within 30 days of consent. If a skeletal survey was done more than 30 days before consent, it may be acceptable with **the Sponsor's** study medical monitor approval. 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. If present at Baseline, bone lesion (s) must be monitored throughout the study only as needed to document response according to the IMWG URC and modified EBMT criteria or if clinically indicated. For subjects who did not progress during treatment with bone lesions present at Baseline, skeletal survey will **no longer be required**. During long-term follow-up, skeletal survey evaluation **will also no longer be required**.

[p] Subjects are required to have a plasmacytoma evaluation if known or suspected clinically at Baseline (within 45 days prior to Cycle 1 Day 1 dosing) and at End of Study Treatment/Early Discontinuation. This does not need to be repeated if previously done within 30 days of consent. If the assessment was done more than 30 days before consent, it may be acceptable with **the Sponsor's** study medical monitor approval. If present at Baseline, plasmacytoma evaluation is to be repeated during treatment only to document response according to the IMWG-URC and modified EBMT criteria or if clinically indicated. If clinically indicated due to history of extramedullary disease, the same technique (may include ultrasound, CT scan, MRI, PET, or other standard of care method) must be employed for each measurement. For subjects with plasmacytoma at Baseline and did not progress during treatment , plasmacytoma will **no longer be required**. During long-term follow-up, plasmacytoma evaluation **will also no longer be required**.

[q] Bone marrow aspirate or biopsy is required at Baseline (within 45 days prior to Cycle 1 Day 1 dosing) to quantitate percent myeloma cell involvement. Obtain bone marrow aspirate sample for fluorescence in situ hybridization (FISH) studies. A portion of the sample may be used for optional genomic biomarker analysis, for all patients who consent. If Baseline bone marrow aspirate or biopsy were previously obtained and included cytogenetics and FISH (with results available) within 45 days prior to Cycle 1 Day 1 dosing, collection does not need to be repeated unless the patient consents to the optional biomarker genomic samples, which include collection of additional bone marrow aspirate(s). Repeat bone marrow aspirate when appropriate to confirm achievement of stringent complete response (sCR) or complete response (CR) within 30 days (+ 5 days) of confirmation assessment. Bone marrow aspirate will also be collected at disease progression **if clinically indicated** (may be collected at End of Study Treatment/Early Discontinuation due to PD**; it will no longer be required** during Long-**t**erm Follow-**u**p) for subjects who consent to optional genomic biomarker analysis.

[r] Optional genomic biomarker samples- blood and saliva: For subjects who consent to participate, blood and saliva samples (in addition to a portion of the bone marrow aspirate obtained for FISH analysis; no new sample is required, as applicable) will be collected at Baseline (within 45 days prior to Cycle 1 Day 1 dosing).

[s] Sampling times are indicated in Section 11.4 of the protocol, and volumes are provided in the Laboratory Manual.

APPENDIX B2 SCHEDULE OF STUDY ASSESSMENTS – PHASE 1B DOSE EXPANSION 2/7 SCHEDULE (CONT'D)

[t] Oprozomib treatment will be administered on Days 1, 2, 8, 9, 15, 16, 22, and 23 during 28-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason. On days on which oprozomib and dexamethasone are administered concurrently (i.e., on Days 1, 2, 8, 9, 15, 16, 22, 23 of each cycle), dexamethasone should be taken at least 30 minutes prior to oprozomib. Oprozomib should be taken with food. On the PK collection days, dosing of oprozomib in relation to the meal intake (within 2 hours before and 1 hour after dose) will be recorded.

[u] Subjects will receive 20 mg of dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day treatment cycle.

[v] Pomalidomide will be administered Days 1–21 of each 28-day cycle up to Cycle 24. Pomalidomide should be taken in the fasted state (i.e., 2 hours before or after a meal).

[w] Record all AEs from time of consent through 30 days after the last dose of study drug or before start of subsequent anticancer treatment (whichever occurs first). Start to record concomitant medications from 30 days prior to Day 1 until 30 days after the last dose of study drug. If there is any change in the subject's concomitant medications during the study, it must be recorded on the eCRF.

[x] All patients will be followed for survival status by telephone contact or other method approximately every 3 months (± 1 week), or as needed, until study closure.

APPENDIX C RESPONSE CRITERIA FOR MULTIPLE MYELOMA

Table D1 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 ○ If the serum and urine M-protein are not measurable, a decrease of > 90% in the difference between the involved and uninvolved sFLC levels is required in place of the M-protein criteria
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 present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required[d, e]
Stable	• Not meeting criteria for CR, VGPR, PR, or PD
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 patients 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 patients without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow plasma cell 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

Footnotes are defined on next page

Table D1 Summary of International Myeloma Working Group-Uniform Response Criteria (IMWG-URC) (cont'd)

Response Subcategory[a]	Response Criteria

Sources: Blade 1998; Durie 2006; Rajkumar 2011.

CR = complete response; sCR = stringent complete response; FLC = 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 progressive disease only needs to be met, and confirmed, in one parameter.

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

[c] Presence/absence of clonal cells is based on 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 patients 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, patients with measurable disease restricted to SPEP will need to be followed only by SPEP. Correspondingly, patients with measurable disease restricted to UPEP will need to be followed only by UPEP.

[e] Determination of PD based on based on M-protein, hypercalcemia, or FLC while on study requires two consecutive assessments made at any time before classification of progressive disease 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.

Table D2 Definition of Minimal Response per EBMT Criteria

Minimal Response	
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
	If the serum and urine M-protein are not measurable, a decrease of 25%–49% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria.
	For patients with nonsecretory 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)

Sources: Bladé 1998; Kyle 2009.

EBMT = European Group for Blood and Marrow Transplantation; FLC = free light chain; MR = minimal response.

[a] The response category MR requires 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 D EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC) CORE MODULE (QLQ-C30) AND EORTC MULTIPLE MYELOMA MODULE (QLQ-MY20)

Subjects should be instructed to fill out the EORTC QLC-C30 (Version 3) and EORTC QLC-MY20 questionnaires to the best of their abilities. The study staff will be responsible for confirming that the subject has completed the questionnaires.

Citations for the EORTC QLQ-C30 and the EORTC QLQ-MY20 are provided in the Reference List (Aaronson 1993; Fayers 2001; Cocks 2007).

APPENDIX E NEUROTOXICITY SUBSCALE OF THE GYNECOLOGIC ONCOLOGY GROUP'S FUNCTIONAL ASSESSMENT OF CANCER THERAPY (FACT/GOG-NTX4 [VERSION 4])

Subjects with neurotoxicities should be instructed to fill out the FACT/GOG-Ntx4 (Version 4) to the best of their abilities. The study staff will be responsible for confirming that the subject has completed the questionnaire.

APPENDIX F EQ-5D-5L (V.2)

Subjects should be instructed to fill out the EQ-5D-5L (v.2) questionnaire to the best of their abilities. The study staff will be responsible for confirming that the subject has completed the questionnaire.

APPENDIX G EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE SCALE

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

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

APPENDIX H DRUG-DRUG INTERACTION POTENTIAL OF OPROZOMIB AND POMALIDOMIDE

Oprozomib

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

[a] Not available in the United States.

Because oprozomib is a P-gp substrate, use of P-gp inhibitors and inducers (see table below) should be carefully monitored and such drugs should be substituted for others if necessary.

Pomalidomide

In accordance with the Pomalidomide Prescribing Information, use of the following concomitant medications is to be carefully monitored and these drugs should be substituted for others if necessary.

Drugs That May Increase Pomalidomide Plasma Concentrations

CYP3A, CYP1A2, or P-gp inhibitors: Co-administration of POMALYST with drugs that are strong inhibitors of CYP1A2, CYP3A (e.g., ketoconazole) or P-gp could increase exposure and should be avoided.

Drugs That May Decrease Pomalidomide Plasma Concentrations

CYP3A, CYP1A2, or P-gp inducers: Co-administration of POMALYST with drugs that are strong inducers of CYP1A2, CYP3A (e.g., rifampin) or P-gp could decrease exposure and should be avoided.

Smoking

Cigarette smoking may reduce pomalidomide exposure due to CYP1A2 induction. Subjects should be advised that smoking may reduce the efficacy of pomalidomide.

The tables below provide lists of the inhibitors and inducers of concern.

CYP 3A inhibitor	CYP1A2 inhibitor	
Strong:	**Strong:**	**P-gp inhibitor**
boceprevir	ciprofloxacin	amiodarone
clarithromycin	enoxacin	azithromycin
conivaptan	fluvoxamine	captopril
grapefruit juice		carvedilol
indinavir		clarithromycin
itraconazole		conivaptan
ketoconazole		cyclosporine
lopinavir/ritonavir		diltiazem
mibefradil		dronedarone
nefazodone		erythromycin
nelfinavir		felodipine
posaconazole		itraconazole
ritonavir		ketoconazole
saquinavir		lopinavir and ritonavir
telaprevir, telithromycin, voriconazole		quercetin
		quinidine, ranolazine, ticagrelor, verapamil

CYP 3A inducer		
Strong:	**CYP1A2 inducer**	**P-gp inducer**
avasimibe		avasimibe
carbamazepine		carbamazepine
phenytoin		phenytoin
rifampin		rifampin
St. John's wort		St John's wort
		tipranavir/ritonavir

APPENDIX I POMALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES, AND ACCEPTABLE BIRTH CONTROL METHODS

Risks Associated with Pregnancy

Pomalidomide was found to be teratogenic in a developmental study in rabbits. Pomalidomide is an analogue of thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If pomalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby.

Criteria for Females of Childbearing Potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Counseling

For an FCBP, pomalidomide is contraindicated unless all of the following are met (i.e., FCBP must be counseled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting study treatment, throughout the entire duration of study treatment, dose interruption, and 28 days after the End of Study Treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as pomalidomide is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol
- She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide

The Investigator must ensure that females of childbearing potential:

- Comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, pomalidomide is contraindicated unless the following are met (i.e., all females NOT of childbearing potential must be counseled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide

The effect of pomalidomide on spermatogenesis is not known and has not been studied.

Therefore, male subjects taking pomalidomide must meet the following conditions (i.e., all males must be counseled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- Understand the potential teratogenic risk if engaged in sexual activity with a woman of childbearing potential
- Understand the need for the use of a condom, even if he has had a vasectomy, if engaged in sexual activity with a female of childbearing potential.

Contraception

Females of childbearing potential enrolled in this protocol must agree to use 2 reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) dose interruptions; and 4) for at least 28 days after study treatment discontinuation.

The 2 methods of reliable contraception must include 1 highly effective method and 1 additional effective (barrier) method. An FCBP must be referred to a qualified provider of contraceptive methods if needed.

The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
    - Intrauterine device (IUD)
    - Hormonal (birth control pills, injections, implants)
    - Tubal ligation
    - Partner's vasectomy
- Additional effective methods:
    - Male condom
    - Diaphragm
    - Cervical cap

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a subject is currently using combined oral contraception the subject should switch to another one of the effective methods listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception.

The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered, particularly in subjects with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 50 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting study drug

Female Subjects

Females of childbearing potential must have 2 negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to starting pomalidomide. The first pregnancy test must be performed within 10-14 days prior to the start of pomalidomide and the second pregnancy test must be performed within 24 hours prior to the start of pomalidomide. The subject may not receive study drug until the investigator has verified that the results of these pregnancy tests are negative.

Male Subjects

Must practice complete abstinence or agree to use a condom during sexual contact with FCBP while participating in the study, during dose interruptions, and for at least 90 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Female Subjects

- Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at Day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at Days 14 and 28 following study drug discontinuation.
- At each visit, the investigator must confirm with the FCBP that she is continuing to use 2 reliable methods of birth control.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a study subject, pomalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male Subjects

- Counseling about the requirement for condom use during sexual contact with FCBP and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study subject during study participation, the investigator must be notified immediately.

Additional precautions

- Subjects should be instructed never to give this medicinal product to another person and to return any unused capsules to the investigator at the End-of-Treatment.
- Subjects should not donate blood during therapy and for at least 28 days following discontinuation of pomalidomide.
- Male subjects should not donate semen or sperm during therapy or for at least 90 days following discontinuation of pomalidomide.
- Only enough pomalidomide for 1 cycle of therapy may be dispensed with each cycle of therapy.

APPENDIX J POMALIDOMIDE EDUCATION AND COUNSELLING GUIDANCE DOCUMENT

Protocol Number: **OPZ007**

Patient Name (Print): _____ DOB: _____/_____/_____ (mm/dd/yyyy)

Female

If female, check one:

☐ FCBP (female of childbearing potential): Sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months)

☐ NOT FCBP

To be completed prior to each dispensing of pomalidomide

Do Not Dispense pomalidomide if:

- The patient is pregnant.
- No pregnancy tests were conducted for a FCBP.
- The patient states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual intercourse) [at least 28 days prior while taking pomalidomide, during dose interruption, and 28 days after discontinuation of pomalidomide].

FCBP

1. **I verified that the required pregnancy tests performed are negative.**
2. **I counseled FCBP regarding the following:**

- Potential fetal harm: If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking pomalidomide. The teratogenic potential of pomalidomide in humans cannot be ruled out. Females of childbearing potential must agree not to become pregnant while taking pomalidomide.

- Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual intercourse [at least 28 days prior, while taking pomalidomide, during dose interruption, and 28 days after discontinuation of pomalidomide].
- Continuation of TWO reliable methods of birth control or complete abstinence if therapy is interrupted.
- That even if she has amenorrhea she must comply with advice on contraception.
- Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:
    - Highly effective methods:
        - Intrauterine device (IUD)
        - Hormonal (birth control pills, injections, implants)
        - Tubal ligation
        - Partner's vasectomy
    - Additional effective methods:
        - Male condom
        - Diaphragm
        - Cervical cap
- Pregnancy tests before and during treatment, even if the patient agrees not to have reproductive heterosexual intercourse. Two pregnancy tests will be performed prior to receiving study drug, one within 10–14 days and the second within 24 hours of the start of pomalidomide.
- Frequency of pregnancy tests to be done:
    - Every week during the first 28 days of this study and a pregnancy test every 28 days during the patient's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
    - If the patient missed a period or has unusual menstrual bleeding.
    - When the patient is discontinued from the study and at Day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at Days 14 and 28 after study drug discontinuation.
- Stop taking pomalidomide immediately in the event of becoming pregnant and to call their study doctor as soon as possible.
- NEVER share pomalidomide with anyone else.

- Do not donate blood while taking pomalidomide and for 28 days after stopping pomalidomide.
- Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.
- Do not break, chew, or open pomalidomide capsules.
- Return unused pomalidomide to the investigator.

3. Provide Pomalidomide Information Sheet to the patient.

Female not of childbearing potential (natural menopause for at least 24 consecutive months, a hysterectomy, or bilateral oophorectomy):

1. I counseled the female NOT of childbearing potential regarding the following:

- Potential fetal harm (Refer to item #2 in FCBP).
- NEVER share pomalidomide with anyone else.
- Do not donate blood while taking pomalidomide and for 28 days after stopping pomalidomide.
- Do not break, chew, or open pomalidomide capsules.
- Return used pomalidomide capsules to the investigator.

2. Provide Pomalidomide Information Sheet to the patient.

Male

1. I counseled the Male patient regarding the following:

- Potential fetal harm (Refer to item #2 in FCBP).
- To engage in complete abstinence or use a condom when engaging in sexual intercourse (including those who have had a vasectomy) with a FCBP, while taking pomalidomide, during dose interruptions, and for 28 days after stopping pomalidomide.
- Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking pomalidomide should be advised to call their healthcare provider immediately if they get pregnant.
- NEVER share pomalidomide with anyone else.
- Do not donate blood while taking pomalidomide and for 28 days after stopping pomalidomide.
- Do not donate semen or sperm while taking pomalidomide and for 90 days after stopping pomalidomide.
- Do not break, chew, or open pomalidomide capsules.

- Return unused pomalidomide capsules to the Investigator.

2. Provide Pomalidomide Information Sheet to the patient.

Investigator/Counselor Name (Print): _____

(circle applicable)

Investigator/Counselor Signature: _____ Date: _____/_____/_____

(circle applicable)

Maintain a copy of the completed Education and Counseling Guidance Document in the patient records.

APPENDIX K POMALIDOMIDE INFORMATION SHEET FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Pomalidomide Information Sheet before you start taking pomalidomide and each time you get a new supply, since there may be new information. This Pomalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about pomalidomide?

Pomalidomide may cause birth defects (deformed babies) or death of an unborn baby.
Pomalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Pomalidomide has not been tested in pregnant women but may also cause birth defects. Pomalidomide was found to cause birth defects when tested in pregnant rabbits.

If you are a female who is able to become pregnant:

- Do not take pomalidomide if you are pregnant or plan to become pregnant
    - For 28days before starting pomalidomide
    - While taking pomalidomide
    - During dose interruptions of pomalidomide
    - For 28 days after stopping pomalidomide
- Stop taking pomalidomide if you become pregnant during pomalidomide treatment
- Do not breastfeed while taking pomalidomide
- You must have pregnancy testing done at the following times:
    - Within 10–14 days and again 24 hours prior to the first dose of pomalidomide
    - Weekly for the first 28 days
    - Every 28 days after the first month or every 14 days if you have irregular menstrual periods
    - If you miss your period or have unusual menstrual bleeding

- 28 days after the last dose of pomalidomide (14 and 28 days after the last dose if menstrual periods are irregular)

- You must either not have any sexual relations with a man or use 2 reliable, separate forms of effective birth control at the same time:
  - For 28 days before starting pomalidomide
  - While taking pomalidomide
  - During dose interruptions of pomalidomide and for 28 days after stopping pomalidomide
  - The study doctor will be able to advise you where to get additional advice on contraception.
  - If you suspect you are pregnant at any time during the study, you must stop pomalidomide immediately and immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation and to Onyx Therapeutics.

If you are a female not of childbearing potential:

In order to ensure that an unborn baby is not exposed to pomalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to the fetus in females of childbearing potential whose male partner is receiving pomalidomide is unknown at this time.

- Male patients (including those who have had a vasectomy) must either not have any sexual relations with a female who can become pregnant or a pregnant female or must use a condom during sexual intercourse with a pregnant female or a female that can become pregnant:
  - While you are taking pomalidomide
  - During dose interruptions of pomalidomide
  - For 90 days after you stop taking pomalidomide
- Male patients should not donate sperm or semen while taking pomalidomide and for 90 days after stopping pomalidomide.
- If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation and to Onyx Therapeutics.

Pomalidomide restrictions in sharing pomalidomide and donating blood:

- Do not share pomalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.
- Do not give blood while you take pomalidomide and for 28 days after stopping pomalidomide.
- Do not break, chew, or open pomalidomide capsules.
- You will be supplied with no more than 1 cycle of pomalidomide
- Return unused pomalidomide capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

APPENDIX L ACTG BRIEF PERIPHERAL NEUROPATHY SCREENING TOOL

Source: NIAID Adult AIDS Clinical Trials Group

1. Elicit Subjective Symptoms

Ask the patient 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."

APPENDIX M ACTG BRIEF PERIPHERAL NEUROPATHY SCREENING TOOL (CONT'D)

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 patient'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 patient 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

APPENDIX M ACTG BRIEF PERIPHERAL NEUROPATHY SCREENING TOOL (CONT'D)

4. Evaluate Deep Tendon Reflexes

With the patient seated, the examiner uses one hand to press upward on the ball of the foot, dorsiflexing the patient'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 patient 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

From Peripheral Neuropathy
Primary Care of Veterans with HIV
Office of Clinical Public Health Programs
Veterans Health Administration, 2009

APPENDIX M SAMPLE BRIEF PAIN INVENTORY – SHORT FORM (BPI-SF)

Source: Cleeland 2006.

Date: _____ Study ID: _____

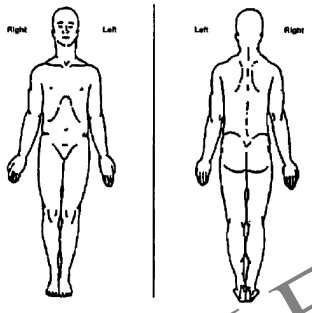
Hospital: _____

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

Page 1 of 2

Date: _____ **Study ID:** _____

Hospital: _____

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐ No Relief	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐0 Does Not Interfere	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9	☐10 Completely Interferes

B. Mood

☐0 Does Not Interfere	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9	☐10 Completely Interferes

C. Walking ability

☐0 Does Not Interfere	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9	☐10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐0 Does Not Interfere	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9	☐10 Completely Interferes

E. Relations with other people

☐0 Does Not Interfere	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9	☐10 Completely Interferes

F. Sleep

☐0 Does Not Interfere	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9	☐10 Completely Interferes

G. Enjoyment of life

☐0 Does Not Interfere	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9	☐10 Completely Interferes

Page 2 of 2

APPENDIX N EXAMPLE ELECTRONIC SERIOUS ADVERSE EVENT CONTINGENCY REPORT FORM

AMGEN
Study # 20130411
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	Race	If applicable, provide End of Study date
		☐F ☐M		

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?	If serious, enter 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? <Pdevice> No Yes / <Pdevice> No Yes / <Pdevice> No Yes / <Pdevice> No Yes	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)	Prior to, or at time of Event: 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 #
Oprozomib	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Oprozomib	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

FORM-056006 *Version 7.0 Effective Date: 1 February 2016*

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Approved

AMGEN
Study # 20130411
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

Approved

AMGEN Study # 20130411 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 -	Title	Date
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.		

APPENDIX O 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: 20130411

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 Page 1 of 1

APPENDIX P EXAMPLE AMGEN LACTATION NOTIFICATION WORKSHEET

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: 20130411

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. Page 1 of 1

Approved

APPENDIX O SUMMARY OF CHANGES IN STUDY OPZ007 AMENDMENT 2.0

Study OPZ007 was amended to include the following:

1. Revised inclusion and exclusion criteria to allow subjects with prior carfilzomib exposure to be considered for inclusion in the study, if carfilzomib was not withdrawn due to toxicity.
2. Revised exclusion criteria to allow subjects with prior pomalidomide exposure to be considered for inclusion in the dose-escalation portion of the study, if pomalidomide was neither dose-reduced nor withdrawn due to toxicity.
3. Revised alkylator language to specify that only subjects who have been treated with adequate alkylator therapy are eligible to be considered for inclusion in the Phase 1b dose-escalation portion and Phase 3 portion of the study.
4. An exclusion criterion for previous GI bleed was added, proton-pump inhibitors were changed from recommended to required, and additional text has been added to the dose modification table for nonhematologic toxicities and guidance to investigators because of toxicities observed in Study 2011-001.
5. The planned number of study sites for Part 1 of the study was increased from 20 to 35 sites, and the number of sites planned for the Dose-Escalation versus Dose-Expansion portions were clarified (15 and 20 sites, respectively).
6. The health-related quality of life measurement by Brief Pain Inventory – Short Form was added as an exploratory objective and endpoint for the dose-expansion portion of the study, and as a secondary objective and endpoint for the Phase 3 portion of the study.
7. The text for secondary and exploratory objectives for Part 2 (randomized Phase 3 portion of the study) was revised for accuracy and consistency within the protocol.
8. The text “at sponsor discretion” was added for Part 1 (Phase 1b dose-escalation and dose-expansion portions of the study) for flexibility if MTD cannot be achieved with 4 mg of pomalidomide.
9. The “>” sign before Grade 3 fatigue in the Dose-Limiting Toxicities sections was removed as there is no > Grade 3 fatigue per NCI-CTCAE.
10. The carfilzomib status stratification factors were revised to “carfilzomib naïve/sensitive versus carfilzomib-refractory” to reflect allowed enrollment of carfilzomib-refractory patients to the study.
11. The sample size justification text was revised for clarity.
12. The 8 hour postdose PK sample timepoint was removed, and a 3 hour postdose PK sample timepoint was added to further characterize the PK profile for oprozomib.
13. Genomic measurements language was revised for clarity.

14. Endpoints language was revised for accuracy and consistency within the protocol.
15. The efficacy and safety analyses sections were revised for clarity.
16. The clinical background information for Study 2009-003 and Study 2011-001 were updated per the most recent information.
17. Updated clinical background information was added for Study 2012-001 and OPZ003 for consistency with other oprozomib protocols.
18. Text that allows for the potential use of blister packs in Phase 3 of the study was added to the Study Drug Accountability section.
19. The text "or fosaprepitant" was added for consistency with other oprozomib protocols to allow IV administration of this antiemetic if needed.
20. Additional guidance for subjects who may experience orthostatic hypotension was added.
21. A new subsection "11.5 Patient-Reported Outcomes Assessments" was added in the Study Procedures section to further clarify these assessments in the dose-expansion and Phase 3 portions of the study.
22. The term "on study" and additional text was added for clarity on the long-term follow-up based on disease progression status.
23. Subgroups of interest were revised for clarity, including potential inclusion of subjects with prior carfilzomib exposure in the study.
24. For Appendices A1, A2, B1, B2, C1, and C2, "X"s in the Schedule of Assessment tables were removed and added, and the text of footnotes was revised for clarity and consistency with the protocol body text.
25. Definition of "Baseline" (within 45 days prior to Cycle 1 Day 1 dosing) versus Screening (Days -1 to -28 prior to Cycle 1 Day 1 dosing) was added, and skeletal survey, plasmacytoma evaluation, bone marrow aspirate and FISH analyses, and optional genomic biomarker assessments on blood and saliva in Appendices A1, A2, B1, B2, C1, and C2 were moved from Screening to Baseline to provide clarity on the use of the tests. Screening tests are mandated to confirm eligibility, whereas baseline tests are used for disease assessments after patient enrollment.
26. The ACTG Brief Peripheral Neuropathy Screening Tool was added as Appendix M.
27. The Brief Pain Inventory – Short Form was added as Appendix N.

In addition, administrative updates, editorial changes, and style and formatting revisions have been made to improve clarity and consistency throughout the document. Changes noted in specific sections were also made in the protocol synopsis and elsewhere in the document, as applicable. Significant changes are presented in the table below. Detailed changed text is displayed for **first major** occurrence only. All affected sections are noted in the "Section(s)"

column. Text that has been deleted is presented in strikethrough format. Added text is presented in bold format.

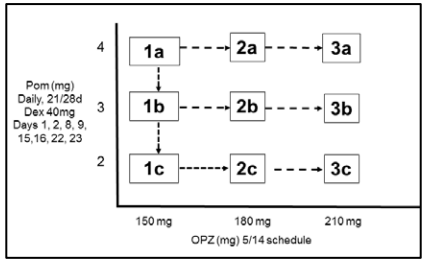
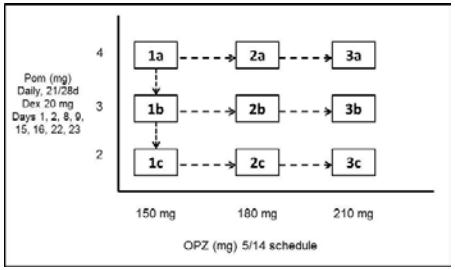
Section(s)	Changed from	Changed to	Rationale
Cover Page Signature Page Protocol Acceptance Page	–	*Added:* Amendment 2 and 08 July 2014	Updated for new amendment
Confidentiality and approval statements	This document is signed with electronic signatures at Onyx Therapeutics, Inc. (a wholly owned subsidiary of Onyx Pharmaceuticals, Inc.).	This document is signed with electronic signatures at Onyx Therapeutics~~, Inc.~~ (a wholly owned subsidiary of Onyx Pharmaceuticals ~~Inc.~~**, an Amgen subsidiary).**	Updated confidentiality and approval statements where Onyx Therapeutics and Onyx Pharmaceuticals are listed to be consistent with current company name and study sponsorship
Global: In all sections listing "Inc."	–	*Deleted: Inc.*	Removed all references to "Inc." to be consistent with current company name and study sponsorship
Global: Oprozomib tablets (where applicable)	–	*Added: ER*	In instances where this was missing, it was clarified that Oprozomib ER Tablets will be used
Global: Oprozomib and dexamethasone dosing regimens	Days 1–2, 8–9, 15–16, and 22–23	Days 1, 2, 8, 9, 15, 16, 22, and 23	Oprozomib and dexamethasone dosing regimens were made consistent throughout the protocol
Global: In all instances of "End of Study" and "End of Treatment"	"End of Study" or "End of Treatment"	End of **Study Treatment**	Corrected for accuracy and consistency throughout the protocol, and to distinguish between "End of Study" and "End of Study Treatment"
Global: In instances where the timing of disease response	Treatment cycles will last 28 days. Disease response assessments will be performed at the end of every 4-week cycle for the first 18 months on study, and at	Treatment cycles will last 28 days. Disease response assessments will be performed at the end of every 4-week cycle for the first 18 months on study, and at	Added text for clarity

Section(s)	Changed from	Changed to	Rationale
assessments are described	the end of every other cycle (every 8 weeks) thereafter.	the end of every other cycle (every 8 weeks) thereafter, **beginning with Month 20.**	
Global: In instances of "first dose" (where applicable)	"…first dose…"	"…first dose **of study drug**..." or "…first dose **of study treatment**…"	Added "of study drug" or "of study treatment" for clarity
Synopsis: Study objectives Section 4.1 Part 1: Phase 1b Dose-Escalation and Expansion Portions of the Study **(by Schedule)**	Part 1: Phase 1b Dose Escalation and Expansion Portions of the Study	Part 1: Phase 1b Dose-Escalation and **Dose-**Expansion Portions of the Study **(by schedule)**	Added text to clarify that each individual schedule will be assessed independently for Part 1 of the study
Synopsis: Study Objectives Section 4.1.3 Exploratory Objectives	Part 1: Phase 1b Dose Escalation and Expansion Portions of the Study Exploratory Objectives • To evaluate quality of life (in the dose expansion phase only) on the basis of patient-reported outcomes tools listed below: o Global health scale as measured by European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Module (QLQ-C30) questionnaire o Health status assessed by the European Quality of Life descriptive system EQ-5D-5L (EuroQol EQ-5D-5L) o Disease symptoms subscale as measured by EORTC Multiple Myeloma Module (QLQ-MY20) questionnaire o Neurotoxicity symptoms as measured by the Functional Assessment of Cancer Therapy Scale / Gynecological Oncology Group – Neurotoxicity (FACT/GOG-Ntx4 [(Version 4]) for patients with neurotoxicity score	Part 1: Phase 1b Dose Escalation and **Dose-**Expansion Portions of the Study Exploratory Objectives • To evaluate ~~quality of life~~ (in the dose-expansion ~~phase~~ **portion** only) ~~on~~ the ~~basis of~~ patient-reported outcomes **(PRO) using the** tools listed below: o **Bone pain and the impact of bone pain measured with the Brief Pain Inventory - Short Form (BPI-SF)** o **Health-related quality of life (HRQoL) measured by the** global health ~~scale~~ **status/QoL scale** ~~as measured by~~ **of the** European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Module (QLQ-C30) questionnaire o Health status assessed by ~~the European Quality of Life descriptive system~~ EQ-5D-5L ~~(EuroQol EQ-5D-5L)~~ o Disease symptoms ~~subscale~~ as measured by **the disease symptoms subscale of the** EORTC Multiple Myeloma Module	Added Brief Pain Inventory – Short Form as a HRQoL exploratory objective in the dose-expansion portion of the study

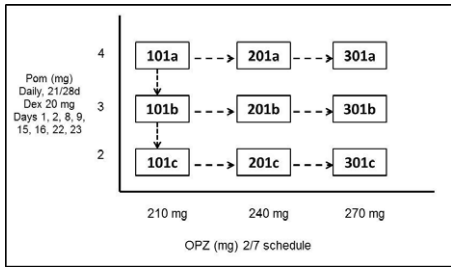
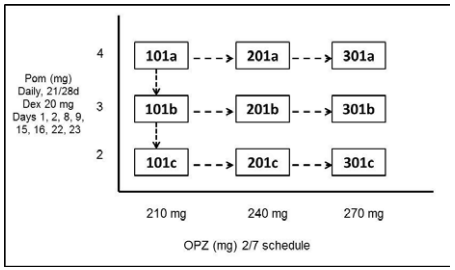
Section(s)	Changed from	Changed to	Rationale
		(QLQ-MY20) questionnaire o Neurotoxicity symptoms as measured by the **neurotoxicity subscale of the** Functional Assessment of Cancer Therapy ~~Scale~~ / Gynecological Oncology Group – Neurotoxicity (FACT/GOG-Ntx4 [(Version 4]) ~~for patients with neurotoxicity score~~ **questionnaire**	
Synopsis: Secondary objectives Section 4.2.2 Secondary Objectives	Part 2: Randomized Phase 3 Portion of the Study To compare the following between subjects treated with OPomd and those treated with Pomd: … • Improvement in renal function over time, as defined by an increase in glomerular filtration rate (GFR) of at least 10 mL/min over baseline • Improvement in hemoglobin over time, as defined by an increase of at least 2 g/dL over baseline • Population–based PK parameters of oprozomib in the OPomd regimen • Safety and tolerability • Health-related quality of life (HRQoL) QLQ-30 global health status score measured by EORTC QLQ-C30 • Disease symptoms as measured by the disease symptoms subscale of EORTC QLQ-MY20 • Health status as assessed with EuroQol EQ-5D-5L	Part 2: Randomized Phase 3 Portion of the Study • To compare the following between subjects treated with OPomd and those treated with Pomd: … o **Incidence of i**mprovement in renal function ~~over time~~, as defined by an increase in ~~glomerular filtration rate~~ (GFR) of at least 10 mL/min over baseline **at least once after the start of treatment** o **Incidence of i**mprovement in hemoglobin ~~over time~~, as defined by an increase of at least 2 g/dL over baseline **at least once after the start of treatment** o ~~Population-based PK parameters of oprozomib in the OPomd regimen~~ o Safety and tolerability o **Bone pain and the impact of bone pain measured with the BPI-SF** o Health-related quality of life (HRQoL) ~~QLQ-30 global health status score~~ measured by the global health status/QoL scale of the EORTC QLQ-C30 o Disease symptoms as measured by the disease symptoms subscale of EORTC QLQ-MY20 o **Neurotoxicity symptoms as measured by the neurotoxicity subscale of the FACT/GOG-**	Removed and added text for accuracy of secondary objectives for Part 2 of the study

Section(s)	Changed from	Changed to	Rationale
		Ntx4 (Version 4) ○ Health status ~~as~~ assessed with ~~EuroQol~~ EQ-5D-5L • **To evaluate population-based PK parameters of oprozomib in the OPomd regimen**	
Synopsis: Study objectives Section 4.2.3 Exploratory Objectives	Part 2: Randomized Phase 3 Portion of the Study … Exploratory Objectives To compare the following between subjects treated with OPomd and those treated with Pomd: • PFS and ORR as determined by the investigator • Duration of response (DOR), defined as the time from the first evidence of confirmed PR or better to disease progression or death due to any cause as determined by the investigator according to the IMWG-URC and modified EBMT criteria • Clinical benefit rate (CBR) as determined by the investigator according to the modified EBMT criteria • Duration of clinical benefit (DOCB), defined as the time from first evidence of ≥ MR as determined by ORCA and the investigator according to the modified EBMT criteria • Genomic biomarkers that may correlate with antitumor activity and resistance following treatment with proteasome inhibitors • The incidence of neuropathy events (defined as Grade 2 or higher peripheral neuropathy incidence) • The number of neuropathy events (defined as Grade 2 or higher peripheral neuropathy incidence, and neurotoxicity symptoms scores assessed by FACT/GOG-Ntx4 [Version 4]) • Health status assessed with subscale scores of	Part 2: Randomized Phase 3 Portion of the Study … Exploratory Objectives To compare the following between subjects treated with OPomd and those treated with Pomd: • PFS and ORR as determined by the investigator **according to the IMWG-URC** • Duration of response (DOR), defined as the time from the first evidence of confirmed PR or better to disease progression or death due to any cause as determined by the investigator according to the IMWG-URC ~~and modified EBMT criteria~~ • Clinical benefit rate (CBR) as determined by the investigator according to **the IMWG-URC** and the modified EBMT criteria • Duration of clinical benefit (DOCB), defined as the time from first evidence of ≥ MR **or better to disease progression or death due to any cause,** as determined by ORCA and the investigator according to **the IMWG-URC and the** modified EBMT criteria • Genomic biomarkers that may **be** correlate**d** with antitumor activity and resistance following treatment with proteasome inhibitors • ~~The incidence of~~ neuropathy events (defined as Grade 2 or higher peripheral neuropathy ~~incidence~~) • ~~The number of neuropathy events (defined as Grade 2 or higher peripheral neuropathy incidence, and neurotoxicity symptoms scores assessed by~~	Revised text for corrections and for consistency within the protocol

Section(s)	Changed from	Changed to	Rationale
	EORTC QLQ-C30 (excluding global health status scale) and EORTC QLQ-MY20 (excluding disease symptom subscale)	~~FACT/GOG-Ntx4 [Version 4])~~ • ~~Health status~~ HRQoL assessed with subscale scores of EORTC QLQ-C30 (excluding global health status scale) and EORTC QLQ-MY20 (excluding disease symptom subscale)	
Synopsis: Study design Synopsis: Study population Section 5 Study design	This study will include subjects with primary refractory or relapsed and refractory multiple myeloma, i.e., those who have demonstrated disease progression on or within 60 days of their last therapy, and who have received at least 2 prior lines of therapy including bortezomib and lenalidomide or thalidomide and adequate alkylator therapy.	This study will include subjects with primary refractory or relapsed and refractory multiple myeloma, i.e., those who have demonstrated disease progression on or within 60 days of their last therapy, and who have received at least 2 prior lines of therapy **(**including bortezomib and lenalidomide **and/**or thalidomide, and **in the dose-expansion and Phase 3 portions of the study only, been treated with** adequate alkylator therapy**)**.	Revised alkylator language to specify that only subjects who have been treated with adequate alkylator therapy are eligible to be considered for inclusion in the Phase 1b dose-escalation portion and Phase 3 portion of the study
Synopsis: Study design	Part 1: Phase 1b Dose Escalation and Expansion Portions of the Study … If the starting dose of oprozomib cannot be safely administered with the labeled pomalidomide dose, then up to 2 possible alternative paths for oprozomib with lower pomalidomide doses will be explored. (See tables below for primary and alternative dose-escalation paths.) Dose escalation will continue until ≥ 2 DLTs occur in a cohort, which will be declared the maximal administered dose for that dose level of pomalidomide (if more than 1 dose level is explored). The prior cohort will be expanded to at least 6 subjects if not previously done to establish that dose as the MTD. There may be more than 1 MTD for oprozomib if more than 1 dose level of pomalidomide is studied. The MTD of oprozomib associated with each dose level of pomalidomide assessed will be the dose level where < 2 DLTs in 6 subjects are observed. There will be no planned maximum dose of oprozomib	Part 1: Phase 1b Dose**-**Escalation and **Dose-**Expansion Portions of the Study **…** If the starting dose of oprozomib cannot be safely administered with the labeled pomalidomide dose, **or at sponsor discretion,** ~~after the MTD with 4 mg of pomalidomide is determined,~~ then up to 2 possible alternative paths for oprozomib with lower pomalidomide doses will be explored. (See tables below for primary and alternative dose-escalation paths.) Dose escalation will continue until **sponsor discretion, the maximum planned dose of pomalidomide is reached, or** ≥ 2 DLTs occur in a cohort, whoever occurs first~~which will be declared the maximal administered dose for that dose level of pomalidomide (if more than 1 dose level is explored)~~. The prior cohort will be expanded to at least 6 subjects if not previously done to establish that dose as the MTD. There may be more than 1 MTD for oprozomib if more than 1 dose level of pomalidomide is studied.	Added text for flexibility if MTD cannot be achieved with 4 mg of pomalidomide

Section(s)	Changed from	Changed to	Rationale
	to be studied as it is being added to the FDA approved regimen of pomalidomide/dexamethasone. The starting dose of oprozomib for the 5/14 schedule is 150 mg, 3 dose levels below the established 5/14 single-agent MTD of 240 mg. …	The MTD of oprozomib associated with each dose level of pomalidomide assessed will be the dose level where < 2 DLTs in 6 subjects are observed. There ~~will be~~ **is** no planned maximum dose of oprozomib to be studied as it is being added to the FDA approved regimen of pomalidomide/dexamethasone, **however, this could be imposed at any time during the course of the study, based on sponsor discretion.** The starting dose of oprozomib for the 5/14 schedule is 150 mg, 3 dose levels below the established 5/14 single-agent MTD of 240 mg. …	
Synopsis: Study design Section 5.1.1 Dose Escalation Schema for the 5/14 Oprozomib Dosing Schedule	The starting dose for the 5/14 schedule will be 150 mg of oprozomib and 4 mg of pomalidomide. The 5/14 primary and alternate paths are summarized below. 5/14 Schedule Study Dose-Escalation Paths*  * There is no predefined maximum dose level of oprozomib being studied.	The starting dose for the 5/14 schedule will be 150 mg of oprozomib and 4 mg of pomalidomide. The 5/14 primary and alternate paths are summarized below; **these are examples, and are not inclusive of all possible dose-escalation paths.** 5/14 Schedule **Primary** Study Dose-Escalation Paths~~*~~[a]  **5/14 = Dosing on Days 1–5 and 15–19; Dex = dexamethasone; OPZ = oprozomib; Pom = pomalidomide.** ~~*~~ [a] There is no predefined maximum dose level of oprozomib being studied.	Added text to clarify that the dose-escalation paths are examples, and not inclusive of all possible dose-escalation paths. Revised in schema "Dex 20 mg Days 1, 2, 8, 9…" for consistency with the rest of the protocol
Synopsis Study	Table 3 Primary Dose-Escalation Path for Oprozomib	Table 3 Primary Dose-Escalation Path for Oprozomib	Revised titles and notes for

Section(s)	Changed from	Changed to	Rationale
Design Section 5.1.1 Dose Escalation Schema for the 5/14 Oprozomib Dosing Schedule Section 5.1.2 Dose Escalation Schema for the 2/7 Oprozomib Dosing Schedule	and Pomalidomide on 5/14 Schedule in Phase 1b … Note: This is an example of the primary dose-escalation cohort and dose-escalation will continue in 30 mg increments of oprozomib until the MTD is identified. Table 6 Primary Dose-Escalation Path for Oprozomib and Pomalidomide on the 2/7 Schedule in Phase 1b … Note: This is an example of the primary dose-escalation cohort and dose-escalation will continue in 30 mg increments of oprozomib until the MTD is identified.	~~and Pomalidomide~~ on 5/14 Schedule **with Pomalidomide 4 mg** in Phase 1b … Note: This is an example of the primary dose-escalation cohort and dose-escalation will continue in 30-mg increments of oprozomib **at sponsor discretion or** until the MTD is identified. Table 6 Primary Dose-Escalation Path for Oprozomib ~~and Pomalidomide~~ on the 2/7 Schedule **with Pomalidomide 4 mg** in Phase 1b … Note: This is an example of the primary dose-escalation cohort and dose-escalation will continue in 30-mg increments of oprozomib a**t sponsor discretion or** until the MTD is identified.	Table 3 and Table 6 for clarity.
Synopsis: Study design Section 5.1.1 Dose Escalation Schema for the 5/14 Oprozomib Dosing Schedule Section 5.1.2 Dose Escalation Schema for the 2/7 Oprozomib Dosing Schedule	Table 4 Alternative Dose-Escalation Path 1 for Oprozomib andPomalidomide on 5/14 Schedule in Phase 1b if Cohort 1a Exceeds the MTD Table 5 Alternative Dose-Escalation Path 2 for Oprozomib and Pomalidomide in Phase 1b if Cohort 1b Exceeds the MTD Table 7 Alternative Dose-Escalation Path 1 for Oprozomib and Pomalidomide on 2/7 Schedule in Phase 1b if Cohort 101a Exceeds the MTD Table 8 Alternative Dose-Escalation Path 2 for Oprozomib and Pomalidomide on 2/7 Schedule in Phase 1b if Cohort 101b Exceeds the MTD	Table 4 Alternative Dose-Escalation Path 1 for Oprozomib ~~and Pomalidomide~~ on 5/14 Schedule **with Pomalidomide** in Phase 1b if Cohort 1a Exceeds the MTD**, or at Sponsor Discretion** Table 5 Alternative Dose-Escalation Path 2 for Oprozomib ~~and Pomalidomide~~ **on 5/14 Schedule with Pomalidomide** in Phase 1b if Cohort 1b Exceeds the MTD**, or at Sponsor Discretion** Table 7 Alternative Dose-Escalation Path 1 for Oprozomib ~~and Pomalidomide~~ on 2/7 Schedule **with Pomalidomide** in Phase 1b if Cohort 101a Exceeds the MTD **or at Sponsor Discretion** Table 8 Alternative Dose-Escalation Path 2 for	Added "or at Sponsor Discretion" to Table 4, Table 5, Table 7, and Table 8 titles match earlier added text, and revised titles for clarity

Section(s)	Changed from	Changed to	Rationale
		Oprozomib ~~and Pomalidomide~~ on 2/7 Schedule **with Pomalidomide** in Phase 1b if Cohort 101b Exceeds the MTD **or at Sponsor Discretion**	
Synopsis: Study design Section 5.1.2 Dose Escalation Schema for the 2/7 Oprozomib Dosing Schedule	The starting doses for the 2/7 oprozomib dosing schedule will be 210 mg of oprozomib and 4 mg of pomalidomide. The 2/7 primary and alternate paths are summarized below. 2/7 Schedule Study Dose-Escalation Paths  	The starting doses for the 2/7 oprozomib dosing schedule will be 210 mg of oprozomib and 4 mg of pomalidomide. The 2/7 primary and alternate paths are summarized below; **these are examples, and are not inclusive of all possible dose-escalation paths.** 2/7 Schedule **Primary** Study Dose-Escalation Paths[a]  2/7 = Dosing on Days 1, 2, 8, 9, 15, 16, 22, and 23; Dex = dexamethasone; OPZ = oprozomib; Pom = pomalidomide. **[a] There is no predefined maximum dose level of oprozomib being studied.**	Added text to clarify that the dose-escalation paths are examples, and not inclusive of all possible dose-escalation paths. Revised in schema "Dex 20 mg Days 1, 2, 8, 9…" for consistency with the rest of the protocol. Added note below figure for consistency with the figure of 5/14 Schedule Study Dose-Escalation Paths.
Synopsis: Study design	At the sponsor's discretion, once the MTD for oprozomib is reached on 1 or both schedules, additional dose escalation with oprozomib may continue with lower doses of pomalidomide down to the 2 mg dose level. The sponsor, with input from the Cohort Safety Review Committee ([CSRC] consisting of investigators, sponsor's medical monitor, and sponsor's Drug Safety representative), will determine which single dose combination to use for the dose expansion (i.e., the RP3D) portion of the study. The	At the sponsor's discretion, once the MTD for oprozomib is reached on 1 or both schedules, **or if the initial cohort exceeds the MTD,** additional dose escalation with oprozomib may continue with lower doses of pomalidomide down to the 2-mg dose level. The sponsor, with input from the Cohort Safety Review Committee ([CSRC] consisting of investigators, sponsor's medical monitor, and sponsor's **d**rug **s**afety representative, will determine which ~~single dose combination~~ **dose and schedule of oprozomib in combination with Pomd** to use for the dose-expansion	Revised text for consistency within the protocol

Section(s)	Changed from	Changed to	Rationale
	RP3D may differ from the MTD, but will not be higher than the MTD, and will be selected based upon the assessment of the safety, tolerability, PK, PDn, preliminary activity, and other variables to be observed across multiple cycles of combination therapy.	(i.e., the RP3D) portion of the study. **The sponsor has the option of expanding 1 or both schedules in order to establish the RP3D and schedule.** The RP3D may differ from the MTD, but will not be higher than the MTD, and will be selected based upon the assessment of the safety, tolerability, PK, PDn, preliminary activity, and other variables to be observed across multiple cycles of combination therapy.	
Synopsis: Study Design Section 10.5 Definition of Dose-Limiting Toxicity	Dose-Limiting Toxicities … ○ > Grade 3 fatigue lasting < 14 days is not considered a DLT …	Dose-Limiting Toxicities … ○ ≥ Grade 3 fatigue lasting < 14 days is not considered a DLT …	Removed ">" sign for accuracy as there is no > Grade 3 fatigue per NCI-CTCAE
Synopsis: Study Design Section 5.1.4 Subject Replacement	In the Phase 1b portion of the study, subjects must meet the following criteria to be considered evaluable for MTD determination during the 4-week DLT evaluation period unless a study drug-related DLT occurs before the subject receives all planned doses of oprozomib for both the 5/14 and 2/7 dosing schedules: …	In the Phase 1b portion of the study, subjects must meet the following criteria to be considered evaluable for MTD determination during the 4-week DLT evaluation period unless a ~~study drug-related~~ DLT occurs before the subject receives all planned doses of oprozomib for both the 5/14 and 2/7 dosing schedules: …	Deleted text for clarity
Synopsis: Study Design Section 5.1.5 Dose Expansion Section 5.2 Part 2: Randomized Phase 3 Portion of the Study	**Dose Expansion** The criteria for selecting the RP3D for 1 or both schedules of oprozomib at the sponsor's discretion will include assessment of the safety, tolerability, and preliminary activity observed across multiple cycles of therapy. In addition, both PK and PDn assessments to demonstrate adequate exposure and proteasome inhibition will be a key factor. Therefore, the RP3D may differ from the MTD. Once the MTD(s) has been determined and the RP3D has been selected, a minimum of 20 additional subjects for 1 or both schedules of oprozomib at the sponsor's discretion will be enrolled in the dose-expansion portion of Part 1in order to continue the evaluation of the safety and	**Dose Expansion** The criteria for selecting the RP3D for 1 or both schedules of oprozomib at the sponsor's discretion will include assessment of the safety, tolerability, and preliminary activity observed across multiple cycles of therapy. In addition, both PK and PDn assessments to demonstrate adequate exposure and proteasome inhibition will be a key factor. Therefore, the RP3D may differ from the MTD. Once the MTD(s) has been determined and the ~~RP3D~~ **recommended dose for the expansion phase** has been selected, a minimum of 20 additional subjects for 1 or both schedules of oprozomib at the sponsor's discretion will be enrolled in the dose-expansion portion of Part 1in order to	Revised text for clarity

Section(s)	Changed from	Changed to	Rationale
	efficacy of the regimen as a prelude to initiation of the Phase 3 portion of the study. The safety of subjects in the Dose Expansion will be monitored on an ongoing basis by the CSRC during bimonthly calls. Enrollment to the Phase 3 portion will not commence until the CSRC has evaluated all available safety information from a minimum of 10 subjects who have completed ≥ 2 cycles of therapy at the R3PD and enrollment of the remaining 10 subjects in Dose Expansion has occurred in 1 or both schedules if both were opened.	continue the evaluation of the safety and efficacy of the regimen as a prelude to initiation of the Phase 3 portion of the study. The safety of subjects in the Dose Expansion will be monitored on an ongoing basis by the CSRC during ~~bimonthly~~ **regularly scheduled** calls. Enrollment to the Phase 3 portion will not commence until the CSRC has evaluated all available safety information from a minimum of 10 subjects who have completed ≥ 2 cycles of therapy ~~at the R3PD~~ and enrollment of the remaining 10 subjects in Dose Expansion has occurred in 1 or both schedules if both were opened. **This information will inform the selection of a RP3D and schedule by the sponsor and CSRC.**	
Synopsis: Study design Section 5.4.1 Randomization Section 14.5.2.2 Part 2 Randomized Phase 3 Portion of the Study	Part 2: Randomized Phase 3 Portion of the Study Randomization After screening and eligibility determination, eligible subjects will be randomized in a 2:1 ratio to receive a regimen consisting of OPomd or Pomd plus oprozomib placebo, respectively. Central randomization will be implemented in this part of the study through the use of an interactive voice response system / interactive web response system (IVRS/IWRS). Eligible subjects will be stratified by: • Age: < 75 years versus ≥ 75 years • Number of prior therapies: 2 versus 3 or more • Carfilzomib status: Carfilzomib naïve versus carfilzomib sensitive Within each stratum, treatment assignment will be made using a random permuted blocked randomization scheme.	Part 2: Randomized Phase 3 Portion of the Study Randomization After screening and eligibility determination, eligible subjects will be randomized in a 2:1 ratio to receive a regimen consisting of OPomd or Pomd plus ~~oprozomib~~ placebo, respectively. Central randomization will be implemented in this part of the study through the use of an **I**nteractive **V**oice **R**esponse **S**ystem / **I**nteractive **W**eb **R**esponse **S**ystem (IVRS/IWRS). Eligible subjects will be stratified by: • Age: < 75 years versus ≥ 75 years • Number of prior therapies: 2 versus 3 or more • Carfilzomib status: Carfilzomib-naïve/**sensitive** versus carfilzomib-**refractory** ~~sensitive.~~ **Carfilzomib-sensitive multiple myeloma patients are defined as having had previously achieved a PR or greater with therapy that includes carfilzomib (or carfilzomib monotherapy), and did not experience PD until more than 60 days after their last dose of carfilzomib. Carfilzomib-refractory**	Correction made to remove "oprozomib" before "placebo" Revised carfilzomib status stratification factors to reflect potential inclusion of subjects with prior carfilzomib exposure in the study

Section(s)	Changed from	Changed to	Rationale
		multiple myeloma is defined as disease that is nonresponsive while on primary or salvage therapy that includes carfilzomib, or that progresses on or within 60 days of last therapy. Within each stratum, treatment assignment will be made using a ~~random~~ permuted block~~ed~~ randomization scheme.	
Synopsis: Number of investigational sites Section 5 Study Design	Up to 20 study sites will participate in Part 1 of the study (Phase 1b Dose-Escalation and Dose-Expansion portion of the study). Approximately 70 sites will participate in Part 2 of the study (Phase 3 portion of the study).	**Approximately** ~~Up to~~ **35** ~~20~~ study sites will participate in Part 1 of the study (**15 sites for the** Phase 1b **d**ose-**e**scalation **and 20 sites for the d**ose-**e**xpansion portion**s** of the study). **An additional 35 sites, for a total of a**pproximately 70 sites will participate in Part 2 of the study (Phase 3 portion of the study).	Increased the planned number of study sites for Part 1 of the study, and clarified how many sites are planned for the Dose-Escalation versus Dose-Expansion portions
Synopsis: Planned number of subjects Section 14.7 Determination of Sample Size	Part 1: Phase 1b (Dose Escalation and Expansion Portions of the Study) A total enrollment of approximately 82 subjects is planned for Part 1 of the study. During the Phase 1b Dose Escalation portion of Part 1, up to 21 subjects will be enrolled for each schedule. … Part 2: Randomized Phase 3 Portion of the Study During Part 2, the planned enrollment is approximately 270 subjects. Therefore, a total enrollment of approximately 352 subjects is planned.	Part 1: Phase 1b (Dose-Escalation and **Dose-**Expansion Portions of the Study) A total enrollment of ~~up to~~ **approximately** 82 subjects is planned for Part 1 of the study. During the Phase 1b **d**ose-escalation **p**ortion of Part 1, approximately 21 subjects will be enrolled for each schedule. … Part 2: Randomized Phase 3 Portion of the Study During Part 2, the planned enrollment is approximately 270 subjects. Therefore, ~~a~~ **the** total **planned** enrollment ~~of~~ **will be** approximately 352 subjects ~~is planned~~.	Revised text for clarity and for clarity
Synopsis: Sample size justification	Part 2: Randomized Phase 3 Portion of the Study The estimated sample size for the Phase 3 portion of the study is based on comparison of PFS (death or disease progression events) distributions for subjects treated with Pomd plus placebo versus those treated with OPomd based on the log-rank test statistic. It is assumed that the risk of a PFS event for subjects	Part 2: Randomized Phase 3 Portion of the Study **For the Phase 3 portion of the study, 157 PFS events are required to detect a 45.7% reduction in the risk of PFS (HR=0.543) with 95% power and a 1-sided significance level of 0.025. Enrollment of 270 subjects (2:1 OPomd versus Pomd, respectively) is consistent with reaching the required 157 events**	Revised text for clarity

Section(s)	Changed from	Changed to	Rationale
	randomized to OPomd will be 45.7% lower than for subjects randomized to Pomd. Therefore, the target hazard ratio (HR) is 0.543. The statistical hypothesis being tested is as follows: H_0: PFS (Pomd) = PFS (OPomd) H_a: PFS (Pomd) < PFS(OPomd) For a 1-sided $\alpha = 0.025$ level of significance and 95% power, 157 PFS events are required. …	**in approximately 14 months, assuming an enrollment rate of approximately 22 subjects per month, a drop-out rate of 5% at 18 months, and a median PFS of 3.8 and 7 months for Pomd and OPomd, respectively.** ~~The estimated sample size for the Phase 3 portion of the study is based on comparison of PFS (death or disease progression events) distributions for subjects treated with Pomd plus placebo versus those treated with OPomd based on the log-rank test statistic. It is assumed that the risk of a PFS event for subjects randomized to OPomd will be 45.7% lower than for subjects randomized to Pomd. Therefore, the target hazard ratio (HR) is 0.543. The statistical hypothesis being tested is as follows:~~ ~~H_0: PFS (Pomd) = PFS (OPomd)~~ ~~H_a: PFS (Pomd) < PFS(OPomd)~~ ~~For a 1-sided $\alpha = 0.025$ level of significance and 95% power, 157 PFS events are required.~~	
Synopsis: Study population	The study population will consist of subjects with primary refractory or relapsed and refractory, symptomatic multiple myeloma that have been treated with at least 2 prior lines of therapy including lenalidomide and bortezomib or thalidomide and been treated with adequate alkylator therapy, who have progressed on or within 60 days of their last therapy, and who are considered to be appropriate for this clinical study by their treating physicians.	The study population will consist of subjects with primary refractory or relapsed and refractory, ~~symptomatic~~ multiple myeloma ~~that had been treated with~~**, i.e., those who have demonstrated disease progression on or within 60 days of their last therapy, and who have received** at least 2 prior lines of therapy **(**including ~~lenalidomide and~~ bortezomib **and lenalidomide and/**or thalidomide, and **in the dose-expansion and Phase 3 portions of the study only,** been treated with adequate alkylator), ~~and who have progressed on or within 60 days of their last therapy,~~ and who are considered to be appropriate for this clinical study by their treating physicians.	Revised text for consistency within the protocol
Synopsis: Inclusion Criteria Section 6.1 Inclusion Criteria	1. Multiple myeloma that is primary refractory or relapsed and refractory after at least 2 lines of standard therapy for multiple myeloma including: a. ≥ 2 consecutive cycles of both bortezomib	1. Multiple myeloma that is primary refractory**,** ~~or~~ relapsed and refractory**, or intolerant** after at least 2 lines of standard therapy for multiple myeloma including:	Revised alkylator language to specify that only subjects who have been treated with adequate alkylator therapy

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	and lenalidomide or thalidomide (alone or in combination) i. Patients who received bortezomib as their last therapy who were not refractory but developed bortezomib intolerance, as defined by the development of Grade 2 peripheral neuropathy with pain or ≥ Grade 3 peripheral neuropathy after ≥ 2 consecutive cycles, are eligible b. Adequate alkylator therapy defined as: i. High-dose melphalan or other alkylating agent as conditioning for autologous or allogeneic stem cell transplant (SCT), or ii. ≥ 6 cycles of induction therapy, or iii. Progressive disease after ≥ 2 cycles	a. ≥ 2 consecutive cycles of both bortezomib and lenalidomide or thalidomide (alone or in combination) ~~i. Patients who received bortezomib as their last therapy who were not refractory but developed bortezomib intolerance, as defined by the development of Grade 2 peripheral neuropathy with pain or ≥ Grade 3 peripheral neuropathy after ≥ 2 consecutive cycles, are eligible~~ b. **In the dose-expansion and Phase 3 portions of the study only: In addition to the above, treatment with a**dequate alkylator therapy defined as: i. High-dose melphalan or other alkylating agent as conditioning for autologous or allogeneic stem cell transplant (SCT), or ii. ≥ 6 cycles of induction therapy, or iii. Progressive disease after ≥ 2 cycles	are eligible to be considered for inclusion in the Phase 1b dose-escalation portion and Phase 3 portion of the study Moved definition of bortezomib intolerance from Inclusion Criterion 1 to Inclusion Criterion 3 for clarity
Synopsis: Inclusion Criteria Section 6.1 Inclusion Criteria	2. Measurable disease as indicated by 1 or more of the following: d. Serum M-protein ≥ 500 mg/dL e. Urine M-protein ≥ 200 mg/24 h f. For subjects without measurable M-protein by serum protein electrophoresis (SPEP) or urine protein electrophoresis (UPEP), involved free light chain (FLC) concentration ≥ 10 mg/dL provided serum free light chain (SFLC) ratio is abnormal	2. Measurable disease as indicated by 1 or more of the following: a. Serum M-protein ≥ 500 mg/dL b. Urine M-protein ≥ 200 mg/24 h c. **Only f**or subjects without measurable M-protein by serum protein electrophoresis (SPEP) ~~or~~ **and** urine protein electrophoresis (UPEP), involved free light chain (FLC) concentration ≥ 10 mg/dL provided serum free light chain (SFLC) ratio is abnormal	Added "only" and added "and" for clarity
Synopsis: Inclusion Criteria Section 6.1 Inclusion Criteria	3. Disease progression on or within 60 days of completion of the last therapy as long as the last treatment was not carfilzomib.	3. Disease progression on or within 60 days of completion of the last therapy**, or intolerance to bortezomib if received as their last therapy** ~~as long as the last treatment was not carfilzomib.~~ **a. Patients who received bortezomib as their last therapy who were not refractory but**	Revised to allow subjects with prior carfilzomib exposure to be considered for inclusion in the study Moved definition of

Section(s)	Changed from	Changed to	Rationale
		developed bortezomib intolerance, as defined by the development of Grade 2 peripheral neuropathy with pain or ≥ Grade 3 peripheral neuropathy after ≥ 2 consecutive cycles, are eligible	bortezomib intolerance from Inclusion Criterion 1 to Inclusion Criterion 3 for clarity
Synopsis: Inclusion Criteria Section 6.1 Inclusion Criteria	4. Prior carfilzomib is not required but is allowed if a subject 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 subject: a. Had at least a PR to prior carfilzomib therapy b. Was not removed from carfilzomib therapy due to toxicity c. Was not removed from carfilzomib therapy for progressive disease nor experienced progressive disease within 6 months of any prior carfilzomib therapy.	4. Prior carfilzomib ~~is not required but~~ is allowed if a subject **was not removed from carfilzomib therapy due to toxicity, unless approved by the Onyx study medical monitor** ~~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 subject:~~ ~~a. Had at least a PR to prior carfilzomib therapy~~ ~~b. Was not removed from carfilzomib therapy due to toxicity~~ c. ~~Was not removed from carfilzomib therapy for progressive disease nor experienced progressive disease within 6 months of any prior carfilzomib therapy.~~	Revised to allow subjects with prior carfilzomib exposure to be considered for inclusion in the study, if carfilzomib was not withdrawn due to toxicity
Synopsis: Exclusion Criteria Section 6.2 Exclusion Criteria	7. Prior treatment of any duration with pomalidomide	7. Prior ~~treatment of any duration with~~ pomalidomide **exposure** **a. For the dose-escalation portion of the study: Subjects requiring pomalidomide dose reduction or removal due to toxicity** b. **For the dose-expansion portion and Part 2 of the study: Prior pomalidomide treatment of any duration**	Revised to allow subjects with prior pomalidomide exposure to be considered for inclusion in the dose-escalation portion of the study, if pomalidomide was neither dose-reduced nor withdrawn due to toxicity
Synopsis: Exclusion Criteria Section 6.2 Exclusion Criteria	11. Primary refractory or relapsed and refractory to carfilzomib alone or in combination with at least 2 cycles at a dose of at least 20/27 mg/m^2	11. ~~Primary refractory or relapsed and refractory to carfilzomib alone or in combination with at least 2 cycles at a dose of at least 20/27 mg/m^2~~	Revised to allow subjects with prior carfilzomib exposure to be considered for inclusion in the study; subsequent Exclusion Criteria were renumbered accordingly

Section(s)	Changed from	Changed to	Rationale
Synopsis: Exclusion Criteria Section 6.2 Exclusion Criteria	–	**14. History of previous clinically significant GI bleed in the 6 months prior to first dose of study drug**	Added an Exclusion Criterion for previous GI bleed to potentially reduce the risk for GI hemorrhage; subsequent Exclusion Criteria were renumbered accordingly
Synopsis: Criteria for evaluation: Other Section 11.4.1.1. Phase 1b Dose Escalation and Expansion Section 14.5.5 Pharmacokinetic Analyses	Pharmacokinetics In the Phase 1b Dose Escalation and Expansion portions of the study, blood samples will be collected from all subjects for determination of plasma concentrations of oprozomib at 1 predose time point and up to 7 postdose time points on Day 1 of Cycle 1 and Cycle 2 (0.25, 0.5, 1, 2, 4, 6, and 8 hours postdose) and 1 predose time point on Day 2 of Cycle 1 for both schedules. In the Phase 3 portion of the study, PK samples will be collected from all randomized subjects at Cycle 1 Day 1 and Cycle 3 Day 1 and will be analyzed for oprozomib concentrations.	Pharmacokinetics In the Phase 1b **d**ose-**e**scalation and **dose-e**xpansion portions of the study, blood samples will be collected from all subjects for determination of plasma concentrations of oprozomib at 1 predose time point and up to 7 postdose time points on Day 1 of Cycle 1 and Cycle 2 (0.25, 0.5, 1, **3**, 2, 4, and 6~~, and 8~~ hours postdose) and 1 predose time point on Day 2 of Cycle 1 for both schedules. In the Phase 3 portion of the study, PK samples will be collected from all randomized subjects at Cycle 1 Day 1 and Cycle 3 Day 1 and will be analyzed for oprozomib concentrations **in OPomd subjects.**	Removed 8 hour postdose PK sample timepoint and added 3 hour postdose PK sample timepoint to further characterize the PK profile for oprozomib Added text for clarity
Synopsis: Criteria for evaluation: Other Section 11.4.3 Genomic Measurements	Genomics Analysis of genomic biomarkers that may predict response and resistance following treatment with proteasome inhibitors will be conducted for all subjects from all phases of the study who consent to optional genomic biomarker analysis. These analyses will be performed on Screening bone marrow aspirate (a portion of the bone marrow aspirate sample obtained at Screening will be used; no additional sample is required), blood, and saliva. Additional bone marrow samples for biomarkers may be collected at the time of progression or at the End of Treatment visit from all subjects who consent.	Genomics Analysis of genomic biomarkers that may predict response and resistance following treatment with proteasome inhibitors will be conducted for all subjects **receiving oprozomib** from all phases of the study who consent to optional genomic biomarker analysis. These analyses will be performed on ~~Screening~~ **a** bone marrow aspirate ~~(~~**obtained at Baseline (within 45 days prior to Cycle 1 Day 1 dosing, only after all other eligibility criteria have been met** (a portion of the bone marrow aspirate obtained at ~~Screening~~ **Baseline** will be used; no additional sample is required), **as well as a sample of** blood~~,~~ and saliva, **also collected at Baseline. Bone marrow aspirate or**	Revised text for clarity; definition of "Baseline" added

Section(s)	Changed from	Changed to	Rationale
		biopsy collection does not need to be repeated if previously completed within 45 days prior to Cycle 1 Day 1 dosing, and for Phase 3 only, if it was processed at the central laboratory. Additional bone marrow samples for biomarkers may be collected at ~~the time of~~ **disease** progression ~~or at the~~ **(**End of **Study** Treatment ~~visit~~ **due to progressive disease [PD], or Long-term Follow-up)** from all subjects who consent.	
Synopsis: Statistical methods and analyses Section 14.1 Study Endpoints	Endpoints Part 1: Phase 1b Dose-Escalation and **Dose-**Expansion Portions of the Study Primary Endpoints-Part 1 • Nature of DLTs • ~~Nature and severity of AEs~~ **Adverse events** and **select** laboratory abnormalities graded according to NCI-CTCAE, ~~v~~ **Version** 4.03 • ~~Changes from baseline in~~ **V**ital signs and **select** clinical laboratory results during and following study drug administration Secondary Endpoints-Part 1 • Overall response ~~rate of OPomd~~ defined as the ~~proportion of subjects with~~ **best** response of sCR, CR, VGPR, or PR as determined by investigator ~~and defined by~~ **according to** the IMWG-URC • Clinical benefit ~~rate of OPomd~~, defined as the ~~proportion of subjects with overall~~ best response of MR or better as determined by investigator according to the IMWG-URC and modified EBMT criteria • Pharmacokinetics parameters, including maximum plasma concentration (C_{max}), time to maximum concentration (T_{max}), area under the plasma concentration time curve from time 0 to last time point ($AUC_{0-\tau}$), and area under the plasma concentration time curve from time 0 to time infinity ($AUC_{0-\infty}$) using noncompartmental methods Exploratory Endpoints-Part 1 • Pharmacodynamic biomarkers that may be correlated with antitumor activity **and resistance following treatment with proteasome inhibitors** • Genomic biomarkers that may be correlated with antitumor activity • Change over time in bone pain and the impact of bone pain measured with the BPI-SF (Dose Expansion only) • Change over time in the global health ~~scale~~ **status/QoL scale** of the EORTC QLQ-C30 (Dose Expansion	Revised for accuracy and consistency within the protocol

Section(s)	Changed from	Changed to	Rationale
	only) • Change over time in health status assessed by ~~EuroQol~~ EQ-5D-5L (Dose Expansion only) • Change over time in the disease symptoms subscale of the EORTC QLQ-MY20 (Dose Expansion only) • Change over time in neurotoxicity symptoms measured by the FACT/GOG-Ntx4 score (Version 4) (Dose Expansion only) <u>Part 2: Randomized Phase 3 Portion of the Study</u> <u>Primary Endpoint-Part 2</u> • Progression-free survival, defined as time from randomization to the earlier of disease progression **determined by ORCA according to the IMWG-URC,** or death due to any cause~~, according to ORCA and according to the IMWG-URC and modified EBMT criteria~~ <u>Secondary Endpoints-Part 2</u> • Overall survival, defined as time from randomization to death due to any cause • Overall response, defined as ~~an overall~~ **the best** response of sCR, CR, VGPR, or PR as determined by ORCA ~~and defined by~~ **according to** the IMWG-URC • Clinical benefit, defined as ~~an overall~~ **the best** response of MR or better, **as determined by ORCA** according to the IMWG-URC and modified EBMT criteria~~, as determined by ORCA~~ • Duration of response, defined as the time from the first evidence of confirmed PR or better to disease progression as determined by ORCA according to the IMWG-URC or death due to any cause ~~as determined by ORCA~~ • Improvement in renal function ~~over time~~, as defined by an increase in GFR of at least 10 mL/min • Improvement in hemoglobin ~~over time~~, as defined by an increase of at least 2 g/dL • Duration of response, defined as the time from the first evidence of confirmed PR or better to disease progression or death due to any cause as determined by ORCA • ~~Population based PK parameters including, but not limited to, area under the curve (AUC) and C_{max}, will be determined from OPomd subjects~~ • Adverse events and **select** laboratory abnormalities graded according to NCI-CTCAE, ~~v~~ **Version** 4.03 ~~over time~~ • Vital signs and **select** clinical laboratory results during and following study drug administration ~~over time~~ • Change over time in bone pain and the impact of bone pain measured with the BPI-SF • Change over time in the global health ~~scale~~ **status/QoL scale** of the EORTC QLQ-C30		

Section(s)	Changed from	Changed to	Rationale
	• Change over time in the disease symptoms subscale of the EORTC QLQ-MY20 • Change over time in health status assessed by ~~EuroQol~~ EQ-5D-5L • **Population–based PK parameters including, but not limited to, area under the plasma concentration-time curve (AUC) and C_{max}, will be determined from OPomd subjects** Exploratory Endpoints-Part 2 • Progression-free survival and ~~ORR~~ **overall response**, as determined by the investigator **according to the IMWG-URC** • Duration of response, defined as the time from the first evidence of confirmed PR or better to disease progression **as determined by the investigator according to the IMWG-URC** or death due to any cause ~~as determined by the investigator according to the IMWG-URC and modified EBMT criteria~~ • Clinical benefit ~~rate~~ as determined by the investigator **according to the IMWG-URC and modified EBMT criteria** • Duration of clinical benefit (DOCB), defined as the time from first evidence of ≥ MR **or better to disease progression or death due to any cause,** as determined by ORCA and the investigator according to the IMWG-URC and modified EBMT criteria • Genomic biomarkers that may be correlated with antitumor activity **and resistance following treatment with proteasome inhibitors** • Neuropathy events (defined as Grade 2 or higher peripheral neuropathy ~~incidence~~) • Change in the neurotoxicity symptoms as measured by FACT/GOG-Ntx4 score (Version 4) • Change over time in all domains of the EORTC QLQ-C30 and EORTC QLQ-MY20 (excluding the global health scale and disease symptoms subscale, respectively)		
Synopsis: Statistical methods and analyses	Efficacy Analyses Part 1: Phase 1b Dose Escalation and **Dose-**Expansion Portions of the Study ~~Response assessment data, PFS,~~ **Progression-free survival** and duration of response will be listed for all subjects by dose level and schedule. Overall response rate and clinical benefit rate will be estimated for all subjects treated at the RP3D **along with the associated 95% exact binomial confidence intervals (CIs).** Part 2: Randomized Phase 3 Portion of the Study ~~Median PFS will be estimated for each treatment arm using Kaplan-Meier estimates~~. The ~~95% confidence interval (CI) for the median PFS will be constructed using the method of Brookmeyer (1982)~~ **primary analysis of PFS and other efficacy endpoints will be based on the ITT population, defined as all subjects randomized.** The primary inferential comparison **for PFS** between treatment groups will ~~be based on~~ **use** the ~~stratified~~ log-rank test ~~using~~ **stratified by the** randomization stratification factors. The ~~hazard ratio between the~~		Revised text for clarity

Section(s)	Changed from	Changed to	Rationale
	~~2 treatment arms~~ **HR** will be estimated using a stratified Cox proportional hazards model ~~using randomization stratification factors.~~ ~~Duration of follow-up for PFS will be estimated by reverse~~ **The distribution of PFS, including medians, will be summarized descriptively using the Kaplan-Meier method for each treatment group. Overall survival will be analyzed using the same method as for PFS. Duration of response and DOCB will be summarized for each treatment group by** Kaplan-Meier method ~~(Schemper 1996)~~**; however.** ~~Statistical methods for analyses of OS will be identical to those used for PFS. The Kaplan-Meier methodology will also be used for estimating median DOR.~~ **n**o formal inferential comparisons of DOR will be made, as responders constitute a nonrandom subset of the ITT population. Point estimates and 95% exact **binomial** CIs will be calculated for the ORR and CBR **for each treatment group**. Inferential comparison between treatment groups for ~~this endpoint~~ **these endpoints** will be made using the Cochran-Mantel Haenszel chi-square test, stratified by the randomization stratification factors. Inferential testing of the primary efficacy endpoint and selected secondary endpoints ~~will be assessed~~ **(OS, ORR, CBR, improvement in renal function, improvement in hemoglobin, change over time in QLQ-MY20 total scale, and change over time in QLQ-C30 total scale)** against an overall 1-sided significance level of 0.025 in accordance with a closed testing procedure. Safety Analyses Part 1: Phase 1b Dose Escalation and **Dose-**Expansion Portions of the Study For the Phase 1b portion of the study, safety will be assessed through summaries of DLTs, AEs, changes in **select** laboratory test results, ECGs, vital signs, and oprozomib, pomalidomide, and dexamethasone exposure. All AE data collected will be listed by study site, cohort, subject number, and ~~cycle~~ **study** day.		
Section 3.1 Introduction	_	**This is a Phase 1b/Phase 3 clinical trial of the oral proteasome inhibitor, oprozomib, in subjects with primary refractory or relapsed and refractory multiple myeloma. See Section 5 for a complete description of the study design.** **The protocol has been amended with changes to the study design as new data became available from other ongoing oprozomib studies, and based on review of safety results from these studies. A summary of changes for each amendment is included in the appendix of each version of the protocol. The main purposes for each amendment are summarized below.** **Amendment 1:**	Added text in a new subsection "Introduction" to provide a top level summary of the amendments thus far. All subsequent headings in this section were renumbered accordingly

Section(s)	Changed from	Changed to	Rationale
		1. **Added an alternative oprozomib dosing schedule consisting of 2 consecutive days every 7 days (2/7), as preliminary data suggest that a 2/7 schedule has single-agent activity, and may be better tolerated than the existing schedule of 5 consecutive days every 14 days (5/14 schedule).** 2. **Clarified that plasmapheresis is not permitted at any time during the study.** 3. **The starting dose of oprozomib was changed from 210 mg to 150 mg to provide increased margin of safety for subjects participating in this study. This dose (150 mg) is 3 dose levels below the single-agent MTD and was selected due to the overlapping toxicities of oprozomib with pomalidomide.** 4. **Additional dose modification text was added to the dose modification table for nonhematologic toxicities and guidance to investigators to mitigate Grade 4 gastrointestinal (GI) hemorrhage.** **<u>Amendment 2:</u>** 1. **To allow subjects with prior carfilzomib exposure to be considered for inclusion in the study, if carfilzomib was not withdrawn due to toxicity.** 2. **To allow subjects with prior pomalidomide exposure to be considered for inclusion in the dose-escalation portion of the study, if pomalidomide was neither dose-reduced nor withdrawn due to toxicity.** 3. **To specify that only subjects who have been treated with adequate alkylator therapy are eligible to be considered for inclusion in the Phase 1b dose-escalation portion and Phase**	

Section(s)	Changed from	Changed to	Rationale
		3 portion of the study. 4. **Additional safety guidance regarding Grade 3 or 4 GI hemorrhage (see Section 10.4.2.1.2), mandatory proton-pump inhibitors (see Section 10.6.1.5), and the addition of an exclusion criterion for patients with prior clinically significant bleed in the 6 months prior to first dose of study treatment, because of toxicities observed in Study 2011-001.** 5. **Revisions in synopsis, statistical sections, objectives, and endpoints for accuracy, clarity, and consistency within the protocol.**	
Section 3.2 Multiple Myeloma Background	Median OS from diagnosis was reported at 3 years for high-risk patients, 4 to 5 years for intermediate-risk patients, and 8 to 20 years for standard-risk patients (Mikhael 2013).	Median OS from diagnosis was reported at 3 years for high-risk patients, 4 to 5 years for intermediate-risk patients, and 8 to **10** ~~20~~ years for standard-risk patients (Mikhael 2013).	Corrected text
Section 3.4 Oprozomib Background	Oprozomib is a tripeptide epoxyketone proteasome inhibitor and structural analogue of carfilzomib (Kyprolis) that primarily targets the chymotrypsin-like activity of the 20S proteasome. Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor approved in the US for the treatment of relapsed and refractory multiple myeloma. Similar to carfilzomib, oprozomib is a potent, selective, and irreversible inhibitor of the CT-L activity of the constitutive proteasome (the form of proteasome found in most cell types) and the immunoproteasome (the form of proteasome found in many hematopoietic cells) (Zhou 2009). In addition, when measured against a broad panel of proteases containing metallo-, aspartyl, cysteine, and serine proteases, oprozomib demonstrated minimal reactivity against nonproteasomal proteases.	Oprozomib **(formerly ONX 0912)** is a tripeptide epoxyketone proteasome inhibitor and structural analogue of carfilzomib (Kyprolis) that primarily targets the **CT-L** ~~chymotrypsin-like~~ activity of the 20S proteasome. **Carfilzomib received accelerated approval in the US for the treatment of patients with multiple myeloma who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy (Kyprolis Prescribing Information [Onyx Pharmaceuticals, 2012]).** ~~Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor approved in the US for the treatment of relapsed and refractory multiple myeloma.~~ Similar to carfilzomib, oprozomib is a potent, selective, and irreversible inhibitor of the CT-L activity of the constitutive proteasome (the form of proteasome found in most cell types) and the immunoproteasome (the	Updated text to provide missing information on carfilzomib label, and for consistency with other oprozomib protocols.

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		form of proteasome found in many hematopoietic cells) (Zhou 2009). In addition, when measured against a broad panel of proteases containing metallo-, aspartyl, cysteine, and serine proteases, oprozomib demonstrated minimal reactivity against nonproteasomal proteases.	
Section 3.4.2 Relevant Clinical Background	3.3.2.1 Study 2009-003: **Solid Tumors** **Efficacy** **In Study 2009-003, oprozomib, dosed as powder in capsule, was studied in solid tumor subjects. In the Phase 1 study in refractory solid tumors (n = 44), no subject achieved an objective response. Stable disease (SD) was observed in 6 subjects (30%) in the once daily dosing group and 4 subjects (23.5%) in the split daily dosing group.** **Safety** **The majority of adverse events (AEs) were Grade 1 and 2, manageable, and there were no apparent cumulative toxicities. The most common AEs were in the GI system organ class. This was consistent with preclinical animal studies with oprozomib. Dose-limiting toxicities for the once daily dose group in Study 2009-003 included Grade 3 dehydration/vomiting and Grade 3 hypophosphatemia in the 180 mg cohort. The maximum tolerated dose (MTD) for the once daily x5 days dose group is 150 mg. Dose-limiting toxicities for the split daily x5 days dosing group in Study 2009-003 included Grade 3 hypophosphatemia at 180 mg and Grade 5 upper GI hemorrhage and Grade 3 hallucinations at 210 mg. The MTD for the split dosing is 180 mg.** ~~The first-in-human clinical trial (2009-003) of oprozomib was initiated in May 2010 and completed the last subject visit in November 2012 in 44 subjects with advanced solid tumors; the database was closed 19 March 2013. This was an open-label, Phase 1 study in which subjects initially received Oprozomib in Capsules orally, once daily, on a 5 consecutive day, bimonthly treatment schedule, with cycles repeated every 14 days. The primary objectives of the study were to evaluate the safety, tolerability, and maximum tolerated dose (MTD) of oprozomib in this patient population. Samples for pharmacokinetics (PK) and PDn evaluations were collected at various time points during Cycles 1 and 2. For subjects enrolled under 2009-003 Protocol Amendment 4, oprozomib was administered as a split dose (doses administered 4 to 6 hours apart) to mitigate gastrointestinal (GI) toxicity and to support additional dose escalation after reaching the MTD with single daily dosing. Differences in PDn and tolerability between fasted (Cycle 1) and fed (Cycle 2) states were also explored for subjects enrolled under Protocol Amendment 4.~~ ~~Efficacy Powder in Capsule~~ ~~The Efficacy Evaluable (EE) population comprised 21 of 25 subjects (84.0%) in the once-daily dosing group and 17 of 19 subjects (89.5%) in the twice-daily dosing group who had measureable disease at baseline, completed~~	Updated clinical background information for Study 2009-003 per most recent information

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	~~the first 4 treatment cycles, and either had at least 1 post-treatment response assessment or discontinued treatment due to progressive disease (PD) prior to the first scheduled disease assessment. In the EE population, no subject achieved a partial response (PR). Stable disease (SD) was the best response achieved by 6 subjects (28.6%) in the once-daily dosing group and 4 subjects (23.5%) in the twice-daily dosing group. The median time to progression was 43 days for the once daily group and 57 days for the twice-daily group. The clinical benefit rate (CBR; best response ≥ minimal response [MR]) was 28.6% in the once-daily dosing group and 23.5% in the twice-daily dosing group.~~ ~~Safety~~ ~~Once-Daily Group Powder in Capsule~~ ~~All 25 subjects who received a once-daily dose of Oprozomib in Capsules were included in the safety population. All subjects are off study; reasons for study discontinuation included PD (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 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 GI 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 AE (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.~~ ~~Twice Daily Group Powder in Capsule~~ ~~The safety population comprised all 19 enrolled subjects who received at least 1 dose of Oprozomib in Capsules. All subjects are off study; reasons for study discontinuation included PD (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~~		

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	~~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 GI hemorrhage and 1 subject with Grade 3 hallucinations. The MTD for the twice-daily dosing group was determined to be 180 mg.~~ ~~Nineteen subjects (100.0%) experienced at least 1 treatment-emergent AE. The most frequent AEs 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, dysguesia, and anemia (5 subjects each, 26.3%).~~ ~~The most frequent AEs were GI and Grade 1 and 2 in severity. 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 AEs occurred in the twice-daily dosing group. One subject in the 210-mg cohort died within 30 days of discontinuing study drug due to a GI bleed.~~ ~~Further details are provided in the Oprozomib IB.~~		
Section 3.4.2 Relevant Clinical Background	3.3.2.2. Study 2011-001: **Hematologic Malignancies** **Efficacy** **As of 21 January 2014, the Phase 1b portion of Study 2011-001 has completed enrollment; 61 response-evaluable subjects with hematologic malignancies have received Oprozomib in Capsules in split dosing, or Oprozomib Tablets with daily dosing, on a 5 consecutive day bimonthly (5/14) schedule or a 2 consecutive day weekly (2/7) schedule in Phase 1. Response rates for subjects with multiple myeloma (n = 43) and subjects with Waldenström macroglobulinemia (WM; n =18) by schedule and formulation are summarized in Table 1 and Table 2, respectively.** **Table 1 Phase 1 Response Rates for Subjects with Multiple Myeloma, by Schedule and Formulation** **Formulation/Schedule (n) | Dose Range (mg) | ORR | Clinical Benefit Rate** **PIC 5/14 (10) | 120–210 | 40% | 50%** **Tablets 5/14 (18) | 150–270 | 27.8% | 38.9%** **Tablets 2/7 (15) | 150–330 | 20.0% | 46.7%** **ORR = overall response rate; PIC = powder in capsule.** **Table 2 Phase 1 Response Rates for Subjects with Waldenström macroglobulinemia, by Schedule and Formulation** **Formulation/Schedule (n) | Dose Range (mg) | ORR[a] | Major Response[b]**	Updated clinical background information for Study 2011-001 per most recent information

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Tablets 5/14 (11)	150–270	63.6%	54.5%
Tablets 2/7 (7)	150–330	42.9%	14.3%

MR = minimal response; ORR = overall response rate; PR = partial response.

[a] ORR is defined as ≥ MR.

[b] Major response is defined as ≥ PR.

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

Safety

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

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

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

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

Nineteen (19) 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 IB (Version 6). There were 2 cases of renal failure. There were also 2 Grade 5 GI hemorrhages at the 240 mg dose level on the 5/14 schedule.

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	~~The second clinical trial (2011-001) was initiated in September 2011 in subjects with hematologic malignancies. This is an ongoing, open-label, Phase 1b/2, multicenter study of oprozomib with 37 subjects treated as of March 2013. The primary objectives for the Phase 1b escalation are to evaluate the safety, tolerability, and MTD of oprozomib in this patient population. Differences in oprozomib tolerability and PDn in subjects treated in a fasted and fed state are also being explored. The study was initiated with Oprozomib in Capsules administered orally, twice daily (doses separated by 4 to 6 hours), on a 5 consecutive day, bimonthly (Days 1 to 5 of a 14-day cycle) treatment schedule. For subjects enrolled under 2011-001 Protocol Amendment 2, subjects received Oprozomib Tablets, once daily, either on a 5 consecutive day, bimonthly schedule or a 2 consecutive day, weekly schedule (Days 1, 2, 8, and 9 of a 14-day cycle). Under Protocol Amendment 3, a cohort of subjects with carfilzomib-refractory multiple myeloma (n = 20) will be enrolled in the Phase 2 portion of the study to evaluate the efficacy and safety of oprozomib in this patient population. Subjects with carfilzomib-refractory multiple myeloma will be treated using the 5 consecutive day, bimonthly schedule only.~~ ~~Efficacy~~ ~~*Twice Daily × 5 Bimonthly Powder in Capsule*~~ ~~As of 25 March 2013, 13 subjects have received Oprozomib in Capsules on a 5 consecutive day, bimonthly schedule with split daily dosing. Twelve subjects are evaluable for response assessment and 1 has withdrawn from the study. Among the subjects with multiple myeloma, 3 had a PR, 2 had a MR, 4 had SD, and 2 had PD as their best response. In addition, 1 subject on study with chronic lymphocytic leukemia (CLL) had a PR as best response.~~ ~~*Once Daily × 5 Bimonthly Powder in Capsule*~~ ~~Thirteen multiple myeloma and 5 Waldenström macroglobulinemia (WM) subjects on the once-daily×5 bimonthly schedule were included in the response evaluation. The clinical benefit rates (CBR) were 23.1% (multiple myeloma) and 80.0% (WM). In subjects with multiple myeloma, 1 (150 mg/d) had a very good partial response (VGPR), 2 (210 mg/d) had a PR, 6 (150–240 mg/d) had SD, 1 (150 mg/d) had PD, and 3 were not evaluable for response. In WM subjects, 4 (150–210 mg/d) had a PR and 1 (180 mg/d) had SD.~~ ~~Safety~~ ~~Twice Daily × 5 Bimonthly Powder in Capsule~~ ~~As of 25 March 2013, 13 subjects (5 males, 8 females) with a median age of 62.0 years (range: 52 to 81 years) have received Oprozomib in Capsules on a 5 consecutive day, bimonthly schedule with twice-daily dosing. All 13 subjects received at least 1 dose of study drug and were evaluable for safety. No DLTs were observed at doses up to 210 mg/day. At study entry, 11 subjects had relapsed multiple myeloma and 2 subjects had CLL.~~ ~~At least 1 treatment-emergent AE has been recorded in all 13 subjects. Treatment-emergent AEs seen in ≥ 25% of subjects were nausea (11 subjects), diarrhea (9 subjects), vomiting (9 subjects), fatigue (8 subjects), anemia (6 subjects), thrombocytopenia (4 subjects), and decreased appetite (4 subjects).~~ ~~Seven subjects had at least 1 treatment-emergent Grade 3 AE according to National Cancer Institute-Common~~		

Section(s)	Changed from	Changed to	Rationale
	~~Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03, which were diarrhea (3 subjects), anemia and nausea (2 subjects each), and thrombocytopenia, abdominal pain, fatigue, Herpes zoster ophthalmic, neutropenia, pneumonia, back pain, and vomiting (1 subject each). Three subjects had at least 1 treatment-emergent Grade 4 AE (thrombocytopenia in all 3 subjects). No Grade 5 AEs were reported within 30 days of the last dose of study drug. One death due to PD occurred, 71 days after the last dose of study drug.~~ ~~Three subjects experienced at least 1 treatment-emergent SAE, including pneumonia (1 subject in the 120-mg cohort), Herpes zoster ophthalmic (1 subject in the 120-mg cohort), and nausea (1 subject in the 150-mg cohort). The pneumonia resolved after 2 days without oprozomib dose modification. The Herpes zoster event resolved after 2 days and required the subject's oprozomib dose to be held or delayed. The nausea event resolved after 2 days and required dose reduction and concomitant mediation.~~ ~~Once Daily × 5 Bimonthly Tablet and Once Daily × 2 Tablet~~ ~~As of 01 July 2013, median treatment duration was 11.3 cycles and 8.7 cycles for the once daily×5 bimonthly schedule and once daily × 2 weekly schedule, respectively. There were 2 DLTs, both of which occurred on the once daily × 5 bimonthly schedule: renal failure on a dose of 180 mg/day and tumor lysis syndrome (TLS) on a dose of 240 mg/day. The most common Grade 1–2 adverse events are summarized below in Table 1.~~ ~~Table 1 Grade 1-2 Adverse Events in > 25% of Subjects~~ ~~Grade 1-2 Adverse Events / Number of Subjects~~ ~~Nausea 28~~ ~~Diarrhea 20~~ ~~Fatigue 20~~ ~~Vomiting 14~~ ~~Constipation 11~~ ~~The most common Grade 3-4 AEs (≥ 2 subjects) are summarized in Table 2.~~ ~~Table 2 Grade 3-4 Adverse Events (≥ 2 Subjects)~~ ~~Grade 1-2 Adverse Events / Number of Subjects~~ ~~Diarrhea 9~~ ~~Anemia 4~~ ~~Nausea 4~~ Neutropenia 4		

Section(s)	Changed from	Changed to	Rationale
	~~Hypophosphatemia~~ ~~3~~ ~~Thrombocytopenia~~ ~~3~~ ~~Vomiting~~ ~~3~~ ~~Dehydration~~ ~~2~~ ~~Fatigue~~ ~~2~~ ~~Further details are provided in the Oprozomib IB.~~		
Section 3.4.2 Relevant Clinical Background	–	**3.3.2.3 Study 2012-001: Oprozomib in Combination with Dexamethasone in Multiple Myeloma** **Efficacy** **For the 2012-001 Phase 1b/2 study, as of 31 March 2014, 5 response-evaluable relapsed and/or refractory multiple myeloma subjects received Oprozomib Tablets on a 5 consecutive day bimonthly (5/14) schedule with daily dosing in combination with dexamethasone; 1 subject had MR and 4 subjects had SD as their best response. As of 31 March 2014, 8 response-evaluable subjects have received Oprozomib Tablets administered orally, once daily, on Days 1, 2, 8, and 9 of a 14-day cycle (2/7) in combination with 20 mg of dexamethasone; 1 subject had a VGPR (unconfirmed), 2 subjects had a partial response ([PR] confirmed or unconfirmed), 1 subject had a MR, and 4 subjects had SD as the best response.** **Safety** **The 2012-001 Phase 1b/2 study assessing safety and activity of Oprozomib Tablets in combination with dexamethasone is currently enrolling in the Phase 1b portion of the study.** • **As of May 2014, 12 subjects have been enrolled and treated at doses of 180 mg (n = 5) to 210 mg (n = 7) on the 5/14 schedule, and 4 subjects remain on study. Three (3) subjects have**	Added updated clinical background information for Study 2012-001 for consistency with other oprozomib protocols.

Section(s)	Changed from	Changed to	Rationale
		experienced DLTs at the 210 mg dose, including 1 subject with a subarachnoid hemorrhage (SAH), 1 subject with Grade 3 transaminitis, and 1 subject with Grade 4 thrombocytopenia. In addition, 1 subject had 3 SAEs (esophagitis, urinary tract infection, and pneumonia). Data suggest that the 180-mg dose level will be the tolerable dose in combination with dexamethasone. This dose level exceeds the starting dose for the combination of oprozomib, pomalidomide, and dexamethasone (OPomd). • **As of May 2014, 13 subjects have been enrolled and treated at doses of 180 mg (n = 3), 210 mg (n = 3), 240 mg (n = 3), to 270 mg (n = 4) on the 2/7 schedule, and 7 subjects remain on study. One DLT of Grade 4 thrombocytopenia has been observed. Dose escalation is ongoing at the 300-mg dose level, suggesting that doses lower than 300 mg in combination with dexamethasone are tolerable. Current doses explored in this schedule exceed the starting dose for the combination of OPomd.** **As of 31 March 31 2014, ten (10) subjects experienced serious adverse events (SAEs) across both schedules. The 3 treatment-related SAEs were 1 subject with a SAH, hypertension, and headache, 1 subject with thrombocytopenia, pneumonia, and sepsis, and 1 subject with delirium. Thrombocytopenia and infection were expected events based on the Oprozomib IB (Version 6), but the SAH, hypertension, headache, and delirum were not.**	
Section 3.4.2 Relevant Clinical Background	–	**3.3.2.4 Study OPZ003: Oprozomib in Combination with Lenalidomide and Dexamethasone in Multiple Myeloma** **<u>Efficacy</u>**	Added updated clinical background information for Study OPZ003 for consistency with other

Section(s)	Changed from	Changed to	Rationale
		No efficacy data are available at this time. **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, 3 subjects have been enrolled. Two (2) subjects remain on study. One subject, a [redacted]year old [redacted] experienced a treatment-related SAE of Grade 3 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.**	oprozomib protocols.
Section 3.5.3 Pomalidomide	*Deleted Section 3.5 Clinical Background Pomalidomide; added text to Section 3.5.3 Pomalidomide as shown:* **Pomalidomide (Pomalyst), a thalidomide analogue, is an IMiD that displays similar antiangiogenic activity but far greater antiproliferative and immunomodulatory activity compared with the parent drug (Bartlett 2007; Payvandi 2004). Pomalidomide has also been shown to stimulate antibody-dependent cytotoxic T-cell activity (ADCC) (Bartlett 2007).** **Pomalidomide received accelerated approval in the EU in August 2013 and in the US in February 2013. The European Commission has granted approval for pomalidomide in combination with dexamethasone, for the treatment of relapsed and refractory multiple myeloma who received at least two prior therapies and have demonstrated disease progression on the last drug taken and the US FDA granted accelerated approval for patients with multiple myeloma with 2 prior therapies including both bortezomib and lenalidomide and who are refractory to their last therapy or progressed within 60 days. The approved dose of pomalidomide is 4 mg given 21 days of a 28-day cycle until progressive disease (PD).** **Approval was based on Study MM002, a randomized Phase 2 comparison of pomalidomide in combination with low-dose therapeutic dexamethasone (POM + LoDex) to pomalidomide alone (Jagannath 2012). The overall response rate (ORR) was 34%, with a median PFS of 4.6 months and median OS of 16.5 months. Grade 3 or 4 AEs reported in > 5% of subjects were neutropenia (41%), anemia (22%), pneumonia (22%), thrombocytopenia (19%), fatigue (14%), dyspnea (13%), leukopenia (10%), back pain**	Reorganized sections for clarity and to reduce redundancy

Section(s)	Changed from	Changed to	Rationale
	(10%), and urinary tract infection (9%). Grade 3 or 4 neutropenia occurred in 46% of subjects aged ≤ 65 years and in 35% of subjects aged > 65 years. Febrile neutropenia was observed in only 1 subject in each age group (2%). Overall, 78% of subjects who developed Grade 3 or 4 neutropenia were treated with granulocyte-colony stimulating factor (G-CSF) during study treatment. There was no Grade 3 or 4 peripheral neuropathy (PN) reported, although Grade 1 or 2 PN occurred in 7% of subjects treated with POM + LoDex. Deep vein thrombosis (DVT) occurred in 2 subjects (2%). Pomalidomide appears to provide an efficacious option with a manageable toxicity profile for subjects with refractory or relapsed and refractory multiple myeloma. The approved dose of pomalidomide is 4 mg given 21 days of a 28-day cycle until PD. The MM003 study assessed relapsed and/or refractory subjects with multiple myeloma who had been previously treated with bortezomib and lenalidomide or thalidomide and progressed on or within 60 days of the last therapy. A regimen of pomalidomide and dexamethasone was compared to high-dose dexamethasone. Subjects were randomized 2:1 to receive 28-day cycles of pomalidomide 4 mg on Days 1–21 + dexamethasone 40 mg (20 mg for subjects more than 75 years old) weekly or dexamethasone 40 mg (20 mg for subjects more than 75 years old) on Days1–4, 9–12, and 17–20. Treatment continued until PD or unacceptable toxicity. The primary endpoint was PFS. Secondary endpoints included OS, ~~overall response rate (~~ORR **(**≥ PR), and safety. Analyses were based on intent to treat. A total of 455 subjects were randomized to pomalidomide + low-dose dexamethasone (n = 302) or high-dose dexamethasone (n = 153). The median number of prior therapies was 5 (range: 1–17). Seventy-two percent **(72%)** of subjects were refractory to lenalidomide and bortezomib. Median follow-up was 4 months. Pomalidomide + low-dose dexamethasone significantly extended median PFS (3.6 versus 1.8 months, hazard ratio [HR] = 0.45, p < 0.001) and OS (not reached versus 7.8 months, HR = 0.53, p < 0.001) compared with high-dose dexamethasone. The OS benefit was observed despite 29% of high-dose dexamethasone subjects receiving pomalidomide after PD (Jagannath 2012). With updated data, the ORR was 21% for pomalidomide + low-dose dexamethasone versus 3% for high-dose dexamethasone (p < 0.001) and 24% versus 3% for subjects randomized ≥ 6 months after enrollment (p < 0.001). Median **OS** ~~overall survival~~ was 12.7 months for pomalidomide and 8.1 months for high-dose dexamethasone; HR = 0.74 (p = 0.28). The most frequent Grade 3/4 AEs for pomalidomide + low-dose dexamethasone versus high-dose dexamethasone were neutropenia (42% versus 15%), anemia (27% versus 29%), and infection (24% versus 23%). Discontinuation due to AEs was infrequent (7% versus 6%) (San Miguel 2013). …		
Section 3.5 Dose Rationale	3.5.1 Oprozomib Early development of oprozomib focused on the 5 consecutive day bimonthly (either once or twice daily) (5/14) and 2 consecutive days weekly (2/7) schedules,	3.5.1 Oprozomib Early development of oprozomib focused on the 5 consecutive day bimonthly (either once or twice daily) (5/14) and 2 consecutive days weekly (2/7) schedules,	Text was rearranged and revised for clarity

Section(s)	Changed from	Changed to	Rationale
	both on 14-day treatment cycles. The maximum administered dose for Oprozomib Tablets administered once daily on a 5 consecutive day bimonthly schedule has been reached with a total daily dose of up to 270 mg in subjects with hematologic malignancies, with 1 DLT of TLS and one Grade 3 vomiting out of 6 subjects. At the 240 mg dose, 6 subjects were dosed with 1 DLT of TLS, therefore 240 mg was the declared as the MTD. The starting dose of 150 mg of oprozomib will be added to the FDA approved regimen of pomalidomide/dexamethasone, 3 dose levels below the MTD in the 5/14 schedule in the single-agent study. The starting dose for the 2/7 schedule will be 210 mg, 3 dose levels below the single agent MTD of 300 mg. One DLT of grade 3 orthostatic hypotension was reported in this cohort. The maximum administered dose was reached with a total daily dose of 330 mg with 1 DLT of Grade 3 diarrhea and 1 DLT of Grade 4 thrombocytopenia. The most significant AEs noted are GI toxicities. This study will assess both schedules in Part 1 of the study, as oprozomib has demonstrated preliminary activity in subjects with hematologic malignancies on both schedules. (Kaufman 2013).	both on 14-day treatment cycles. The ~~maximum administered dose~~ **MAD** for Oprozomib Tablets administered once daily on a 5 consecutive day bimonthly schedule has been reached with a total daily dose of up to 270 mg in subjects with hematologic malignancies, with 1 **dose-limiting toxicity** (DLT) of TLS and **1** ~~one~~ Grade 3 vomiting out of 6 subjects. At the 240-mg dose, 6 subjects were dosed with 1 DLT of TLS, therefore 240 mg was the declared as the MTD. **For the 5/14 schedule, t**he starting dose of 150 mg of oprozomib will be added to the **Food and Drug Administration (**FDA**)-**approved regimen of pomalidomide/dexamethasone, 3 dose levels below the MTD **in the single-agent study** ~~in the 5/14 schedule in the single-agent study~~. ~~The starting dose for the 2/7 schedule will be 210 mg, 3 dose levels below the single agent MTD of 300 mg. One DLT of grade 3 orthostatic hypotension was reported in this cohort. The maximum administered dose was reached with a total daily dose of 330 mg with 1 DLT of Grade 3 diarrhea and 1 DLT of Grade 4 thrombocytopenia.~~ **For the 2/7 schedule, the MAD was reached with a total daily dose of 330 mg with 1 DLT of Grade 3 diarrhea and 1 DLT of Grade 4 thrombocytopenia. One DLT of Grade 3 orthostatic hypotension was reported in the 300-mg cohort, therefore 300 mg was declared the MTD. The starting dose for the 2/7 schedule will be 210 mg, 3 dose levels below the single agent MTD of 300 mg.** ~~The most significant AEs noted are GI toxicities.~~ This study will assess both schedules in Part 1 of the study, as oprozomib has demonstrated preliminary activity in subjects with hematologic malignancies on both schedules (Kaufman 2013).	
Section 3.5 Dose Rationale	Dexamethasone will be administered in this study based on data from the SUMMIT trial (Richardson	Dexamethasone will be administered in this study based on data from the SUMMIT trial (Richardson	Deleted text that is now redundant with newly

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	2003) and an expanded access trial (Mikhael 2009), in which dexamethasone was shown to have improved efficacy when administered 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 AEs temporally associated with single-agent oprozomib.	2003) and an expanded access trial (Mikhael 2009), in which dexamethasone was shown to have improved efficacy when administered 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 AEs temporally associated with single-agent oprozomib.~~	added clinical background information for Study 2012-001
Section 3.6 Study Rationale	… Carfilzomib (Kyprolis) 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 CT-L 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). … Data collected in these 2 trials 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 dose and schedule and have provided data indicating both tolerability and efficacy in advanced stage, heavily pretreated multiple myeloma subjects.	… Carfilzomib (Kyprolis) is an irreversible inhibitor of the epoxyketone class (proteasome) **that received accelerated approval in the US for the treatment of patients with multiple myeloma who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy (Kyprolis Prescribing Information [Onyx Pharmaceuticals 2012]). Carfilzomib** 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 CT-L 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). … Data collected in these 2 trials suggested that the 2 consecutive day weekly schedule was better tolerated and demonstrated clinically meaningful response rates.	Added text for clarity

Section(s)	Changed from	Changed to	Rationale
		Subsequent Phase 2 and Phase 3 carfilzomib studies have utilized this dose and schedule and have provided data indicating both tolerability and efficacy in advanced stage, heavily pretreated multiple myeloma subjects. **Both schedules will be assessed with oprozomib to determine which schedule provides an advantage in tolerability and efficacy.**	
Section 5 Study Design	During Part 2 of the study, subjects will be randomized to oprozomib or placebo (subjects in the Pomd arm) at the RP3D and schedule determined during Part 1 of the study. Up to 20 study sites will participate in Part 1 of the study (Phase 1b Dose Escalation and Expansion portions of the study). Approximately 70 sites will participate in Part 2 of the study (Phase 3 portion of the study).	During Part 2 of the study, subjects will be randomized to oprozomib **in combination with pomalidomide and dexamethasone (OPomd)** ~~or placebo (subjects in the Pomd arm)~~ at the RP3D and schedule determined during Part 1 of the study **or placebo in combination with pomalidomide and dexamethasone (Pomd).** Approximately 35 study sites will participate in Part 1 of the study (15 sites for the Phase 1b dose-escalation and 20 **additional** sites for the dose-expansion portions of the study). **An additional 35 sites, for a total of a**pproximately 70 sites will participate in Part 2 of the study (Phase 3 portion of the study).	Revised text for clarity.
Section 5 Study Design	*Moved from:* 5.1.2 Dose-Escalation Schema for the 2/7 Oprozomib Dosing Schedule Treatment cycles for both parts of the study will last 28 days. Disease assessments will be performed every 4 weeks for subjects in both arms for 18 months. Further disease assessments will be conducted every 8 weeks after this period. Details of the study assessments required for this study are provided in Appendices A1 and A2.	*Moved to:* *(End of)* 5 Study Design **Treatment cycles are 28 days in duration. Two (2) oprozomib dosing schedules will be assessed during dose-escalation. Subjects will receive oprozomib once daily either on Days 1–5 and 15–19, referred to hereafter as the 5/14 schedule, or an alternate schedule of once daily on Days 1, 2, 8, 9, 15, 16, 22, and 23, referred to hereafter as the 2/7 schedule. Pomalidomide will be given on Days 1–21 and dexamethasone will be given on Days 1, 2, 8, 9, 15, 16, 22, and 23 of every 28-day cycle.**	Revised text for clarity and moved text to the appropriate location in the protocol
Section 5.1 Part 1: Phase 1b Dose-Escalation and **Dose-**Expansion	… The safety of subjects in the Dose Expansion will be monitored on an ongoing basis by the CSRC during bimonthly calls. Enrollment to the Phase 3 portion will	… The safety of subjects in the Dose Expansion will be monitored on an ongoing basis by the CSRC during bimonthly calls. ~~Enrollment to the Phase 3 portion will~~	Deleted text as it is redundant with the text in the following section (5.2 Part 2: Randomized Phase

Section(s)	Changed from	Changed to	Rationale
Portions of the Study	not commence until the CSRC has evaluated all available safety information from a minimum of 10 subjects who have completed ≥ 2 cycles of therapy at the RP3D and enrollment of the remaining 10 subjects in Dose Expansion has occurred in 1 or both schedules if both were opened.	~~not commence until the CSRC has evaluated all available safety information from a minimum of 10 subjects who have completed ≥ 2 cycles of therapy at the RP3D and enrollment of the remaining 10 subjects in Dose Expansion has occurred in 1 or both schedules if both were opened.~~	3 Postion of the Study)
Section 5.1.3 Dose-Limiting Toxicities	Deleted text from Section 5.1.4 Subject Replacement and added it to this section as shown: Subjects in both dosing schedules will be evaluated for DLTs according to the NCI-CTCAE, version 4.03 during the 28-day period of Cycle 1 combination therapy. Intrasubject dose escalation to the RP3D may be permitted once that dose has been determined and after a discussion has occurred between the treating physician and Onyx study medical monitor. The decision to escalate to the next higher dose of oprozomib in the Phase 1b portion of the study will be based on an assessment of study drug-related DLTs during Cycle 1 **by the CSRC**. **The CSRC consists of investigators, the Onyx medical monitor, and Onyx Drug Safety representative. Each subject in the cohort under review will be discussed and assessed. Once all data have been presented, the CSRC will decide on the most appropriate course of action regarding dose escalation based on guidance in Section 5.1.** **Study drug is defined as the combination of oprozo alidomide, and dexamethasone.** Study drug-related is defined as a reasonable likelihood of clinical causality based on time of event, biology, dechallenge improvement and that the AE was not likely explained by the subject's clinical state, underlying disease, concomitant medication, or study/nonstudy procedure. Definition of DLTs and additional details are provided in Section 10.5.		Reorganized text so that it is in the appropriate location in the protocol. Added definition of "study drug"
Section 5.2 Randomized Phase 3 (Part 2) Portion of the Study	Part 2 will consist of a placebo-controlled, double-blind RP3D component.	Part 2 will consist of a placebo-controlled, double-blind ~~RP3D~~ **randomized Phase 3** component.	Corrected text
Section 5.3 Estimated Study Duration and Study Closure	The total study duration is expected to be approximately 32-33 months. • The Phase 1b portion of the study will take approximately 7–8 months to complete. • Approximately 5 months will be required to enroll and evaluate response status of subjects in the dose expansion portion of the study. • Approximately 13 additional months will be required to enroll subjects in the Phase 3 portion of the study.	The total study duration is expected to be approximately 32–33 months. • The Phase 1b portion of the study will take approximately 7–8 months to complete • Approximately 5 months will be required to enroll and evaluate response status of subjects in the dose-expansion portion of the study • Approximately 13 additional months will be required to enroll subjects in the Phase 3 portion of the study	Deleted redundant text

Section(s)	Changed from	Changed to	Rationale
	• Assuming an enrollment rate of 22 subjects per month, it is estimated that the final analysis of PFS will occur approximately 17 months after the first subject is enrolled in the Phase 3 portion of the study. Prior to initiating the Phase 3 portion of the study, an assessment of the safety and efficacy data from a minimum of 10 subjects treated during the expansion portion of the study and the enrollment of the remaining 10 subjects in the expansion cohort will be completed in 1 or both schedules if each will be opened per the sponsor's discretion.	• Assuming an enrollment rate of 22 subjects per month, it is estimated that the final analysis of PFS will occur approximately 17 months after the first subject is enrolled in the Phase 3 portion of the study ~~Prior to initiating the Phase 3 portion of the study, an assessment of the safety and efficacy data from a minimum of 10 subjects treated during the expansion portion of the study and the enrollment of the remaining 10 subjects in the expansion cohort will be completed in 1 or both schedules if each will be opened per the sponsor's discretion.~~	
Section 5.4.2 Blinding	For Phase 3 only, an independent, external Data Monitoring Committee (DMC) will monitor the conduct of the study and undertake periodic unblinded assessments of safety data to optimize the safety of study subjects and ensure integrity of the study.	For Phase 3 only, an independent, external Data Monitoring Committee (DMC) will monitor the conduct of the study and undertake periodic unblinded assessments of safety data to **protect** ~~optimize~~ the safety of study subjects and ensure integrity of the study.	Revised text for accuracy.
Section 9.4 Study Drug Accountability	Onyx (or designee) and the investigator will maintain records of each shipment of investigational product (IP). Upon receipt of IP, the designated recipient at the study site will inspect the shipment, verify the number and condition of the vials, and prepare an inventory or drug accountability record. The records will document shipment dates, method of shipment, batch numbers, product presentation, quantity of bottles contained in the shipment, and dispensation to individual subjects using the subject identification number.	Onyx (or designee) and the investigator will maintain records of each shipment of investigational product (IP). Upon receipt of IP, the designated recipient at the study site will inspect the shipment, verify the number and condition of the **bottles or blister packs** ~~vials~~, and prepare an inventory or drug accountability record. The records will document shipment dates, method of shipment, batch numbers, product presentation, quantity of bottles **or blister packs** contained in the shipment, and dispensation to individual subjects using the subject identification number.	Corrected text and added text to allow for the potential use of blister packs in Phase 3 of the study
Section 10.1 Oprozomib Treatment Administration	It is recommended that oprozomib not be taken on an empty stomach. Subjects will be instructed to take the oprozomib doses after eating with approximately 8 ounces of water.	It is recommended that oprozomib not be taken on an empty stomach. Subjects will be instructed to take the oprozomib doses after eating with approximately 8 ounces of water. **On the PK collection days, dosing of oprozomib in relation to the meal intake (within 2 hours before and 1 hour after dose) will be**	Added text for consistency with other oprozomib protocols

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		recorded.	
Section 10.3 Dose Modification Guidelines	This section provides dose reduction and other modification guidelines for oprozomib, pomalidomide, and dexamethasone to manage possible toxicity. Administration of oprozomib or pomalidomide will be discontinued in the event of a treatment-related toxicity that, in the opinion of the investigator, warrants permanent discontinuation. Monotherapy with dexamethasone is not allowed in the Phase 1b Dose-Escalation and Expansion portions of the study. In the event that oprozomib or pomalidomide is permanently discontinued in Phase 3 only, dexamethasone may be continued.	This section provides dose reduction and other modification guidelines for oprozomib, pomalidomide, and dexamethasone to manage possible toxicity. Administration of oprozomib or pomalidomide will be discontinued in the event of a treatment-related toxicity that, in the opinion of the investigator, warrants permanent discontinuation. Monotherapy with dexamethasone is not allowed in the Phase 1b **d**ose-**e**scalation and **dose-e**xpansion portions of the study. **In the event that oprozomib or pomalidomide is permanently discontinued in Phase 3 only, dexamethasone may be continued.**	Added text for clarity
Section 10.4.1 Dose Reductions	… Modifications of the dose of oprozomib/placebo will occur in up to three 30-mg decrements down to a minimum of 150 mg. Additional reductions will be managed by schedule change. … Treatment guidelines for specific hematologic toxicities are outlined in Section 10.4.2.1.1 and nonhematologic toxicities in Section 10.4.2.1.2. In addition to dose reductions, administration of oprozomib, and pomalidomide may be temporarily interrupted for a maximum of 4 weeks in the event of a treatment-related toxicity. … If dexamethasone dosing is permanently stopped due to toxicity in accordance with the dose modification guidelines described in Table 15, the subject should stay on oprozomib and/or pomalidomide, depending on the arm to which they are randomized, and continue to follow protocol required therapy, procedures, and assessments. In the event oprozomib or pomalidomide is permanently discontinued in Phase 3 only,	… Modifications of the dose of oprozomib/placebo will occur in up to three 30-mg decrements down to a minimum **dose** of 150 mg. Additional reductions will be managed by schedule change. … Treatment guidelines for specific hematologic toxicities are outlined in Section 10.4.2.1.1 and nonhematologic toxicities in Section 10.4.2.1.2. In addition to dose reductions, administration of oprozomib, ~~and~~ pomalidomide, **and dexamethasone** may be temporarily interrupted for a maximum of 4 weeks in the event of a treatment-related toxicity. … If dexamethasone dosing is permanently stopped due to toxicity in accordance with the dose modification guidelines described in Table 15, the subject should stay on oprozomib and/or pomalidomide, depending on the arm to which they are randomized, and continue to follow protocol required therapy, procedures, and assessments. **Subjects may continue to take antiemetic doses of dexamethasone (4 mg) on days**	Corrected text and rearranged text for clarity

Section(s)	Changed from	Changed to	Rationale
	dexamethasone may be continued. Subjects may continue to take antiemetic doses of dexamethasone (4 mg) on days of oprozomib dosing at the investigator's discretion.	**of oprozomib dosing, if tolerated, at the investigator's discretion.** In the event oprozomib or pomalidomide is permanently discontinued in Phase 3 only, dexamethasone may be continued. ~~Subjects may continue to take antiemetic doses of dexamethasone (4 mg) on days of oprozomib dosing at the investigator's discretion.~~	
Section 10.4.2.1.1 Hematologic Toxicities	Additional guidance regarding hematologic toxicities and dosing actions is as follows: • To initiate a new cycle of pomalidomide, the neutrophil count must be at least 500 per mcL and the platelet count must be at least 50,000 per mcL. If toxicities occur after dose reductions to 1 mg, then discontinue pomalidomide. • 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 after discussion with the Onyx study medical monitor. No more than 3 dose reductions down to a minimum of 150 mg will be permitted for an individual subject on study and additional reductions will be managed by schedule change. If toxicity continues, oprozomib should be discontinued.	Additional guidance regarding hematologic toxicities and dosing actions is as follows: • To initiate a new cycle of pomalidomide, the neutrophil count must be at least 500 per mcL and the platelet count must be at least 50,000 per mcL. If toxicities **continue to** occur after dose reductions to **down** 1 mg, then discontinue pomalidomide. • 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 **of oprozomib** may be permitted after discussion with the Onyx study medical monitor. No more than 3 dose reductions down to a minimum of 150 mg will be permitted for an individual subject on study and additional reductions will be managed by schedule change. If toxicity continues, oprozomib should be discontinued.	Added text for clarity
Section 10.4.2.1.2 Nonhematologic Toxicities – Table 14	Symptom: Grade 4 GI Hemorrhage	*Added the following to the table:* **Symptom: Grade 1 or 2 GI hemorrhage** **Findings: Assessed as oprozomib-related** **Oprozomib Dosing Action:** • **DELAY until Grade 0** • **DECREASE one dose level for Grade 2** **Pomalidomide Dosing Action: Full dose at**	Additional text has been added to the dose modification table for nonhematologic toxicities and guidance to investigators to potentially reduce the risk for GI hemorrhage

Section(s)	Changed from	Changed to	Rationale
		physician discretion *Changed to:* Symptom: Grade **3 or** 4 GI Hemorrhage	
Section 10.4.2.1.2 Nonhematologic Toxicities	Additional guidance regarding nonhematologic toxicities and dosing actions is as follows: • Nontreatment-related events: If the toxicity resolves to ≤ Grade 1 or baseline and the toxicity is not treatment-related, oprozomib may be restarted at the same dose level. • If the subject tolerates the reduced dose for 1 cycle, the subject's dose may be re-escalated to the dose being taken prior to the dose reduction. • If required by continued or recurrent toxicity, a second or third dose reduction may be permitted after discussion with the Onyx study medical monitor. No more than 3 dose reductions down to a minimum of 150 mg will be permitted for an individual subject on study and additional reductions will be managed by schedule change. If toxicity continues, oprozomib should be discontinued. • Subjects who develop Grade 4 GI hemorrhage should not be rechallenged with oprozomib. Oprozomib should be permanently discontinued.	Additional guidance regarding nonhematologic toxicities and dosing actions is as follows: • Nontreatment-related events: If the toxicity resolves to ≤ Grade 1 or baseline and the toxicity is not treatment-related, oprozomib may be restarted at the same dose level • If the subject tolerates the reduced dose for 1 cycle, the subject's dose may be re-escalated to the dose being taken prior to the dose reduction • If required by continued or recurrent toxicity, a second or third dose reduction **of oprozomib** may be permitted after discussion with the Onyx study medical monitor. No more than 3 dose reductions down to a minimum of 150 mg will be permitted for an individual subject on study and additional reductions will be managed by schedule change. If toxicity continues, oprozomib should be discontinued. • Subjects who develop Grade **3 or** 4 GI hemorrhage should not be rechallenged with oprozomib. Oprozomib should be permanently discontinued. Endoscopy should be strongly considered for any subject with GI hemorrhage.	Added text for clarity and to reflect change in dose modification guidelines for GI hemorrhage
Section 10.6.1.2 Antinausea and Antiemetics	It is strongly recommended that subjects be premedicated with a 5-HT_3 inhibitor, such as ondansetron or granisetron, prior to administration of the first dose of oprozomib each day and throughout the day as needed to prevent nausea and vomiting. If nausea/vomiting at any grade persists, aprepitant is recommended if needed. Additional antiemetics may	It is strongly recommended that subjects be premedicated with a 5-HT_3 inhibitor, such as ondansetron or granisetron, prior to administration of the first dose of oprozomib each day and throughout the day as needed to prevent nausea and vomiting. If nausea/vomiting at any grade persists, aprepitant **or fosaprepitant** is recommended. Additional	Added "or fosaprepitant" for consistency with other oprozomib protocols to allow IV administration of this antiemetic if needed

Section(s)	Changed from	Changed to	Rationale
	be used if needed per investigator discretion.	antiemetics may be used per investigator discretion.	
Section 10.6.1.5 Acid-related Medications	Lansoprazole or another oral proton-pump inhibitor is recommended for the duration of treatment to prevent peptic disease or other GI disorders.	Lansoprazole or another oral proton-pump inhibitor is ~~recommended~~ **required (unless subject has intolerance or hypersensitivity)** for the duration of treatment to prevent peptic disease or other GI toxicities.	Revised text for consistency with other oprozomib protocols and to potentially reduce the risk for GI hemorrhage
Section 10.6.1.7 Tumor Lysis Syndrome	Tumor Lysis Syndrome Laboratory Abnormalities Subjects with laboratory abnormalities prior to dosing that are consistent with lysis of tumor cells (e.g., as defined by increases in at least 3 of the following 4 categories: [1] a 2-fold increase of lactate dehydrogenase above the ULN; [2] increases in serum creatinine, uric acid, or phosphorus > 50% over baseline; [3] potassium > 30% above the ULN; or [4] calcium decreases from baseline of > 20% in the absence of concomitant bisphosphonate therapy) (Sezer 2006) should not receive the scheduled dose prior to institution of the aforementioned preventive measures.	Tumor Lysis Syndrome Laboratory Abnormalities Subjects with laboratory abnormalities prior to dosing that are consistent with lysis of tumor cells (e.g., as defined by **abnormalities** ~~increases~~ in at least 3 of the following 4 categories: [1] a 2-fold increase of lactate dehydrogenase above the ULN; [2] increases in serum creatinine, uric acid, or phosphorus > 50% over baseline; [3] potassium > 30% above the ULN; or [4] calcium decreases from baseline of > 20% in the absence of concomitant bisphosphonate therapy) (Sezer 2006). **Subjects** ~~should~~ **must** not receive the scheduled dose prior to institution of the aforementioned preventive measures.	Revised as corrections and for consistency with other oprozomib protocols
Section 10.6.1.8 Orthostatic Hypotension	_	**10.6.1.8 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. An etiology should be sought for the orthostatic hypotension to determine its cause is neurogenic, non-neurogenic or iatrogenic. Dose modifications should be taken in accordance with Table 13 and Table 14.** • **For those subjects with orthostatic hypotension who are taking antihypertensives, 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**	Added additional guidance for subjects who may experience orthostatic hypotension.

Section(s)	Changed from	Changed to	Rationale
		subject is getting appropriate hydration in accordance with protocol requirements of 6–8 eight ounce glasses of fluids in the 24−48 hours prior to dosing and on every day 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 per investigator discretion, such as increased oral intake, florinef or midodrine, others depending on the etiology. Holding the dose and dose reduction upon resolution may be a consideration.** • **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 (Appendices A1, A2, B1, B2, C1, and C2)**	
Section 10.6.2 Optional and Allowed Concomitant Medications	• Additional antiemetics that are not required may be used as well as antidiarrheal agents as necessary	• Additional antiemetics ~~that are not required may be used as well as~~ antidiarrheal agents, **and/or laxatives** as necessary	Removed extraneous text, and added "and/or laxatives" for consistency with other oprozomib protocols
Section 10.6.3 Excluded Concomitant Medications	Other antimyeloma agents are not permitted prior to the subject developing confirmed progressive disease.	Other antimyeloma **or investigational** agents are not permitted prior to the subject developing confirmed progressive disease.	Added text for clarity
Section 11.1.1 Vital Signs	Vital signs will include measurement of orthostatic blood pressure, pulse rate, and temperature. Subjects should lie down for 5 minutes and then have blood	**All v**ital sign~~s~~ **assessments** will include measurement of orthostatic blood pressure, pulse rate, **respiration rate,** and temperature. Subjects should lie down for	Revised text for consistency with other oprozomib protocols

Section(s)	Changed from	Changed to	Rationale
	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 mmHg systolic, 10 mmHg diastolic or lightheadedness/dizziness between supine and standing blood pressures would indicate orthostatic hypotension. Usually an increase in pulse of 10 beats/min is associated with but not required for identification of orthostatic hypotension. Subject's dosage and use of antihypertensive agents in the setting of orthostatic hypotension should be evaluated and reassessed on an ongoing basis while on study. Fluid intake should be assessed to confirm the subject is acting in accordance with protocol requirements. Re-education should occur if subject is not adhering to protocol requirements. Fluid status should be repleted to normal levels. If protocol requirements for oral intake of fluids are already being met, additional measure should be taken to increase volume status per investigator discretion. Ongoing monitoring of fluid status is warranted and should also be managed per investigator discretion. In addition, vital signs monitoring may be extended beyond the time periods specified in the Schedules of Assessments (Appendices A1, A2, B1, B2, C1, and C2) as needed.	5 minutes and then have blood pressure and pulse measured **consistently in either arm**. **Following the supine blood pressure/pulse reading,** ~~This should be followed by having~~ the subject **should** stand and the blood pressure and pulse should be repeated **after** ~~at~~ 1 and 3 minutes. Any drop of 20 mmHg systolic, 10 mmHg diastolic or lightheadedness/dizziness between supine and standing blood pressures would indicate orthostatic hypotension. Usually an increase in pulse of 10 beats/min is associated with but not required for identification of orthostatic hypotension. **For time points where PK and vital signs are to be done together, vital signs should be obtained first as the act of phlebotomy may impact vital sign measurement results.** ~~Subject's dosage and use of antihypertensive agents in the setting of orthostatic hypotension should be evaluated and reassessed on an ongoing basis while on study. Fluid intake should be assessed to confirm the subject is acting in accordance with protocol requirements. Re-education should occur if subject is not adhering to protocol requirements. Fluid status should be repleted to normal levels. If protocol requirements for oral intake of fluids are already being met, additional measure should be taken to increase volume status per investigator discretion. Ongoing monitoring of fluid status is warranted and should also be managed per investigator discretion. In addition, vital signs monitoring may be extended beyond the time periods specified in the Schedules of Assessments (Appendices A1, A2, B1, B2, C1, and C2) as needed.~~	
Section 11.3 Disease Response Assessments	… Disease response and progression assessments include: • Serum protein electrophoresis (SPEP) • Urine protein electrophoresis (UPEP) • Serum immunofixation, serum free light chain	… Disease response and progression assessments include: • Serum protein electrophoresis (SPEP) • Urine protein electrophoresis (UPEP) • Serum immunofixation, serum free light chain	Separated bullet points for clarity; revised text to reflect updated Schedules of Assessment

Section(s)	Changed from	Changed to	Rationale
	(SFLC) • Urine immunofixation • Serum calcium, bone marrow sample as clinically indicated to confirm CR • Radiographic assessments including plasmacytoma evaluation if baseline assessments were positive and as clinically indicated per the response criteria • Skeletal survey if baseline assessments were positive and as clinically indicated per the response criteria Serum protein electrophoresis and immunofixation assessments will be conducted according to the schedule outlined in Appendices A1, A2, B1, B2, C1, and C2, Schedule of Assessments. Immunofixation will only be required after Screening and End of Study Treatment, if results of the previous SPEP are zero/undetectable. Urine protein electrophoresis and immunofixation will be performed on a 24-hour urine specimen collected from all subjects during the Screening period and at the End of Study Treatment visit. The UPEP with 24-hour urine collection will be conducted according to the schedule outlined in Appendices A1, A2, B1, B2, C1, and C2, Schedule of Assessments, and is required: 1) only if Screening UPEP was ≥ 200 mg/24 hours, and 2) to confirm a disease response or disease progression. If the Screening UPEP was negative, spot urine is required at each time point. If positive for paraprotein, a 24-hour urine collection with UPEP must be done at the next assessment and at each subsequent assessment unless the UPEP shows an absence of paraprotein. Serum free light chain assay and kappa:lambda (K/λ) ratio will be conducted according to the schedule	(SFLC) • Urine immunofixation • Serum calcium~~, bone marrow sample as clinically indicated to confirm CR~~ • **Bone marrow sample as clinically indicated to confirm CR** • Radiographic assessments including plasmacytoma evaluation if baseline assessments were positive and as clinically indicated per the response criteria • Skeletal survey if baseline assessments were positive and as clinically indicated per the response criteria Serum protein electrophoresis and immunofixation assessments will be conducted according to the schedule outlined in Appendices A1, A2, B1, B2, C1, and C2, Schedule of Assessments. Immunofixation will only be required after Screening**, Baseline (Day -7 to 1),** and End of Study Treatment, if results of the previous SPEP are zero/undetectable. Urine protein electrophoresis and immunofixation will be performed on a 24-hour urine specimen collected from all subjects during the Screening period**, Baseline (Day -7 to 1),** and at the End of Study Treatment visit. The UPEP with 24-hour urine collection will be conducted according to the schedule outlined in Appendices A1, A2, B1, B2, C1, and C2, Schedule of Assessments, and is required: 1) only if ~~Screening~~ **Baseline** UPEP was ≥ 200 mg/24 hours, and 2) to confirm a disease response or disease progression. If the ~~Screening~~ **Baseline** UPEP was negative, spot urine is required at each time point. If positive for paraprotein, a 24-hour urine collection with UPEP must be done at the next assessment and at each subsequent assessment unless the UPEP shows an absence of	

Section(s)	Changed from	Changed to	Rationale
	outlined in the Schedule of Assessments, Appendices A1, A2, B1, B2, C1, and C2. Only in subjects without measurable serum and urine M-protein levels (serum M-protein < 0.5 g/dL or urine M-protein < 200 mg/24 hours) at Screening will SFLC assays be used to determine eligibility and response. In subjects with measurable SPEP and/or UPEP, SFLC may be used in conjunction with those assessments to determine response per disease response criteria but only SPEP and/or UPEP will be used to determine eligibility.	paraprotein. Serum free light chain assay and kappa:lambda (K/λ) ratio will be conducted according to the schedule outlined in the Schedule of Assessments, Appendices A1, A2, B1, B2, C1, and C2. Only in subjects without measurable serum and urine M-protein levels (serum M-protein < 0.5 g/dL or urine M-protein < 200 mg/24 hours) at ~~Screening~~ **Baseline** will SFLC assays be used to determine eligibility and response. In subjects with measurable SPEP and/or UPEP, SFLC may be used in conjunction with those assessments to determine response per disease response criteria but only SPEP and/or UPEP will be used to determine eligibility.	
Section 11.3 Disease Response Assessments	… All response categories (CR, sCR, VGPR, PR, MR, PD) 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. All subjects will be followed until disease progression (confirmed by 2 consecutive measurements that are also verified by the Onyx medical monitor prior to treatment discontinuation), unacceptable toxicity, or withdrawal of consent, whichever occurs first. Disease progression will be determined using the IMWG-URC (Appendices A1, A2, B1, B2, C1, and C2). Serum M component increases of ≥ 1.0 g/dL are sufficient to define progression if the starting component is ≥ 0.5 g/dL according to these criteria. However, it is understood from these criteria that a single measurement is adequate in cases of clear increased bone marrow plasma cell percentage, development of new or worsened bone lesions from a skeletal survey, or development of new or worsened soft tissue plasmacytomas.	… All response categories (CR, sCR, VGPR, PR, MR, PD) 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.~~ All subjects will be followed until disease progression (confirmed by 2 consecutive measurements that are also verified by the Onyx medical monitor prior to treatment discontinuation), unacceptable toxicity, or withdrawal of consent, whichever occurs first. Disease progression will be **determined and confirmed with the medical monitor by two consecutive assessments** using the IMWG-URC (Appendices A1, A2, B1, B2, C1, and C2). Serum M component increases of ≥ 1.0 g/dL are sufficient to define progression if the starting component is ≥ 0.5 g/dL according to these criteria. However, it is understood from these criteria that a single measurement is adequate in cases of clear increased bone marrow plasma cell percentage, development of new or worsened bone lesions from a skeletal survey, or development of new or worsened soft tissue	Revised text for clarification of the requirements for the assessment of disease disease progression

Section(s)	Changed from	Changed to	Rationale
		plasmacytomas.	
Section 11.4.3 Genomic Measurements	Whole genome sequencing (WGS), whole exome sequencing (WES), and/or whole transcriptome sequencing will be conducted on isolated tumor ($CD138^+$) cells from bone marrow samples taken at Screening and disease progression. In addition, WGS or WES will be performed on a normal tissue sample (e.g., saliva, $CD3^+$ T-cells, or isolated PBMCs) in order to determine the presence of somatic mutations in tumor cell samples. Data will be analyzed to examine specific hypotheses about whether drug response is related to alterations in genes regulated by or involved in activation of nuclear factor kappa light chain enhancer of activated B cell (NF-κB) transcription factors as well as genes involved in immunoglobulin production and plasma cell protein homeostasis. These data will also be used to derive new hypotheses about mechanisms of drug response, resistance, and safety.	Whole genome sequencing (WGS), whole exome sequencing (WES), ~~and/or~~ 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 Screening and disease progression. In addition, WGS or WES will be performed on a normal tissue sample (e.g., saliva **or peripheral blood**~~, $CD3^+$ T-cells, or isolated PBMCs~~) in order to determine the presence of somatic mutations in tumor cell samples. Data will be analyzed to examine specific hypotheses about whether drug response is related to alterations in genes regulated by or involved in activation of nuclear factor kappa light chain enhancer of activated B cell (NF-κB) transcription factors as well as genes involved in immunoglobulin production and plasma cell protein homeostasis. **Immunoglobulin levels in tumor cells will be quantified by enzyme-linked immmunosorbent assay (ELISA) and/or other protein quantification methods.** These data will also be used to derive new hypotheses about mechanisms of drug response, resistance, and safety.	Added text for clarity and consistency with other oprozomib protocols
Section 11.5 Quality of Life Assessments	-	*Added subsection:* **11.5 Patient-Reported Outcomes Assessments** **Beginning with Cycle 1, HRQoL/PRO assessments are to be completed at the beginning of every cycle prior to drug administration through End of Study Treatment/Early Discontinuation visit during the dose-expansion portion of the trial, and at the beginning of every cycle prior to drug administration through End of Study Treatment/Early Discontinuation visit and then every 12 weeks during the long-term follow-up in the Phase 3 portion of the study. The HRQoL/PRO**	Added subsection to further clarify the quality of life assessments to be performed in the dose-expansion and Phase 3 portions of the study

Section(s)	Changed from	Changed to	Rationale
		assessments include: • **BPI-SF (see Appendix N for a sample Brief Pain Inventory – Short Form)** • **EORTC QLQ-C30 (Appendix E)** • **EORTC QLQ-MY20 (Appendix E)** • **Neurotoxicity subscale of the FACT/GOG-Ntx4 (Appendix F)** • **EQ-5D-5L (Appendix G)**	
Section 12 Study and Study Treatment Discontinuation	… An individual subject who discontinues study treatment for PD is considered to have completed the study after the safety follow-up visit. …	… An individual subject who discontinues study treatment for PD **will be followed for OS in long-term follow-up** ~~is considered to have completed the study after the safety follow-up visit~~. …	Revised text for clarity
Section 12.1 Study Treatment Discontinuation	… Subjects who discontinue from study treatment will be monitored for AEs for 30 days after the last dose of oprozomib or before the start of subsequent anticancer treatment (whichever occurs first). Treatment discontinuation due to progression should be recorded on the Treatment/Discontinuation eCRF as "Disease Progression." Onyx Therapeutics, or designee must be notified within 24 hours if a subject is withdrawn from treatment for any reason (i.e., disease progression, toxicity, etc.). Disease progression must be confirmed by the medical monitor **before** any subject is discontinued from study treatment.	… Subjects who discontinue from study treatment will be monitored for AEs for 30 days after the last dose of oprozomib or **immediately** before the start of subsequent anticancer treatment (whichever occurs first). Treatment discontinuation due to progression should be recorded on the **Study Drug Completion** ~~Treatment~~/Discontinuation eCRF as "Disease Progression." Onyx Therapeutics, or designee must be notified within 24 hours if a subject is withdrawn from treatment for any reason (i.e., disease progression, toxicity, etc.). Disease **progression with 2 consecutive disease assessments** must be confirmed by the medical monitor **before** any subject is discontinued from study treatment.	Corrected text and revised text for clarification of the requirements for the duration of AE collection
Section 12.2 Study Discontinuation	The sponsor, Onyx Therapeutics, Inc., may elect to discontinue the study at any time. Each subject will be followed until death or study closure. The reason for	~~The sponsor, Onyx Therapeutics, Inc., may elect to discontinue the study at any time.~~ Each subject will be followed until death or study closure. The reason for	Deleted text as it was in the inappropriate location in the protocol

Section(s)	Changed from	Changed to	Rationale
	discontinuation from the study will be documented on the eCRF. …	discontinuation from the study will be documented on the eCRF. …	
Section 12 Study and Study Treatment Discontinuation Section 12.3 Long-Term Follow-up	Long-Term Follow-up After completion of the post treatment visit, subjects will be followed for disease and survival status by telephone contact or other method every 3 months in addition to disease assessments. Long-term follow-up will continue until the subject has withdrawn consent for further participation, is lost to follow-up, has died, or the sponsor makes a decision to close the study. For any subject who is lost to follow-up, the study site will attempt to ascertain survival information via public database search. Informed consent to obtain these data will be obtained from subjects at the time of enrollment.	Long-Term Follow-up After completion of the ~~post treatment~~ **End of Study Treatment** visit, subjects will be followed for disease **progression, OS, and quality of life (QOL).** ~~and survival status by telephone contact or other method every 3 months in addition to disease assessments.~~ **Subjects will be followed based on their disease progression status at End of Study Treatment.** **Progression and Overall Survival** • **For subjects who have not progressed at end of study treatment, disease response assessments will be performed every 4 weeks through 18 months on study, and then every 8 weeks thereafter, beginning with Month 20, until progression or initiation of next therapy** • **Subjects who progressed at end of study treatment or long-term follow-up will be followed for survival status approximately every 3 months, or as needed** **Quality of Life** **For Phase 3 only, in long-term follow-up, QOL questionnaires will be collected from subjects (regardless of disease status) every 12 weeks.** Long-term follow-up will continue until the subject has withdrawn consent for further participation, is lost to follow-up, has died, or the sponsor makes a decision to close the study. For any subject who is lost to follow-up, the study site will attempt to ascertain survival information via public database search. ~~Informed consent to obtain these data will be obtained from subjects at the time of enrollment.~~	Added "on study" and additional text for clarity on the long-term follow-up based on disease progression status

Section(s)	Changed from	Changed to	Rationale
Section 12.4 Study Termination	Onyx has the right to terminate this study or a study site from participating in a study at any time. …	Onyx has the right to terminate this study**, either schedule,** or a study site from participating in a study at any time. …	Added text to provide flexibility in terminating either schedule
Section 14.2 Analysis of the Conduct of the Study	Enrollment, subject disposition, study treatment administration, and discontinuation from the study will be summarized. Eligibility exceptions and major protocol deviations will be summarized.	Enrollment, subject disposition, study treatment administration, and discontinuation from the study will be summarized. Eligibility exceptions and ~~major~~ **important** protocol deviations will be summarized.	Revised to match ICH E3 Guidance
Section 14.3 Data Monitoring Committee	In Part 1 of the study, safety will be monitored by a CSRC for both the Phase 1b **dose-escalation** and **dose-e**xpansion portions of the study. In the Phase 3 portion of the study, no formal efficacy interim analyses are planned for the PFS primary endpoint. An interim analysis of OS**,**—the key secondary endpoint**,**—is planned at the time of primary analysis of PFS. **Details of the monitoring plan for OS are described in Section 14.5.2.2.** Overall survival may ~~also~~ be evaluated ~~without penalty~~ by the DMC in their **ongoing safety** review of ~~benefit-risk~~ during the course of the study. ~~Details of the monitoring plan for OS are described in Section 14.5.2.2.~~ **As the objective of this evaluation is not to declare OS efficacy before the planned efficacy interim and final analyses of OS, alpha level will not be adjusted for these reviews.** An independent DMC will be convened for ~~this~~ **the Phase 3 portion of the** study and will act in an advisory capacity to the sponsor with respect to safeguarding the interests of study subjects, assessing interim safety and efficacy (OS secondary only) data, and for monitoring the overall conduct of the study. To enhance the integrity of the study, the DMC may also formulate recommendations relating to the selection, recruitment, and retention of subjects, management of subjects, improving adherence to protocol treatment, and the procedures for data management and quality control. The DMC will meet to review safety data on a periodic basis, but no less frequently than approximately every 6 months. The initial meeting should occur within 3 months after approximately 30 subjects are enrolled in the Phase 3 ~~part~~ **portion** of the study. Unplanned safety review meetings of the DMC may be called at any time by the sponsor or the DMC Chair if additional review of safety data is warranted. The membership criteria and other details of the DMC will be described in the DMC Charter.		Revised text for clarity
Section 14.4 Analysis of Treatment Group Comparability	Descriptive statistics will be used to summarize baseline subject characteristics, treatment administration, efficacy, and safety outcomes. Summaries of discrete data will include number of subjects and incidence as a frequency and as a percentage. Summaries of continuous data will include	Descriptive statistics will be used to summarize baseline subject characteristics~~, treatment administration, efficacy, and safety outcomes~~. Summaries of discrete data will include number of subjects and incidence as a frequency and as a percentage. Summaries of continuous data will include	Corrected text

Section(s)	Changed from	Changed to	Rationale
	mean, standard deviation, median, minimum, maximum, and sample size.	mean, standard deviation, median, minimum, maximum, and sample size.	
Section 14.4.1 Treatment Exposure and Medication Compliance	… The average relative dose intensity for each treatment group will be calculated by summarizing the average relative dose intensity for individual subjects. These results will be provided to determine the presence of any major differences between the treatment groups for the planned versus actual dose and schedule of pomalidomide and dexamethasone administered. For each subject, a compliance measure will be calculated based on the information provided in the CRFs. Compliance will be defined as the percentage of the actual number of days with treatment intake over the expected number of days with treatment intake. Summary statistics will be provided on percent compliance by treatment group.	… The average relative dose intensity for each treatment group will be calculated by summarizing the average relative dose intensity for individual subjects. ~~These~~ **The** results **for pomalidomide and dexamethasone** will be provided to determine the presence of any major differences between the treatment groups for the planned versus actual dose and schedule of ~~pomalidomide and dexamethasone administered~~ **these two (2) study medications.** ~~For each subject, a compliance measure will be calculated based on the information provided in the CRFs. Compliance will be defined as the percentage of the actual number of days with treatment intake over the expected number of days with treatment intake. Summary statistics will be provided on percent compliance by treatment group.~~	Revised text for clarity and as corrections
Section 14.5.1.1 Safety Population	All subjects receiving any amount of study treatment (oprozomib, pomalidomide, or dexamethasone) will be included in safety analyses.	All subjects receiving any amount of study treatment (oprozomib, **placebo,** pomalidomide, or dexamethasone) will be included in safety analyses.	Corrected text by adding "placebo"
Section 14.5.2 Efficacy Analyses	All efficacy analyses will be presented separately for Part 1 and Part 2 of the study. <u>Part 1: Phase 1b Dose Escalation and **Dose-**Expansion Portions of the Study</u> Overall response rate is defined as the proportion of subjects with a best ~~overall~~ response of sCR, CR, VGPR, or PR as determined by investigator according to the IMWG-URC. Clinical benefit rate ~~(CBR)~~ is defined as ~~a~~ **the proportion of subjects with a best response of** PR or better according to IMWG-URC or a best response of MR according to the EBMT criteria, as determined by the investigator. A point **estimate** and 95% exact binomial confidence interval (CI) will be calculated for both ORR and CBR for all subjects treated at the RP3D (during **dose** escalation and expansion for each schedule). A descriptive summary of ORR and responses will also be provided by dose cohort. ~~Response assessment data~~ **Progression-free survival and DOR** will be listed for all subjects in the efficacy population by dose cohort level **and schedule**. <u>Part 2: Randomized Phase 3 Portion of the Study</u>		Revised for clarity and as corrections

<table>
<tr><th>Section(s)</th><th>Changed from</th><th>Changed to</th><th>Rationale</th></tr>
<tr><td></td><td colspan="2">Unless otherwise noted, all primary and secondary efficacy analyses will include all randomized subjects analyzed according to the ITT ~~analysis~~ principle (Section 14.5.1), i.e., subjects will be ~~grouped~~ analyzed by the treatment assigned at randomization.
<u>Primary Efficacy Analysis</u>
The primary efficacy endpoint for the Phase 3 portion of the study is PFS, defined as the time from randomization to the earlier of disease progression or death due to any cause. Disease progression will be determined using the IMWG-URC (Appendix D). Response and disease progression will be determined using a validated computer algorithm (ORCA) as well as by local investigators. The primary analysis of PFS will be based on ORCA-assessed outcomes. The PFS outcomes assessed by the investigators will serve as a supportive analysis of the primary analysis of PFS.
For purposes of calculating PFS, the start date for PD is the date at which progression is first observed. The duration of PFS will be right-censored according to the conventions described in Table 18
Table 18 Date of Progression or Censoring for Progression-free Survival
<table>
<tr><th>Situation</th><th>Date of Progression or Censoring</th><th>Outcome</th></tr>
<tr><td>No baseline disease assessments</td><td>Date of randomization</td><td>Censored</td></tr>
<tr><td>No postbaseline disease assessments and alive</td><td>Date of randomization + 1 day</td><td>Censored</td></tr>
<tr><td>New anticancer treatment started before documentation of PD or death</td><td>Date of last disease assessment prior to start of a new anticancer treatment</td><td>Censored</td></tr>
<tr><td>Death or PD immediately after more than 1 consecutively missed disease assessment visit</td><td>Date of last disease assessment visit without documentation of PD that is before the first missed visit</td><td>Censored</td></tr>
<tr><td>Alive and without PD documentation</td><td>Date of last disease assessment</td><td>Censored</td></tr>
<tr><td>Death or PD between planned disease assessments</td><td>Date of death or first disease assessment showing PD, whichever occurs first</td><td>Progressed</td></tr>
<tr><td>Death before first disease assessment</td><td>Date of death</td><td>Progressed</td></tr>
</table>
PD = progressive disease.

The primary analysis of PFS will be conducted ~~after approximately~~ when 157 PFS events have occurred.</td><td></td></tr>
</table>

Section(s)	Changed from	Changed to	Rationale
	~~The hypothesis to be tested is as given below:~~ ~~H_0: PFS (Pomd) = PFS (OPomd)~~ ~~H_a: PFS (Pomd) < PFS (OPomd)~~ The primary inferential comparison between treatment groups **for PFS** will be based on the stratified log-rank test at an overall 0.025 (1-sided) significance level using randomization stratification factors **as strata**: • Age: < 75 years versus ≥ 75 years • Number of prior therapies: 2 versus 3 or more • Carfilzomib status: carfilzomib-naïve/**sensitive** versus carfilzomib-~~sensitive~~ **refractory** The hazard ratio between the 2 treatment arms will be estimated using a stratified Cox proportional hazards model. The distribution of PFS ~~times~~, **including medians,** will be summarized descriptively using the Kaplan-Meier method~~. Median PFS will be~~ estimated for each treatment group ~~from the 50th percentile of the corresponding Kaplan-Meier estimates.~~ The 95% CI**s** for median **and other quartiles of** PFS will be constructed using the method of Brookmeyer **and Crowley** (1982). Duration of follow-up for PFS will be estimated by the reverse Kaplan-Meier method of Schemper (1996). Secondary Efficacy Analyses ~~At the time of the primary PFS analysis, the first of 2 interim analyses that are planned for the key secondary endpoint of OS will also be conducted.~~ Overall survival is defined as the time from randomization to death due to any cause. Subjects who are alive or lost to follow-up as of the data analysis cutoff date will be right censored. The censoring date will be determined from the subject's **last known** date ~~**alive** of last contact or data analysis cutoff date, whichever event occurs first.~~ ~~Determination of the required number of events and timing of analyses for comparison of OS for subjects randomized to treatment with Pomd plus placebo versus those randomized to treatment with OPomd is based upon the following assumptions:~~ ~~The risk of death in subjects randomized to OPomd is 32% lower than that of subjects randomized to Pomd; i.e., the target hazard ratio is 0.68~~ ~~The hypothesis test of interest is:~~ ~~H_o: OS (Pomd) = OS (OPomd)~~ ~~H_a: OS (Pomd) < OS (OPomd)~~ ~~Inference will be made using the log-rank testing procedure.~~ ~~• 1-sided 0.025 level of significance~~ ~~• 75% power~~ ~~• 1 interim and 1 final analysis (30%, 100%)~~		

Section(s)	Changed from	Changed to	Rationale

~~• mOS (Pomd) = 16 months and mOS (OPomd) = 23.5 months~~

~~• Duration of OS is exponentially distributed~~

~~• 10% Lost to Follow-Up at 60 months~~

Final analysis of OS will be performed when 211 deaths have occurred. Two hundred and eleven (211) ~~A total of 211~~ deaths will provide 75% power to detect a 32% decrease in the risk of ~~46.9% increase in median~~ OS for OPomd versus Pomd (~~16 vs. 23.5 months~~ **HR = 0.68**) at the 1-sided 0.025 level of significance. **Under exponential distribution, 23.5 months versus 16 months is assumed for median OS for the OPomd and Pomd arms, respectively.** The assumed median OS of 16 months for the Pomd group is based on a Phase 2 study of pomalidomide/dexamethasone (Jagannath 2012). **Under these assumptions, and assuming 10% lost to follow-up for OS at 60 months, 211 deaths are expected to occur approximately 56 months after the study starts.**

The interim analysis for OS will occur at the time of the primary analysis of PFS. The primary analysis of PFS is anticipated to occur approximately 14 months after the first subject is randomized. Approximately 30% of the total number of death events is expected at the time of the primary PFS analysis. The interim and final analysis of OS will be performed using an O'Brien-Fleming group sequential monitoring plan. The monitoring plan will include an upper boundary for benefit constructed using a false-positive error rate of 0.025 (Table 19). The Lan-Demets alpha spending function approach will be used to adjust the O'Brien-Fleming boundary if the actual interim analysis does not correspond to the projected information time.

Table 19 O'Brien-Fleming Monitoring Boundary for Benefit

Information Fraction	Death Events	Study Month	Boundary (Reject H_o)	1-Sided Significance Level	Alpha Spent
30%	63	14	3.929	0.000042	0.000
100%	211	56	1.96	0.025	0.025

Statistical analyses conducted for OS will be identical to those described for PFS. In addition to the key secondary endpoint of OS, ~~secondary efficacy analyses~~ **inferential testing** will be conducted for ORR, CBR, ~~time to~~ improvement in renal function, ~~time to~~ improvement in hemoglobin, change ~~from baseline~~ **over time** in QLQ-MY20 total scale, and change ~~from baseline~~ **over time** in QLQ-C30 total scale.

Inferential testing of **primary and** selected secondary endpoints will be ~~assessed~~ **performed** against an overall 1-sided significance level of 0.025 in accordance with a closed testing procedure (CTP). The CTP will be used to account for inflation of the overall type 1 error rate due to hypothesis testing of multiple ~~secondary~~ endpoints.

The CTP will be structured as follows: If the null hypothesis for the primary efficacy endpoint of PFS is rejected

Section(s)	Changed from	Changed to	Rationale
	at the 1-sided 0.025 level of significance, then testing of the aforementioned secondary endpoints will proceed in a sequential step-down manner. ~~The nominal level of significance at interim analysis will be as presented above in Table 19, consistent with the monitoring plan for the key secondary endpoint of OS.~~ Testing of **selected** secondary efficacy endpoints will continue, provided the null hypothesis for each previously tested endpoint is rejected. Otherwise, no further testing will be done. The sequential order in which ~~secondary~~ efficacy endpoints will be tested is as follows: • **PFS** • OS • ORR • CBR • ~~Time to~~ **I**mprovement in renal function • ~~Time to~~ **I**mprovement in hemoglobin • Change ~~from baseline~~ **over time** in QLQ-C30 global health scale • Change ~~from baseline~~ **over time** in QLQ-MY20 disease symptoms subscale Overall response rate will be estimated based on the proportion of subjects in each treatment group who achieve sCR, CR, VGPR, or PR as their best response across the entire treatment duration. The inferential comparison between treatment groups for this endpoint will be made using the Cochran-Mantel Haenszel chi-square test, stratified by the randomization stratification factors. Approximate 95% CI**s** will be calculated by treatment group for the true ORR. An estimate of the common odds ratio for ~~the odds of~~ overall response will be provided as a measure of the relative treatment effect. The odds ratio (and 95% CI) will be estimated using the Mantel-Haenszel method. The Pomd ~~plus placebo arm~~ **group** will serve as the reference treatment group in the calculation of the odds ratio. ~~Homogeneity of the odds ratio across randomization strata will be examined at a significance level of 0.05 by the Breslow-Day test.~~ Clinical benefit rate ~~(CBR)~~ will be estimated based on the proportion of subjects in each group who achieve sCR, CR, VGPR, PR, or MR and will be analyzed in the same manner as described previously for ORR. Improvement in renal function is defined as an increase in glomerular filtration rate (GFR) of ~~at least~~ ≥ 10 mL/min. Improvement in hemoglobin is defined as an increase of ≥ 2g/dL. ~~Inferences for time to~~ **Incidence of i**mprovement in renal function and **improvement in** hemoglobin will ~~parallel those for the other time-to-event outcomes of PFS and OS.~~ **be analyzed in the same manner as described previously for ORR.** ~~The Kaplan-Meier methodology~~ **Duration of response and DOCB** will ~~also be used for estimating median DOR.~~ **be summarized for each treatment group by Kaplan-Meier method; however n**o formal inferential		

Section(s)	Changed from	Changed to	Rationale
	comparisons ~~of DOR~~ will be made, as responders constitute a nonrandom subset of the ITT population.…		
Section 14.5.3 Safety Analyses	The safety population will be used in all safety analyses (see Section 14.5.1.1). Results of safety analyses will be presented separately for Part 1 and Part 2 of the study. Part 1: Phase 1b Dose Escalation and **Dose-**Expansion Portions of the Study For the Phase 1b portion of the study, safety **data will be summarized for each cohort and for the pooled cohorts. Safety** will be assessed through summaries of DLTs, AEs, changes in laboratory test results, ECGs, vital signs, and oprozomib, pomalidomide, and dexamethasone exposure. ~~All AE data collected will be listed by study site, cohort, subject number, and cycle day.~~ Part 2: Randomized Phase 3 Portion of the Study For the Phase 3 portion of the study, safety data will be summarized grouped according to treatment actually received. ~~For both Part 1 and Part 2 of the study, safety analyses will include all AEs occurring on or after treatment on Cycle 1 Day 1. Summaries of AEs will include number and percentage of subjects experiencing 1 or more AEs, relationship to study drug, and severity.~~ Treatment-emergent AEs are defined as AEs that start on or after the first day study treatment is administered and within 30 days of the last administration of study treatment or before start of subsequent anticancer treatment (whichever occurs first). **Treatment-emergent AEs** ~~Adverse events~~ will be summarized by the number and percentage of subjects who experienced the event, according to system organ class and preferred term. A subject experiencing multiple instances of the same AE will be counted once within each system organ class and similarly counted once within each preferred term. ~~These conventions will be appropriately modified to calculate AE incidence rates separately for each cycle that study therapy is administered.~~ Adverse event incidence rates may also be calculated based on other measures of subject exposure (e.g., total number of treatment cycles administered). Adverse events will also be summarized by NCI-CTCAE **V**ersion 4.03 severity grade and by relationship to each study drug. For AEs not adequately addressed by NCI-CTCAE version 4.03, the severity grading described in Table 17 may be used. Additional summaries may also be provided for SAEs and events resulting in the permanent discontinuation of therapy. All AEs will be included in individual subject listings. Incidence, severity, and duration of specific signs and symptoms indicative of neuropathy and other neurotoxicities will be assessed. The appropriate terms in these categories will be codified and analyses performed to provide a subject incidence of those with the relevant events. Laboratory parameters will be summarized using descriptive statistics, by postdose shifts **in toxicity grades of select laboratory parameters** relative to baseline, changes from baseline, and data listings of clinically significant abnormalities. The changes in hematology, chemistry, and other laboratory values will be summarized descriptively for each scheduled and unscheduled protocol assessment time point. Changes will be calculated relative to the values collected at baseline and on the first day of each cycle of treatment. The incidence of Grade 3 and 4 hematological toxicities (including neutropenia, thrombocytopenia, and anemia)		Revised for clarity and as corrections

Section(s)	Changed from	Changed to	Rationale
	will be provided by treatment cycle and across all treatment cycles. The use of blood transfusions (platelets, RBC) and/or growth factor support will be **summarized** ~~reported in the Concomitant Medications section. Similar analyses will be done for selected chemistry tests (including liver and renal function tests)~~. Subject listings of all laboratory data collected during the study will be presented. Laboratory values outside normal limits will be identified in the subject listings ~~and will include flags for high and low values~~. Vital sign results (systolic and diastolic blood pressure, pulse, respiration, and temperature) and ECGs will be summarized descriptively ~~for each scheduled and unscheduled protocol time point. Changes will be calculated relative to the assessments at baseline and on the first day of each cycle of therapy~~.		
Section 14.5.4 Subgroup Analyses and Effects of Baseline Factors	To determine whether the treatment effect is consistent across various subgroups, the estimate of the hazard ratio (or odds ratio) for treatment group (with 95% CI) will be provided for the primary and selected secondary efficacy endpoints and plotted within each of the following baseline variables, provided there is a reasonable sample size in the subgroups of interest: • ~~Refractory status: primary refractory versus relapsed, and refractory versus bortezomib intolerant~~ • Number of prior therapies: 2 versus 3 or more (stratification factor) • Age (< 75 years versus ≥ 75 years) (stratification factor) • Prior carfilzomib (naïve/**sensitive** versus ~~sensitive~~ **refractory**) (stratification factor) • **Refractory status:** Primary refractory versus relapsed**-refractory**, ~~and refractory~~ versus bortezomib-intolerant • Refractory to lenalidomide • Refractory to bortezomib **(refractory to lenalidomide and bortezomib)** • Double refractory • FISH risk status: High-risk group versus standard-risk group. ~~The high-risk group consists of the genetic subtypes t(4; 14), t(14;16), and deletion 17p. The standard-risk group consists of all other reported subtypes.~~ • No prior transplant versus prior transplant • Bone marrow infiltration by plasma cells ≤ 50% versus > 50% **at baseline** • Renal function ≤ 60 mL/min versus > 60 mL/min **at baseline** • Age (< 65 years versus ≥ 65 years) • Race (Caucasian versus all others) • Sex (male versus female) • ~~Study center~~		Revised text for clarity, including the potential inclusion of subjects with prior carfilzomib exposure in the study

Section(s)	Changed from	Changed to	Rationale
Section 14.7 Determination of Sample Size	The CSRC will review the data and provide guidance in selection of the RP3D. Therefore the RP3D may differ from the MTD.	The CSRC will review the data and provide guidance in selection of the RP3D. Therefore the RP3D may differ from the MTD, **but will not be higher than the MTD.**	Added text for clarity and for consistency within the protocol
Section 14.7 Determination of Sample Size	Part 2: Randomized Phase 3 Portion of the Study ~~The estimated sample size~~ **F**or the Phase 3 portion of the study ~~is based on comparison of the PFS (death or disease progression events) distributions for subjects treated with Pomd plus placebo versus those treated with OPomd based upon the log-rank test statistic. It is assumed that the PFS risk for subjects randomized to OPomd will be 45.7% lower than for subjects randomized to Pomd. Therefore, the target HR of interest is 0.543. In order to have 95% power with~~ **157 PFS events are required to detect a 45.7% reduction in the risk of PFS (HR = 0.543) with 95% power and a** 1-sided ~~α = 0.025 level of~~ significance **level of 0.025.** ~~for testing no difference in PFS risk versus a 45.7% reduction in risk between the 2 treatments, 157 PFS events are required.~~ Enrollment of 270 subjects (2:1 OPomd versus Pomd, respectively) is consistent with reaching the required 157 events in approximately 14 months, assuming an enrollment rate of approximately 22 subjects per month, a 5% drop-out rate at 18 months, and a median PFS of 3.8 and 7 months for Pomd and OPomd, respectively. Therefore, ~~a~~ **the** total **planned** enrollment ~~of~~ **will be** approximately 352 subjects ~~is planned~~ for the entire study.		Revised text for clarity
Section 16 References	–	**Cleeland CS. The measurement of pain from metastatic bone disease: capturing the patient's experience. Clin Cancer Res. 2006;12(20 Pt 2):6236s–42s.** **Oken MM, Creech RH, Tormey DC, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649–55.** **Onyx Pharmaceuticals. Kyprolis (carfilzomib) for Injection full prescribing information. 2012.**	Added references
Appendix A1, A2, B1, B2, C1, and C2	Appendices updated per body of protocol. See updated appendices for further details.		Removed and added "X"s in the Schedule of Assessment tables and revised text of footnotes for clarity and consistency with the protocol body text
Appendix D	Response Criteria for Multiple Myeloma		Revised text for minor corrections

Section(s)	Changed from	Changed to	Rationale
Appendix M	–	*Added:* **Appendix M ACTG Brief Peripheral Neuropathy Screening Tool**	Added ACTG Brief Peripheral Neuropathy Screening Tool as Appendix M
Appendix N	–	*Added:* **Appendix N Sample Brief Pain Inventory – Short Form**	Added Sample Brief Pain Inventory – Short Form as Appendix N

Document Title:
protocol-OPZ007-a2.docx

Workflow Number:
14118445

UserName: [redacted]
Title: Senior Vice President, Development
Date: Tuesday, 08 July 2014, 07:31 PM Pacific Daylight Time
Meaning: I have reviewed and approved this document.
==========

APPENDIX Q SUMMARY OF CHANGES IN STUDY OPZ007 AMENDMENT 3.0

Study OPZ007 was amended to include the following:

- The Phase 3 portion of the study was never executed; therefore, all text pertaining to the Phase 3 portion of the study was removed.
- Study visits are less frequent with data collection (eg, labs) being pared down to instances of clinical need or adverse event reporting 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. Changes noted in specific sections were also made in the protocol synopsis and elsewhere in the document, as applicable. Significant changes are presented in the table below. Detailed changed text is displayed for first major occurrence only. All affected sections are noted in the "Section(s)" column. Text that has been deleted is presented in strikethrough format. Added text is presented in bold format.

Section(s)	Changed from	Changed to	Rationale
Global	Phase 1b/3	Phase 1b~~/3~~	Removed Phase 3 text to reflect what data was collected for the study
Global	International Conference on Harmonisation (ICH)	International **Council for** Harmonisation (ICH)	Change in regulatory body name
Global	Onyx Drug Safety	**Amgen Global Patient** Safety	New sponsor protocol standard operating procedure (SOP)
Global	Onyx	**Sponsor**	New sponsor protocol SOP
Title page	*New text added*	**NCT Number: NCT01999335**	New protocol SOP
Title page	Onyx Therapeutics 249 East Grand Ave. South San Francisco, CA 94080	Onyx Therapeutics**, Inc.** **One Amgen Center Drive** **Thousand Oaks,** CA 9**1320, USA** **Phone: (805) 447-1000**	Change in sponsor title and contact information

Section(s)	Changed from	Changed to	Rationale
Title page	Study Medical Monitor: [redacted] MD 249 East Grand Avenue Phone: Email: [redacted]	Study Medical Monitor: [redacted] MD **Medical Director, Early Development** **1120 Veterans Blvd** South San Francisco, CA 94080 **USA** **Phone**: Email: [redacted]	Change in responsibilities
Title page	*New text added*	**Amendment 3.0: 07 March 2018**	New amendment identifiers
[Protocol Approval Signature Page]	Protocol Approval Signature Page	[page removed]	New sponsor protocol SOP
Protocol Acceptance Page	Issue/Date: OPZ007 (08 July 2014)	Issue/Date: OPZ007 (**07 March 2018**)	New amendment identifiers
Synopsis (Study objectives)	Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study (by Schedule)	~~Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study (by Schedule)~~	Study is no longer divided into 2 parts

Synopsis (Study objectives) Section 4.2 (Part 2: Randomized Phase 3 Portion of the Study) – Whole Section deleted	Part 2: Randomized Phase 3 Portion of the Study Phase 3 objectives involve comparison of key outcome measures for subjects with primary refractory or relapsed and refractory multiple myeloma who are randomized to either oprozomib or placebo, in combination with pomalidomide and dexamethasone, hereafter denoted by OPomd or Pomd, respectively. Primary Objective • To compare progression free survival (PFS), as determined by Onyx Response Computational Assessment (ORCA) according to the IMWG-URC, between subjects treated with OPomd and those treated with Pomd Secondary Objectives • To compare the following between subjects treated with OPomd and those treated with Pomd: o Overall survival (OS) o Overall response rate (ORR), the clinical benefit rate (CBR), and duration of response (DOR) as determined by ORCA according to the IMWG-URC and modified EBMT criteria o Incidence of improvement in renal function, as defined by an increase in glomerular filtration rate (GFR) of at least 10 mL/min over baseline at least once after the start of treatment o Incidence of improvement in hemoglobin, as defined by an increase of at least 2 g/dL over baseline at least once after the start of treatment o Safety and tolerability o Bone pain and the impact of bone pain measured with the BPI-SF o Health-related quality of life (HRQoL) measured by the global health status/QoL scale of the EORTC QLQ-C30	~~Part 2: Randomized Phase 3 Portion of the Study~~ ~~Phase 3 objectives involve comparison of key outcome measures for subjects with primary refractory or relapsed and refractory multiple myeloma who are randomized to either oprozomib or placebo, in combination with pomalidomide and dexamethasone, hereafter denoted by OPomd or Pomd, respectively.~~ ~~Primary Objective~~ • ~~To compare progression free survival (PFS), as determined by Onyx Response Computational Assessment (ORCA) according to the IMWG-URC, between subjects treated with OPomd and those treated with Pomd~~ ~~Secondary Objectives~~ • ~~To compare the following between subjects treated with OPomd and those treated with Pomd:~~ ~~o Overall survival (OS)~~ ~~o Overall response rate (ORR), the clinical benefit rate (CBR), and duration of response (DOR) as determined by ORCA according to the IMWG-URC and modified EBMT criteria~~ ~~o Incidence of improvement in renal function, as defined by an increase in glomerular filtration rate (GFR) of at least 10 mL/min over baseline at least once after the start of treatment~~ ~~o Incidence of improvement in hemoglobin, as defined by an increase of at least 2 g/dL over baseline at least once after the start of treatment~~ ~~o Safety and tolerability~~ ~~o Bone pain and the impact of bone pain measured with the BPI-SF~~ ~~o Health-related quality of life (HRQoL) measured by the global health status/QoL scale of the EORTC QLQ-C30~~	Removed Phase 3 text to reflect what data was collected for the study

Section(s)	Changed from	Changed to	Rationale
	o Disease symptoms as measured by the disease symptoms subscale of EORTC QLQ-MY20 o Neurotoxicity symptoms as measured by the neurotoxicity subscale of the FACT/GOG-Ntx4 (Version 4) o Health status assessed with EQ-5D-5L • To evaluate population-based PK parameters of oprozomib in the OPomd regimen. Exploratory Objectives To compare the following between subjects treated with OPomd and those treated with Pomd: • PFS and ORR as determined by the investigator according to the IMWG-URC • Duration of response (DOR), defined as the time from the first evidence of confirmed PR or better to disease progression or death due to any cause as determined by the investigator according to the IMWG-URC • Clinical benefit rate (CBR) as determined by the investigator according to the IMWG-URC and modified EBMT criteria • Duration of clinical benefit (DOCB), defined as the time from first evidence of MR or better to disease progression or death due to any cause, as determined by ORCA and the investigator according to the IMWG-URC and modified EBMT criteria • Genomic biomarkers that may correlate with antitumor activity and resistance following treatment with proteasome inhibitors • The incidence of neuropathy (events are defined as Grade 2 or higher peripheral neuropathy) • HRQoL assessed with subscale scores of EORTC QLQ-C30 (excluding global health status scale) and EORTC QLQ-MY20 (excluding disease symptom subscale)	~~o Disease symptoms as measured by the disease symptoms subscale of EORTC QLQ-MY20~~ ~~o Neurotoxicity symptoms as measured by the neurotoxicity subscale of the FACT/GOG-Ntx4 (Version 4)~~ ~~o Health status assessed with EQ-5D-5L~~ ~~• To evaluate population-based PK parameters of oprozomib in the OPomd regimen.~~ ~~Exploratory Objectives~~ ~~To compare the following between subjects treated with OPomd and those treated with Pomd:~~ ~~• PFS and ORR as determined by the investigator according to the IMWG-URC~~ ~~• Duration of response (DOR), defined as the time from the first evidence of confirmed PR or better to disease progression or death due to any cause as determined by the investigator according to the IMWG-URC~~ ~~• Clinical benefit rate (CBR) as determined by the investigator according to the IMWG-URC and modified EBMT criteria~~ ~~• Duration of clinical benefit (DOCB), defined as the time from first evidence of MR or better to disease progression or death due to any cause, as determined by ORCA and the investigator according to the IMWG-URC and modified EBMT criteria~~ ~~• Genomic biomarkers that may correlate with antitumor activity and resistance following treatment with proteasome inhibitors~~ ~~• The incidence of neuropathy (events are defined as Grade 2 or higher peripheral neuropathy)~~ ~~HRQoL assessed with subscale scores of EORTC QLQ-C30 (excluding global health status scale) and EORTC QLQ-MY20 (excluding disease symptom subscale)~~	

Section(s)	Changed from	Changed to	Rationale
Synopsis (Study design)	There are 2 parts to this study. Part 1 includes an open-label, Phase 1b, dose-escalation and dose-expansion portion (equivalent to a small Phase 2), during which the RP3D will be identified.	**This study** includes an open-label, Phase 1b, dose-escalation and dose-expansion portion (equivalent to a small Phase 2), during which the RP3D will be identified.	Removed Phase 3 text to reflect what data was collected for the study
Synopsis (Study design)	During the Phase 1b portion of the study, subjects will receive Oprozomib extended release (ER) Tablets according to their assigned dose cohort.	During th**is** study, subjects will receive Oprozomib extended release (ER) Tablets according to their assigned dose cohort.	Study is no longer divided into 2 Parts.
Synopsis (Study design)	Part 2 will consist of a placebo-controlled, double-blind, randomized Phase 3 component, where subjects will be randomized to receive the RP3D of oprozomib or placebo administered orally in combination with pomalidomide and dexamethasone in 28-day cycles until disease progression or unacceptable toxicity.	~~Part 2 will consist of a placebo-controlled, double-blind, randomized Phase 3 component, where subjects will be randomized to receive the RP3D of oprozomib or placebo administered orally in combination with pomalidomide and dexamethasone in 28-day cycles until disease progression or unacceptable toxicity.~~	Removed Phase 3 text to reflect what data was collected for the study
Synopsis (Study design) Section 5 (Study Design)	This study will include subjects with primary refractory or relapsed and refractory multiple myeloma, i.e., those who have demonstrated disease progression on or within 60 days of their last therapy, and who have received at least 2 prior lines of therapy (including bortezomib and lenalidomide and/or thalidomide, and in the dose-expansion and Phase 3 portions of the study only, been treated with adequate alkylator therapy).	This study will include subjects with primary refractory or relapsed and refractory multiple myeloma, ~~i.e.,~~ those who have demonstrated disease progression on or within 60 days of their last therapy, and who have received at least 2 prior lines of therapy (including bortezomib and lenalidomide and/or thalidomide, and in the dose-expansion ~~and Phase 3~~ portion~~s~~ of the study only, been treated with adequate alkylator therapy).	Removed Phase 3 text to reflect what data was collected for the study

Section(s)	Changed from	Changed to	Rationale
Synopsis (Study design)	All study subjects (i.e., Part 1 and Part 2) will receive oprozomib once daily (or placebo in the case of Phase 3 subjects in the Pomd arm) either on Days 1–5 and 15–19, referred to hereafter as the 5/14 schedule, or an alternate schedule of once daily on Days 1, 2, 8, 9, 15, 16, 22, and 23, referred to hereafter as the 2/7 schedule.	All study subjects ~~(i.e., Part 1 and Part 2)~~ will receive oprozomib once daily ~~(or placebo in the case of Phase 3 subjects in the Pomd arm)~~ either on Days 1–5 and 15–19, referred to hereafter as the 5/14 schedule, or an alternate schedule of once daily on Days 1, 2, 8, 9, 15, 16, 22, and 23, referred to hereafter as the 2/7 schedule.	Removed Phase 3 text to reflect what data was collected for the study
Synopsis (Study design)	Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study	~~Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study~~	Study no longer divided into 2 parts.
Synopsis (Study design)	In Part 1 of the study, the safety, MTD, PK/PDn, and RP3D of oprozomib when given in combination with pomalidomide and dexamethasone will be assessed using a standard 3+3 dose-escalation design.	**T**he safety, MTD, PK/PDn, and RP3D of oprozomib when given in combination with pomalidomide and dexamethasone will be assessed using a standard 3+3 dose-escalation design.	Removed Phase 3 text to reflect what data was collected for the study
Synopsis (Study design)	Part 1: Phase 1b Dose Escalation and Dose Expansion Portions of the Study In Part 1 of the study, the safety, MTD, PK/PDn, and RP3D of oprozomib when given in combination with pomalidomide and dexamethasone will be assessed using a standard 3+3 dose-escalation design. For each of the 2 schedules being studied, groups of 3 to 6 subjects will be enrolled into dose-escalation cohorts. As long as fewer than 33% of subjects experience a dose limiting toxicity (DLT) in a given cohort, escalation will continue by 30 mg increments of oprozomib onto the next designated cohort(s). A minimum of 6 subjects must be treated at the MTD to establish the dose as the MTD. If the starting dose of oprozomib cannot be safely administered with the labeled pomalidomide dose, or at sponsor discretion, then up to	~~Part 1: Phase 1b Dose Escalation and Dose Expansion Portions of the Study~~ ~~In Part 1 of the study, the safety, MTD, PK/PDn, and RP3D of oprozomib when given in combination with pomalidomide and dexamethasone will be assessed using a standard 3+3 dose-escalation design. For each of the 2 schedules being studied, groups of 3 to 6 subjects will be enrolled into dose-escalation cohorts. As long as fewer than 33% of subjects experience a dose limiting toxicity (DLT) in a given cohort, escalation will continue by 30 mg increments of oprozomib onto the next designated cohort(s). A minimum of 6 subjects must be treated at the MTD to establish the dose as the MTD. If the starting dose of oprozomib cannot be safely administered with the labeled pomalidomide dose, or at sponsor discretion, then up to 2~~	Removed duplicated text

Section(s)	Changed from	Changed to	Rationale
	2 possible alternative paths for oprozomib with lower pomalidomide doses will be explored. (See tables below for primary and alternative dose escalation paths.) Dose escalation will continue until sponsor discretion, the maximum planned dose of pomalidomide is reached, or ≥ 2 DLTs occur in a cohort, whichever occurs first. The prior cohort will be expanded to at least 6 subjects if not previously done to establish that dose as the MTD. There may be more than 1 MTD for oprozomib if more than 1 dose level of pomalidomide is studied. The MTD of oprozomib associated with each dose level of pomalidomide assessed will be the dose level where < 2 DLTs in 6 subjects are observed. There is no planned maximum dose of oprozomib to be studied as it is being added to the FDA approved regimen of pomalidomide/dexamethasone, however, this could be imposed at any time during the course of the study, based on Sponsor discretion. The starting dose of oprozomib for the 5/14 schedule is 150 mg, 3 dose levels below the established 5/14 single agent MTD of 240 mg. The starting dose of oprozomib for the 2/7 schedule is 210 mg, 3 dose levels below the established 2/7 single-agent MTD of 300 mg. Following dose escalation, the sponsor has the option of expanding 1 or both schedules in order to establish the RP3D and schedule.	~~possible alternative paths for oprozomib with lower pomalidomide doses will be explored. (See tables below for primary and alternative dose escalation paths.) Dose escalation will continue until sponsor discretion, the maximum planned dose of pomalidomide is reached, or ≥ 2 DLTs occur in a cohort, whichever occurs first. The prior cohort will be expanded to at least 6 subjects if not previously done to establish that dose as the MTD. There may be more than 1 MTD for oprozomib if more than 1 dose level of pomalidomide is studied. The MTD of oprozomib associated with each dose level of pomalidomide assessed will be the dose level where < 2 DLTs in 6 subjects are observed.~~ ~~There is no planned maximum dose of oprozomib to be studied as it is being added to the FDA approved regimen of pomalidomide/dexamethasone, however, this could be imposed at any time during the course of the study, based on Sponsor discretion. The starting dose of oprozomib for the 5/14 schedule is 150 mg, 3 dose levels below the established 5/14 single agent MTD of 240 mg. The starting dose of oprozomib for the 2/7 schedule is 210 mg, 3 dose levels below the established 2/7 single-agent MTD of 300 mg. Following dose escalation, the sponsor has the option of expanding 1 or both schedules in order to establish the RP3D and schedule.~~	
Synopsis (Study design)	During the Phase 1b portion of the study, assessment of DLTs will occur during the 28-day period of Cycle 1 combination therapy.	During th**is** study, assessment of DLTs will occur during the 28-day period of Cycle 1 combination therapy.	Study is no longer divided into 2 parts
Synopsis (Study design)	In the Phase 1b portion of the study, subjects must meet the following criteria to be considered evaluable for MTD determination during the 4-week DLT evaluation period unless a DLT occurs before the subject receives all planned doses of oprozomib for both the 5/14 and 2/7 dosing schedules:	**S**ubjects must meet the following criteria to be considered evaluable for MTD determination during the 4-week DLT evaluation period unless a DLT occurs before the subject receives all planned doses of oprozomib for both the 5/14 and 2/7 dosing schedules:	Study no longer divided into 2 parts

Section(s)	Changed from	Changed to	Rationale
Synopsis (Study design)	Once the MTD(s) has been determined and the recommended dose for the expansion phase has been selected, a minimum of 20 additional subjects for 1 or both schedules of oprozomib at the sponsor's discretion will be enrolled in the dose-expansion portion of Part 1in order to continue the evaluation of the safety and efficacy of the regimen as a prelude to initiation of the Phase 3 portion of the study.	Once the MTD(s) has been determined and the recommended dose for the expansion phase has been selected, a minimum of 20 additional subjects for 1 or both schedules of oprozomib at the sponsor's discretion will be enrolled in the dose-expansion portion **of the study** in order to continue the evaluation of the safety and efficacy of the regimen.	Removed Phase 3 text to reflect what data was collected for the study
Synopsis (Study design)	Enrollment to the Phase 3 portion will not commence until the CSRC has evaluated all available safety information from a minimum of 10 subjects who have completed ≥ 2 cycles of therapy and enrollment of the remaining 10 subjects in Dose Expansion has occurred in 1 or both schedules if both were opened.	~~Enrollment to the Phase 3 portion will not commence until the CSRC has evaluated all available safety information from a minimum of 10 subjects who have completed ≥ 2 cycles of therapy and enrollment of the remaining 10 subjects in Dose Expansion has occurred in 1 or both schedules if both were opened.~~	Removed Phase 3 text to reflect what data was collected for the study
Synopsis (Study design)	Part 2: Randomized Phase 3 Portion of the Study Randomization After screening and eligibility determination, eligible subjects will be randomized in a 2:1 ratio to receive a regimen consisting of OPomd or Pomd plus placebo, respectively. Central randomization will be implemented in this part of the study through the use of an Interactive Voice Response System / Interactive Web Response System (IVRS/IWRS). Eligible subjects will be stratified by: • Age: < 75 years versus ≥ 75 years • Number of prior therapies: 2 versus 3 or more • Carfilzomib status: Carfilzomib-naïve/sensitive versus carfilzomib-refractory. Carfilzomib-sensitive multiple myeloma patients are defined as having had previously achieved a PR or greater with therapy that includes carfilzomib (or carfilzomib monotherapy), and did not experience PD until more than 60 days after their last dose of carfilzomib. Carfilzomib-refractory multiple myeloma is defined as	~~Part 2: Randomized Phase 3 Portion of the Study~~ ~~Randomization~~ ~~After screening and eligibility determination, eligible subjects will be randomized in a 2:1 ratio to receive a regimen consisting of OPomd or Pomd plus placebo, respectively. Central randomization will be implemented in this part of the study through the use of an Interactive Voice Response System / Interactive Web Response System (IVRS/IWRS). Eligible subjects will be stratified by:~~ • ~~Age: < 75 years versus ≥ 75 years~~ • ~~Number of prior therapies: 2 versus 3 or more~~ • ~~Carfilzomib status: Carfilzomib-naïve/sensitive versus carfilzomib-refractory. Carfilzomib-sensitive multiple myeloma patients are defined as having had previously achieved a PR or greater with therapy that includes carfilzomib (or carfilzomib monotherapy), and did not experience PD until more than 60 days after their last dose of carfilzomib. Carfilzomib-refractory multiple myeloma is defined as~~	Removed Phase 3 text to reflect what data was collected for the study

Section(s)	Changed from	Changed to	Rationale
	disease that is nonresponsive while on primary or salvage therapy that includes carfilzomib, or that progresses on or within 60 days of last therapy. Within each stratum, treatment assignment will be made using a permuted block randomization scheme. Randomized treatment is to commence on the day of randomization (Day 1), if possible, but not more than 5 calendar days after randomization. Treatment initiation beyond 5 days after randomization must be approved by the Onyx study medical monitor or designee.	~~disease that is nonresponsive while on primary or salvage therapy that includes carfilzomib, or that progresses on or within 60 days of last therapy.~~ ~~Within each stratum, treatment assignment will be made using a permuted block randomization scheme.~~ ~~Randomized treatment is to commence on the day of randomization (Day 1), if possible, but not more than 5 calendar days after randomization. Treatment initiation beyond 5 days after randomization must be approved by the Onyx study medical monitor or designee.~~	
Synopsis (Number of investigational sites) Section 5 (Study Design)	Approximately 35 study sites will participate in Part 1 of the study (15 sites for the Phase 1b dose-escalation and 20 additional sites for the dose-expansion portions of the study). An additional 35 sites, for a total of approximately 70 sites, will participate in Part 2 of the study (Phase 3 portion of the study).	Approximately 35 study sites will participate in **this** study (15 sites for the dose-escalation and 20 additional sites for the dose-expansion portions of the study).	Removed Phase 3 text to reflect what data was collected for the study
Synopsis (Planned number of subjects)	Part 1: Phase 1b (Dose-Escalation and Dose-Expansion Portions of the Study)	~~Part 1: Phase 1b (Dose-Escalation and Dose-Expansion Portions of the Study)~~	Study is longer divided into 2 parts
Synopsis (Planned number of subjects)	A total enrollment of approximately 82 subjects is planned for Part 1 of the study. During the Phase 1b Dose-Escalation portion of Part 1, approximately 21 subjects will be enrolled for each schedule.	A total enrollment of approximately 82 subjects is planned for th**is** study. During the Dose-Escalation portion, approximately 21 subjects will be enrolled for each schedule.	Study is no longer divided into 2 parts
Synopsis (Planned number of subjects)	A minimum of 20 additional subjects are planned for enrollment for each schedule at the sponsor's discretion and treatment at the RP3D during the Phase 1b Dose-Expansion portion of Part 1 of the study. Part 2: Randomized Phase 3 Portion of the Study During Part 2, the planned enrollment is approximately 270 subjects.	A minimum of 20 additional subjects are planned for enrollment for each schedule at the sponsor's discretion and treatment at the RP3D during the ~~Phase 1b~~ Dose-Expansion portion of ~~Part 1 of~~ the study. ~~Part 2: Randomized Phase 3 Portion of the Study~~ ~~During Part 2, the planned enrollment is approximately 270 subjects.~~	Removed Phase 3 text to reflect what data was collected for the study

Section(s)	Changed from	Changed to	Rationale
	Therefore, the total planned enrollment will be approximately 352 subjects.	~~Therefore, the total planned enrollment will be approximately 352 subjects.~~	
Synopsis (Sample size justification)	Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study	~~Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study~~	Study is no longer divided into 2 parts
Synopsis (Sample size justification)	Part 2: Randomized Phase 3 Portion of the Study For the Phase 3 portion of the study, 157 PFS events are required to detect a 45.7% reduction in the risk of PFS (hazard ratio [HR] = 0.543) with 95% power and a 1-sided significance level of 0.025. Enrollment of 270 subjects (2:1 OPomd versus Pomd, respectively) is consistent with reaching the required 157 events in approximately 14 months, assuming an enrollment rate of approximately 22 subjects per month, a drop-out rate of 5% at 18 months, and a median PFS of 3.8 and 7 months for Pomd and OPomd, respectively.	~~Part 2: Randomized Phase 3 Portion of the Study~~ ~~For the Phase 3 portion of the study, 157 PFS events are required to detect a 45.7% reduction in the risk of PFS (hazard ratio [HR] = 0.543) with 95% power and a 1-sided significance level of 0.025. Enrollment of 270 subjects (2:1 OPomd versus Pomd, respectively) is consistent with reaching the required 157 events in approximately 14 months, assuming an enrollment rate of approximately 22 subjects per month, a drop-out rate of 5% at 18 months, and a median PFS of 3.8 and 7 months for Pomd and OPomd, respectively.~~	Removed Phase 3 text to reflect what data was collected for the study
Synopsis (Study population)	The study population will consist of subjects with primary refractory or relapsed and refractory, multiple myeloma, i.e., those who have demonstrated disease progression on or within 60 days of their last therapy, and who have received at least 2 prior lines of therapy (including bortezomib and lenalidomide and/or thalidomide, and in the dose-expansion and Phase 3 portions of the study only, been treated with adequate alkylator), and who are considered to be appropriate for this clinical study by their treating physicians.	The study population will consist of subjects with primary refractory or relapsed and refractory, multiple myeloma, ~~i.e.,~~ those who have demonstrated disease progression on or within 60 days of their last therapy, and who have received at least 2 prior lines of therapy (including bortezomib and lenalidomide and/or thalidomide, and in the dose-expansion ~~and Phase 3~~ portions of the study only, been treated with adequate alkylator), and who are considered to be appropriate for this clinical study by their treating physicians.	Removed Phase 3 text to reflect what data was collected for the study
Synopsis (Reference therapy dose, and mode of administration)	Placebo Oprozomib placebo tablet for Phase 3	~~Placebo~~ ~~Oprozomib placebo tablet for Phase 3~~	Removed Phase 3 text to reflect what data was collected for the study

Section(s)	Changed from	Changed to	Rationale
Synopsis (Treatment regimen[s])	Oral oprozomib or placebo taken Days 1–5 and 15-19 or Days 1, 2, 8, 9, 15, 16, 22, and 23, pomalidomide taken on 21 of 28 days, and oral dexamethasone taken on Days 1, 2, 8, 9, 15, 16, 22, and 23	Oral oprozomib ~~or placebo~~ taken Days 1–5 and 15–19 or Days 1, 2, 8, 9, 15, 16, 22, and 23, pomalidomide taken on 21 of 28 days, and oral dexamethasone taken on Days 1, 2, 8, 9, 15, 16, 22, and 23	Removed Phase 3 text to reflect what data was collected for the study
Synopsis (Inclusion criteria) Section 6.1 (Inclusion Criteria)	b. In the dose-expansion and Phase 3 portions of the study only: In addition to the above, treatment with adequate alkylator therapy, defined as:	b. In the dose-expansion ~~and Phase 3~~ portion~~s~~ of the study only: In addition to the above, treatment with adequate alkylator therapy, defined as:	Removed Phase 3 text to reflect what data was collected for the study
Synopsis (Exclusion criteria: Disease Related) Section 6.2 (Exclusion Criteria)	b. For the Dose-Expansion portion and Part 2 of the study: Prior pomalidomide treatment of any duration	b. For the Dose-Expansion portion ~~and Part 2~~ of the study: Prior pomalidomide treatment of any duration	Removed Phase 3 text to reflect what data was collected for the study
Synopsis (Criteria for evaluation – Other	In the Phase 1b Dose-Escalation and Dose-Expansion portions of the study, blood samples will be collected from all subjects for determination of plasma concentrations of oprozomib at 1 predose time point and up to 7 postdose time points on Day 1 of Cycle 1 and Cycle 2 (0.25, 0.5, 1, 2, 3, 4, and 6 hours postdose) and 1 predose time point on Day 2 of Cycle 1 for both schedules. In the Phase 3 portion of the study, PK samples will be collected from all randomized subjects at Cycle 1 Day 1 and Cycle 3 Day 1 and will be analyzed for oprozomib concentrations in OPomd subjects.	In the ~~Phase 1b~~ Dose-Escalation and Dose-Expansion portions of the study, blood samples will be collected from all subjects for determination of plasma concentrations of oprozomib at 1 predose time point and up to 7 postdose time points on Day 1 of Cycle 1 and Cycle 2 (0.25, 0.5, 1, 2, 3, 4, and 6 hours postdose) and 1 predose time point on Day 2 of Cycle 1 for both schedules. ~~In the Phase 3 portion of the study, PK samples will be collected from all randomized subjects at Cycle 1 Day 1 and Cycle 3 Day 1 and will be analyzed for oprozomib concentrations in OPomd subjects.~~	Removed Phase 3 text to reflect what data was collected for the study

Section(s)	Changed from	Changed to	Rationale
Synopsis (Criteria for evaluation – Other)	Blood samples for quantitation of proteasome inhibition by oprozomib will be collected from all subjects in the Phase 1b portion of the study.	Blood samples for quantitation of proteasome inhibition by oprozomib will be collected from all subjects in th**is** study.	Study is no longer divided into 2 parts
Synopsis (Criteria for evaluation – Other	Analysis of genomic biomarkers that may predict response and resistance following treatment with proteasome inhibitors will be conducted for all subjects receiving oprozomib from all phases of the study who consent to optional genomic biomarker analysis.	Analysis of genomic biomarkers that may predict response and resistance following treatment with proteasome inhibitors will be conducted for all subjects receiving oprozomib ~~from all phases of the study~~ who consent to optional genomic biomarker analysis.	Removed Phase 3 text to reflect what data was collected for the study
Synopsis (Criteria for evaluation – Other)	Bone marrow aspirate or biopsy collection does not need to be repeated if previously completed within 45 days prior to Cycle 1 Day 1 dosing, and for Phase 3 only, if it was processed at the central laboratory. Additional bone marrow samples for biomarkers may be collected at disease progression (End of Study Treatment due to progressive disease [PD] or Long-term Follow-up) from all subjects who consent.	Bone marrow aspirate or biopsy collection does not need to be repeated if previously completed within 45 days prior to Cycle 1 Day 1 dosing~~, and for Phase 3 only, if it was processed at the central laboratory~~. Additional bone marrow samples for biomarkers may be collected at disease progression (End of Study Treatment due to progressive disease [PD]~~ or Long-term Follow-up~~) from all subjects who consent.	Provide convenience for those on study treatment as study has completed its abbreviated report
Synopsis (Statistical methods and analyses – Safety Population and Efficacy Population)	Safety Population (All Subjects) For Part 1 (Phase 1b Dose Escalation and Expansion) and Part 2 (Randomized Phase 3 Portion) of the study, the safety population includes all subjects receiving any amount of study treatment (oprozomib, placebo, pomalidomide, or dexamethasone). Efficacy Population Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study For the Phase 1b Dose-Escalation and Expansion portions of the study, the efficacy population is equivalent to the safety population.	Safety Population (All Subjects) **T**he safety population includes all subjects receiving any amount of study treatment (oprozomib, pomalidomide, or dexamethasone). Efficacy Population For th**is** study, the efficacy population is equivalent to the safety population.	Removed Phase 3 text to reflect what data was collected for the study

Section(s)	Changed from	Changed to	Rationale
	Part 2: Randomized Phase 3 Portion of the Study For the Phase 3 portion of the study, the efficacy population will include all randomized subjects according to randomized treatment, consistent with the intent-to-treat (ITT) principle.		
Synopsis (Statistical methods and analyses – Endpoints)	Endpoints Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study (by Schedule)	Endpoints ~~Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study (by Schedule)~~	Study is no longer divided into 2 parts
Synopsis (Statistical methods and analyses – Primary, Secondary, and Exploratory headings)	Primary Endpoints-Part 1 Secondary Endpoints-Part 1 Exploratory Endpoints-Part 1	Primary Endpoints~~-Part 1~~ Secondary Endpoints~~-Part 1~~ Exploratory Endpoints~~-Part 1~~	Study is no longer divided into 2 parts
Synopsis (Statistical methods and analyses)	Part 2: Randomized Phase 3 Portion of the Study Primary Endpoint-Part 2 • Progression-free survival, defined as time from randomization to the earlier of disease progression	~~Part 2: Randomized Phase 3 Portion of the Study~~ ~~Primary Endpoint-Part 2~~ • ~~Progression-free survival, defined as time from randomization to the earlier of disease progression~~	Removed Phase 3 text to reflect what data was collected for the study

	determined by ORCA according to the IMWG-URC, or death due to any cause Secondary Endpoints-Part 2 • Overall survival, defined as time from randomization to death due to any cause • Overall response, defined as the best response of sCR, CR, VGPR, or PR as determined by ORCA according to the IMWG-URC • Clinical benefit, defined as the best response of MR or better, as determined by ORCA according to the the IMWG-URC and modified EBMT criteria • Duration of response, defined as the time from the first evidence of confirmed PR or better to disease progression as determined by ORCA according to the IMWG-URC, or death due to any cause • Improvement in renal function, as defined by an increase in GFR of at least 10 mL/min • Improvement in hemoglobin, as defined by an increase of at least 2 g/dL • Adverse events and laboratory abnormalities graded according to NCI-CTCAE, Version 4.03 • Vital signs and clinical laboratory results during and following study drug administration • Change over time in bone pain and the impact of bone pain measured with the BPI-SF • Change over time in the global health status/QoL scale of the EORTC QLQ-C30 • Change over time in the disease symptoms subscale of the EORTC QLQ-MY20 • Change over time in neurotoxicity symptoms measured by the FACT/GOG-Ntx4 score (Version 4) • Change over time in health status assessed by EQ-5D-5L	~~determined by ORCA according to the IMWG-URC, or death due to any cause~~ ~~Secondary Endpoints-Part 2~~ • ~~Overall survival, defined as time from randomization to death due to any cause~~ • ~~Overall response, defined as the best response of sCR, CR, VGPR, or PR as determined by ORCA according to the IMWG-URC~~ • ~~Clinical benefit, defined as the best response of MR or better, as determined by ORCA according to the the IMWG-URC and modified EBMT criteria~~ • ~~Duration of response, defined as the time from the first evidence of confirmed PR or better to disease progression as determined by ORCA according to the IMWG-URC, or death due to any cause~~ • ~~Improvement in renal function, as defined by an increase in GFR of at least 10 mL/min~~ • ~~Improvement in hemoglobin, as defined by an increase of at least 2 g/dL~~ • ~~Adverse events and laboratory abnormalities graded according to NCI-CTCAE, Version 4.03~~ • ~~Vital signs and clinical laboratory results during and following study drug administration~~ • ~~Change over time in bone pain and the impact of bone pain measured with the BPI-SF~~ • ~~Change over time in the global health status/QoL scale of the EORTC QLQ-C30~~ • ~~Change over time in the disease symptoms subscale of the EORTC QLQ-MY20~~ • ~~Change over time in neurotoxicity symptoms measured by the FACT/GOG-Ntx4 score (Version 4)~~ • ~~Change over time in health status assessed by EQ-5D-5L~~	

Section(s)	Changed from	Changed to	Rationale
	• Population based PK parameters including, but not limited to, area under the plasma concentration-time curve (AUC) and C_{max}, will be determined from OPomd subjects Exploratory Endpoints-Part 2 • Progression-free survival and overall response as determined by the investigator according to the IMWG-URC • Duration of response, defined as the time from the first evidence of confirmed PR or better to disease progression as determined by the investigator according to the IMWG-URC or death due to any cause • Clinical benefit as determined by the investigator according to the IMWG-URC and modified EBMT criteria • Duration of clinical benefit (DOCB), defined as the time from first evidence of MR or better to disease progression or death due to any cause, as determined by ORCA and the investigator according to the IMWG-URC and modified EBMT criteria • Genomic biomarkers that may be correlated with antitumor activity and resistance following treatment with proteasome inhibitors • Neuropathy events (defined as Grade 2 or higher peripheral neuropathy) • Change over time in all domains of the EORTC QLQ-C30 and EORTC QLQ-MY20 (excluding the global health scale and disease symptoms subscale, respectively)	~~• Population based PK parameters including, but not limited to, area under the plasma concentration-time curve (AUC) and C_{max}, will be determined from OPomd subjects~~ ~~Exploratory Endpoints-Part 2~~ ~~• Progression-free survival and overall response as determined by the investigator according to the IMWG-URC~~ ~~• Duration of response, defined as the time from the first evidence of confirmed PR or better to disease progression as determined by the investigator according to the IMWG-URC or death due to any cause~~ ~~• Clinical benefit as determined by the investigator according to the IMWG-URC and modified EBMT criteria~~ ~~• Duration of clinical benefit (DOCB), defined as the time from first evidence of MR or better to disease progression or death due to any cause, as determined by ORCA and the investigator according to the IMWG-URC and modified EBMT criteria~~ ~~• Genomic biomarkers that may be correlated with antitumor activity and resistance following treatment with proteasome inhibitors~~ ~~• Neuropathy events (defined as Grade 2 or higher peripheral neuropathy)~~ ~~• Change over time in all domains of the EORTC QLQ-C30 and EORTC~~ ~~QLQ-MY20 (excluding the global health scale and disease symptoms subscale, respectively)~~	

Section(s)	Changed from	Changed to	Rationale
Synopsis (Statistical methods and analyses – Efficacy Analyses)	Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study Progression-free survival and duration of response will be listed for all subjects by dose level and schedule. Overall response rate and clinical benefit rate will be estimated for all subjects treated at the RP3D along with the associated 95% exact binomial confidence intervals (CIs). Part 2: Randomized Phase 3 Portion of the Study The primary analysis of PFS and other efficacy endpoints will be based on the ITT population, defined as all subjects randomized. The primary inferential comparison for PFS between treatment groups will use the log-rank test stratified by the randomization stratification factors. The HR will be estimated using a stratified Cox proportional hazards model. The distribution of PFS, including medians, will be summarized descriptively using the Kaplan-Meier method for each treatment group. Overall survival will be analyzed using the same method as for PFS. Duration of response and DOCB will be summarized for each treatment group by Kaplan-Meier method; however, no formal inferential comparisons will be made for these endpoints, as responders constitute a nonrandom subset of the ITT population. Point estimates and 95% exact binomial CIs will be calculated for the ORR and CBR for each treatment group. Inferential comparison between treatment groups for these endpoints will be made using the Cochran-Mantel Haenszel chi-square test, stratified by the randomization stratification factors. Inferential testing of the primary efficacy endpoint and selected secondary endpoints (OS, ORR, CBR, improvement in renal function, improvement in hemoglobin, change over time in QLQ-MY20 total scale, and change over time in QLQ-C30 total scale) will be performed against an overall 1-sided significance level of 0.025 in accordance with a closed testing procedure.	~~Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study~~ Progression-free survival and duration of response will be listed for all subjects by dose level and schedule. Overall response rate and clinical benefit rate will be estimated for all subjects treated at the RP3D along with the associated 95% exact binomial confidence intervals (CIs). ~~Part 2: Randomized Phase 3 Portion of the Study~~ ~~The primary analysis of PFS and other efficacy endpoints will be based on the ITT population, defined as all subjects randomized. The primary inferential comparison for PFS between treatment groups will use the log-rank test stratified by the randomization stratification factors. The HR will be estimated using a stratified Cox proportional hazards model. The distribution of PFS, including medians, will be summarized descriptively using the Kaplan-Meier method for each treatment group. Overall survival will be analyzed using the same method as for PFS. Duration of response and DOCB will be summarized for each treatment group by Kaplan-Meier method; however, no formal inferential comparisons will be made for these endpoints, as responders constitute a nonrandom subset of the ITT population.~~ ~~Point estimates and 95% exact binomial CIs will be calculated for the ORR and CBR for each treatment group. Inferential comparison between treatment groups for these endpoints will be made using the Cochran-Mantel Haenszel chi-square test, stratified by the randomization stratification factors.~~ ~~Inferential testing of the primary efficacy endpoint and selected secondary endpoints (OS, ORR, CBR, improvement in renal function, improvement in hemoglobin, change over time in QLQ-MY20 total scale, and change over time in QLQ-C30 total scale) will be performed against an overall 1-sided significance level of 0.025 in accordance with a closed testing procedure.~~	Removed Phase 3 text to reflect what data was collected for the study

Section(s)	Changed from	Changed to	Rationale
Synopsis (Statistical methods and analyses – Safety Analyses)	Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study For the Phase 1b portion of the study, safety will be assessed through summaries of DLTs, AEs, changes in laboratory test results, ECGs, vital signs, and oprozomib, pomalidomide, and dexamethasone exposure. All AE data collected will be listed by study site, cohort, subject number, and study day.	For th**is** study, safety will be assessed through summaries of DLTs, AEs, changes in laboratory test results, ECGs, vital signs, and oprozomib, pomalidomide, and dexamethasone exposure. All AE data collected will be listed by study site, cohort, subject number, and study day.	Study is no longer divided into 2 parts
Synopsis (Statistical methods and analyses – Safety Analyses)	Part 2: Randomized Phase 3 Portion of the Study For the Phase 3 portion of the study, safety data will be summarized according to treatment actually received. Safety analyses will be presented separately for Part 1 and Part 2 of the study and will include all AEs occurring on or after treatment on Cycle 1 Day 1 summarized by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (current version of MedDRA), and NCI-CTCAE (Version 4.03) toxicity grade. In addition, all serious adverse events, including deaths, will be listed separately and summarized. Safety will be assessed through summaries of changes in laboratory results, ECGs, and vital signs. Extent of exposure to the study treatment will be summarized using descriptive statistics.	~~Part 2: Randomized Phase 3 Portion of the Study~~ ~~For the Phase 3 portion of the study, safety data will be summarized according to treatment actually received.~~ ~~Safety analyses will be presented separately for Part 1 and Part 2 of the study and will include all AEs occurring on or after treatment on Cycle 1 Day 1 summarized by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (current version of MedDRA), and NCI-CTCAE (Version 4.03) toxicity grade. In addition, all serious adverse events, including deaths, will be listed separately and summarized. Safety will be assessed through summaries of changes in laboratory results, ECGs, and vital signs. Extent of exposure to the study treatment will be summarized using descriptive statistics.~~	Removed Phase 3 text to reflect what data was collected for the study

Section(s)	Changed from	Changed to	Rationale
Section 3.1 (Introduction)	This is a Phase 1b/Phase 3 clinical trial of the oral proteasome inhibitor, oprozomib, in subjects with primary refractory or relapsed and refractory multiple myeloma.	This is a Phase 1b~~/Phase 3~~ clinical trial of the oral proteasome inhibitor, oprozomib, in subjects with primary refractory or relapsed and refractory multiple myeloma.	Removed Phase 3 text to reflect what data was collected for the study
Section 3.1 (Introduction)	*New text added*	**Amendment 3:** **1. Data collection for subjects on active treatment is being pared down due to both the completion of this study's analysis and its abbreviated clinical study report.**	Update text to reflect the rationale for Amendment 3
Section 3.5.1 (Oprozomib)	This study will assess both schedules in Part 1 of the study, as oprozomib has demonstrated preliminary activity in subjects with hematologic malignancies on both schedules (Kaufman 2013).	This study will assess both schedules in th**is** study, as oprozomib has demonstrated preliminary activity in subjects with hematologic malignancies on both schedules (Kaufman**,** 2013).	Study is no longer divided into 2 parts
Section 4 (Study Objectives)	4.1 PART 1: PHASE 1B DOSE-ESCALATION AND DOSE-EXPANSION PORTIONS OF THE STUDY (BY SCHEDULE)	~~4.1 PART 1: PHASE 1B DOSE-ESCALATION AND DOSE-EXPANSION PORTIONS OF THE STUDY (BY SCHEDULE)~~	Study is no longer divided into 2 parts

Section 4.5 (Part 2: Randomization Phase 3 Portion of the Study)	4.5 PART 2: RANDOMIZED PHASE 3 PORTION OF THE STUDY Phase 3 objectives involve comparison of key outcome measures for subjects with primary refractory or relapsed and refractory multiple myeloma who are randomized to either oprozomib or placebo in combination with pomalidomide and dexamethasone, hereafter denoted by OPomd or Pomd, respectively. 4.5.1 PRIMARY OBJECTIVE • To compare progression free survival (PFS), as determined by Onyx Response Computational Assessment (ORCA) according to the IMWG-URC, between subjects treated with OPomd and those treated with Pomd 4.5.2 SECONDARY OBJECTIVES • To compare the following between subjects treated with OPomd and those treated with Pomd: o Overall survival (OS) o Overall response rate (ORR), the clinical benefit rate (CBR), and duration of response (DOR) as determined by ORCA according to the IMWG-URC and modified EBMT criteria o Incidence of improvement in renal function, as defined by an increase in glomerular filtration rate (GFR) of at least 10 mL/min over baseline at least once after the start of treatment o Incidence of improvement in hemoglobin as defined by an increase of at least 2 g/dL over baseline at least once after the start of treatment o Safety and tolerability	~~4.5 PART 2: RANDOMIZED PHASE 3 PORTION OF THE STUDY~~ ~~Phase 3 objectives involve comparison of key outcome measures for subjects with primary refractory or relapsed and refractory multiple myeloma who are randomized to either oprozomib or placebo in combination with pomalidomide and dexamethasone, hereafter denoted by OPomd or Pomd, respectively.~~ ~~4.5.1 PRIMARY OBJECTIVE~~ ~~• To compare progression free survival (PFS), as determined by Onyx Response Computational Assessment (ORCA) according to the IMWG-URC, between subjects treated with OPomd and those treated with Pomd~~ ~~4.5.2 SECONDARY OBJECTIVES~~ ~~• To compare the following between subjects treated with OPomd and those treated with Pomd:~~ ~~o Overall survival (OS)~~ ~~o Overall response rate (ORR), the clinical benefit rate (CBR), and duration of response (DOR) as determined by ORCA according to the IMWG-URC and modified EBMT criteria~~ ~~o Incidence of improvement in renal function, as defined by an increase in glomerular filtration rate (GFR) of at least 10 mL/min over baseline at least once after the start of treatment~~ ~~o Incidence of improvement in hemoglobin as defined by an increase of at least 2 g/dL over baseline at least once after the start of treatment~~ ~~o Safety and tolerability~~	Removed Phase 3 text to reflect what data was collected for the study

Section(s)	Changed from	Changed to	Rationale
	○ Bone pain and the impact of bone pain measured with the BPI-SF ○ Health-related quality of life (HRQoL) measured by the global health status/QoL scale of the EORTC QLQ-C30 ○ Disease symptoms as measured by the disease symptoms subscale of EORTC QLQ-MY20 ○ Neurotoxicity symptoms as measured by the neurotoxicity subscale of the FACT/GOG-Ntx4 (Version 4) ○ Health status assessed with EQ-5D-5L • To evaluate population-based PK parameters of oprozomib in the OPomd regimen 4.5.3 EXPLORATORY OBJECTIVES To compare the following between subjects treated with OPomd and those treated with Pomd: • Progression-free survival (PFS) and ORR as determined by the investigator according to the IMWG-URC • Duration of response (DOR), defined as the time from the first evidence of confirmed PR or better to disease progression or death due to any cause as determined by the investigator according to the IMWG-URC • Clinical benefit rate (CBR) as determined by the investigator according to the IMWG-URC and modified EBMT criteria • Duration of clinical benefit (DOCB), defined as the time from first evidence of MR or better to disease progression or death due to any cause, as determined	~~○ Bone pain and the impact of bone pain measured with the BPI-SF~~ ~~○ Health-related quality of life (HRQoL) measured by the global health status/QoL scale of the EORTC QLQ-C30~~ ~~○ Disease symptoms as measured by the disease symptoms subscale of EORTC QLQ-MY20~~ ~~○ Neurotoxicity symptoms as measured by the neurotoxicity subscale of the FACT/GOG-Ntx4 (Version 4)~~ ~~○ Health status assessed with EQ-5D-5L~~ ~~• To evaluate population-based PK parameters of oprozomib in the OPomd regimen~~ ~~4.5.3 EXPLORATORY OBJECTIVES~~ ~~To compare the following between subjects treated with OPomd and those treated with Pomd:~~ ~~• Progression-free survival (PFS) and ORR as determined by the investigator according to the IMWG-URC~~ ~~• Duration of response (DOR), defined as the time from the first evidence of confirmed PR or better to disease progression or death due to any cause as determined by the investigator according to the IMWG-URC~~ ~~• Clinical benefit rate (CBR) as determined by the investigator according to the IMWG-URC and modified EBMT criteria~~ ~~• Duration of clinical benefit (DOCB), defined as the time from first evidence of MR or better to disease progression or death due to any cause, as determined~~	

Section(s)	Changed from	Changed to	Rationale
	by ORCA and the investigator according to the IMWG-URC and the modified EBMT criteria • Genomic biomarkers that may correlate with antitumor activity and resistance following treatment with proteasome inhibitors • The incidence of neuropathy (events are defined as Grade 2 or higher peripheral neuropathy) • HRQoL assessed with subscale scores of EORTC QLQ-C30 (excluding global health status scale) and EORTC QLQ-MY20 (excluding disease symptom subscale)	~~by ORCA and the investigator according to the IMWG-URC and the modified EBMT criteria~~ • ~~Genomic biomarkers that may correlate with antitumor activity and resistance following treatment with proteasome inhibitors~~ • ~~The incidence of neuropathy (events are defined as Grade 2 or higher peripheral neuropathy)~~ • ~~HRQoL assessed with subscale scores of EORTC QLQ-C30 (excluding global health status scale) and EORTC QLQ-MY20 (excluding disease symptom subscale)~~	
Section 5 (Study Design)	There are 2 parts to this study. Part 1 includes an open-label, Phase 1b, dose-escalation and dose-expansion portion (the equivalent of a small Phase 2) during which the RP3D will be identified.	**T**his study includes an open-label, Phase 1b, dose-escalation and dose-expansion portion (the equivalent of a small Phase 2) during which the RP3D will be identified.	The study is no longer divided into 2 parts
Section 5 (Study Design)	During the Phase 1b portion of the study, subjects will receive Oprozomib ER Tablets according to their assigned dose cohort	During th**is** study, subjects will receive Oprozomib ER Tablets according to their assigned dose cohort	The study is no longer divided into 2 parts
Section 5 (Study Design)	Part 2 will consist of a placebo-controlled, double-blind, randomized Phase 3 component where subjects will be randomized to receive the RP3D of oprozomib or placebo administered orally in combination with pomalidomide and dexamethasone in 28-day cycles until disease progression or unacceptable toxicity.	~~Part 2 will consist of a placebo-controlled, double-blind, randomized Phase 3 component where subjects will be randomized to receive the RP3D of oprozomib or placebo administered orally in combination with pomalidomide and dexamethasone in 28-day cycles until disease progression or unacceptable toxicity.~~	Removed Phase 3 text to reflect what data was collected for the study

Section(s)	Changed from	Changed to	Rationale
Section 5 (Study Design)	During Part 2 of the study, subjects will be randomized to oprozomib in combination with pomalidomide and dexamethasone (OPomd) at the RP3D and schedule determined during Part 1 of the study or placebo in combination with pomalidomide and dexamethasone (Pomd).	~~During Part 2 of the study, subjects will be randomized to oprozomib in combination with pomalidomide and dexamethasone (OPomd) at the RP3D and schedule determined during Part 1 of the study or placebo in combination with pomalidomide and dexamethasone (Pomd).~~	Removed Phase 3 text to reflect what data was collected for the study
Section 5 (Study Design)	Treatment cycles for both parts of the study will last 28 days.	~~Treatment cycles for both parts of the study will last 28 days.~~	Redundant text
Section 5 (Study Design)	Details of the study assessments required for both parts of this study are provided in Appendices A1, A2, B1, B2, C1, and C2.	Details of the study assessments required for this study are provided in Appendices A1, A2, B1, and B2.	Removed reference to Phase 3 part of study.
Section 5.1 (Dose-escalation and Dose-expansion Portions of the Study)	5.1 PART 1: PHASE 1B DOSE-ESCALATION AND DOSE-EXPANSION PORTIONS OF THE STUDY	5.1 ~~PART 1: PHASE 1B~~ DOSE-ESCALATION AND DOSE-EXPANSION PORTIONS OF THE STUDY	The study is no longer divided into 2 parts
Section 5.1 (Dose-escalation and Dose-expansion Portions of the Study)	In Part 1 of the study, the safety, MTD, PK/PDn, and RP3D of oprozomib when given in combination with pomalidomide and dexamethasone will be assessed using a standard 3 + 3 dose-escalation design.	In **this** study, the safety, MTD, PK/PDn, and RP3D of oprozomib when given in combination with pomalidomide and dexamethasone will be assessed using a standard 3 + 3 dose-escalation design.	The study is no longer divided into 2 parts

Section(s)	Changed from	Changed to	Rationale
Section 5.1.1 Dose-escalations Schema for the 5/14 Oprozomib Dosing Schedule	The primary and alternative pathways for dose escalation of oprozomib and pomalidomide in the Phase 1b portion of the study for the 5/14 schedule are summarized in Table 3 through Table 5; these are examples, and are not inclusive of all possible dose-escalation paths.	The primary and alternative pathways for dose escalation of oprozomib and pomalidomide ~~in the Phase 1b portion of the study~~ for the 5/14 schedule are summarized in Table 3 through Table 5; these are examples, and are not inclusive of all possible dose-escalation paths.	The study is no longer divided into 2 parts
Section 5.1.3 (Dose-limiting Toxicities)	The decision to escalate to the next higher dose of oprozomib in the Phase 1b portion of the study will be based on an assessment of study drug-related DLTs during Cycle 1 by the CSRC.	The decision to escalate to the next higher dose of oprozomib in th**is** study will be based on an assessment of study drug-related DLTs during Cycle 1 by the CSRC.	The study is no longer divided into 2 parts
Section 5.1.4 (Subject Replacement)	In the Phase 1b portion of the study, subjects must meet the following criteria to be considered evaluable for MTD determination during the 4-week DLT evaluation period unless a DLT occurs before the subject receives all planned doses of oprozomib for both the 5/14 and 2/7 dosing schedules:	**S**ubjects must meet the following criteria to be considered evaluable for MTD determination during the 4-week DLT evaluation period unless a DLT occurs before the subject receives all planned doses of oprozomib for both the 5/14 and 2/7 dosing schedules:	The study is no longer divided into 2 parts
Section 5.1.5 (Dose Expansion)	Once the MTD and the recommended dose for the expansion phase have been determined, a minimum of 20 additional subjects at 1 or both schedules of oprozomib at the sponsor's discretion will be enrolled in the dose-expansion portion of Part 1 in order to continue the evaluation of the safety and efficacy of the regimen as a prelude to initiation of the Phase 3 portion of the study.	Once the MTD and the recommended dose for the expansion phase have been determined, a minimum of 20 additional subjects at 1 or both schedules of oprozomib at the sponsor's discretion will be enrolled in the dose-expansion portion **of the study** in order to continue the evaluation of the safety and efficacy of the regimen.	Removed Phase 3 text to reflect what data was collected for the study

Section(s)	Changed from	Changed to	Rationale
Section 5.2 (Part 2: Randomization Phase 3 Portion of the Study)	5.2 PART 2: RANDOMIZED PHASE 3 PORTION OF THE STUDY Part 2 will consist of a placebo-controlled, double-blind randomized Phase 3 component. Enrollment to the Phase 3 portion will not commence until the CSRC has evaluated all available safety information from a minimum of 10 subjects who have completed ≥ 2 cycles of therapy and enrollment of the remaining 10 subjects in the dose expansion has occurred at 1 or both schedules per the sponsor's discretion. This information will inform the selection of a RP3D and schedule by the sponsor and CSRC. During Part 2, subjects will be randomized in a 2:1 to receive oprozomib or placebo administered orally in combination with pomalidomide and dexamethasone in 28-day cycles until disease progression or unacceptable toxicity.	~~5.2 PART 2: RANDOMIZED PHASE 3 PORTION OF THE STUDY~~ ~~Part 2 will consist of a placebo-controlled, double-blind randomized Phase 3 component. Enrollment to the Phase 3 portion will not commence until the CSRC has evaluated all available safety information from a minimum of 10 subjects who have completed ≥ 2 cycles of therapy and enrollment of the remaining 10 subjects in the dose expansion has occurred at 1 or both schedules per the sponsor's discretion. This information will inform the selection of a RP3D and schedule by the sponsor and CSRC. During Part 2, subjects will be randomized in a 2:1 to receive oprozomib or placebo administered orally in combination with pomalidomide and dexamethasone in 28-day cycles until disease progression or unacceptable toxicity.~~	Removed Phase 3 text to reflect what data was collected for the study
Section 5.2 (Estimated Study Duration and Study Closure) – previously Section 5.3 in Amendment 2	The total study duration is expected to be approximately 32-33 months.	The total study duration is expected to be approximately **12-13** months.	Changed to reflect removal of Part 2 (Phase 3) of the study
Section 5.2 (Estimated Study Duration and Study Closure) – previously Section 5.3 in Amendment 2	• Approximately 13 additional months will be required to enroll subjects in the Phase 3 portion of the study • Assuming an enrollment rate of 22 subjects per month, it is estimated that the final analysis of PFS will occur approximately 17 months after the first subject is enrolled in the Phase 3 portion of the study	• ~~Approximately 13 additional months will be required to enroll subjects in the Phase 3 portion of the study~~ • ~~Assuming an enrollment rate of 22 subjects per month, it is estimated that the final analysis of PFS will occur approximately 17 months after the first subject is enrolled in the Phase 3 portion of the study~~	Removed Phase 3 text to reflect what data was collected for the study

Section(s)	Changed from	Changed to	Rationale
Section 5.3 (Minimizing Bias) – previously Section 5.4 in Amendment 2	5.4.1 RANDOMIZATION After screening and eligibility determination, eligible subjects will be randomized in a 2:1 ratio to receive a regimen consisting of OPomd or Pomd plus placebo, respectively. Central randomization will be implemented in this part of the study through the use of an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS). Eligible subjects will be stratified by: • Age: < 75 years old versus ≥ 75 years old • Number of prior therapies: 2 versus 3 or more • Carfilzomib status: Carfilzomib-naïve/sensitive versus carfilzomib-refractory. Carfilzomib-sensitive multiple myeloma patients are defined as having had previously achieved a PR or greater with therapy that includes carfilzomib (or carfilzomib monotherapy), and did not experience PD until more than 60 days after their last dose of carfilzomib. Carfilzomib-refractory multiple myeloma is defined as disease that is nonresponsive while on primary or salvage therapy that includes carfilzomib, or that progresses on or within 60 days of last therapy. Within each stratum, treatment assignment will be made using a permuted block randomization scheme. Treatment will begin on the day of randomization, if possible, but not more than 5 calendar days after randomization according to treatment group assignment. Treatment initiation beyond 5 days after randomization must be approved by the Onyx medical monitor or designee.	~~5.4.1 RANDOMIZATION~~ ~~After screening and eligibility determination, eligible subjects will be randomized in a 2:1 ratio to receive a regimen consisting of OPomd or Pomd plus placebo, respectively. Central randomization will be implemented in this part of the study through the use of an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS).~~ ~~Eligible subjects will be stratified by:~~ ~~• Age: < 75 years old versus ≥ 75 years old~~ ~~• Number of prior therapies: 2 versus 3 or more~~ ~~• Carfilzomib status: Carfilzomib-naïve/sensitive versus carfilzomib-refractory. Carfilzomib-sensitive multiple myeloma patients are defined as having had previously achieved a PR or greater with therapy that includes carfilzomib (or carfilzomib monotherapy), and did not experience PD until more than 60 days after their last dose of carfilzomib. Carfilzomib-refractory multiple myeloma is defined as disease that is nonresponsive while on primary or salvage therapy that includes carfilzomib, or that progresses on or within 60 days of last therapy.~~ ~~Within each stratum, treatment assignment will be made using a permuted block randomization scheme.~~ ~~Treatment will begin on the day of randomization, if possible, but not more than 5 calendar days after randomization according to treatment group assignment. Treatment initiation beyond 5 days after randomization must be approved by the Onyx medical monitor or designee.~~	
Section 5.3.1 (Blinding) – previously Section 5.4.2 in Amendment 2	Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study Both the Phase 1b dose-escalation and -expansion portions of Part 1 are open-label.	Both the dose-escalation and dose-expansion portions of **this study** are open-label.	The study no longer is divided into 2 parts

Section(s)	Changed from	Changed to	Rationale
Section 5.3.1 (Blinding) – previously Section 5.4.2 in Amendment 2	Part 2: Randomized Phase 3 Portion of the Study The second part of the study is a Phase 3, randomized, double-blind, placebo-controlled, multicenter clinical trial. In accordance with regulatory reporting requirements, Onyx will unblind the identity of the study medication for all unexpected SAEs that are considered by the investigator to be related to the study drug (oprozomib). Unblinding for other reasons except as noted above before final analysis of the primary efficacy endpoint is not permitted. Under no circumstances are subjects who enroll in this study permitted to be rerandomized to this study and enroll for a second course of treatment. The password-protected and/or encrypted electronic randomization list will be kept in a central repository by the sponsor's unblinding statistician. An open key to the code will not be available at the study site, to the sponsor's monitors, project statisticians, or the project team at Onyx. All other individuals directly involved in this study will remain blinded until the final analysis of the primary efficacy endpoint. For Phase 3 only, an independent, external Data Monitoring Committee (DMC) will monitor the conduct of the study and undertake periodic unblinded assessments of safety data to protect the safety of study subjects and ensure integrity of the study.	~~Part 2: Randomized Phase 3 Portion of the Study~~ ~~The second part of the study is a Phase 3, randomized, double-blind, placebo-controlled, multicenter clinical trial. In accordance with regulatory reporting requirements, Onyx will unblind the identity of the study medication for all unexpected SAEs that are considered by the investigator to be related to the study drug (oprozomib). Unblinding for other reasons except as noted above before final analysis of the primary efficacy endpoint is not permitted.~~ ~~Under no circumstances are subjects who enroll in this study permitted to be rerandomized to this study and enroll for a second course of treatment. The password-protected and/or encrypted electronic randomization list will be kept in a central repository by the sponsor's unblinding statistician. An open key to the code will not be available at the study site, to the sponsor's monitors, project statisticians, or the project team at Onyx. All other individuals directly involved in this study will remain blinded until the final analysis of the primary efficacy endpoint.~~ ~~For Phase 3 only, an independent, external Data Monitoring Committee (DMC) will monitor the conduct of the study and undertake periodic unblinded assessments of safety data to protect the safety of study subjects and ensure integrity of the study.~~	Removed Phase 3 text to reflect what data was collected for the study
Section 9 (Study Drug)	*New text added*	**No changes in drug product, dosage, or treatment-regimen occurred in this protocol amendment from the previous version.**	Added text to explain no changes to dose in Amendment 3

Section(s)	Changed from	Changed to	Rationale
Section 10.1 (Oprozomib Treatment Administration)	10.1 OPROZOMIB AND PLACEBO TREATMENT ADMINISTRATION Oprozomib ER Tablets or placebo (for Phase 3 only) will be administered in single daily doses.	10.1 OPROZOMIB ~~AND PLACEBO~~ TREATMENT ADMINISTRATION Oprozomib ER Tablets ~~or placebo (for Phase 3 only)~~ will be administered in single daily doses.	Removed Phase 3 text to reflect what data was collected for the study
Section 10.1 (Oprozomib Treatment Administration)	In the Phase 1b dose-escalation and dose-expansion portions of the study, subjects who permanently discontinue pomalidomide or oprozomib may continue on study. If both pomalidomide and oprozomib are permanently discontinued, study treatment will be discontinued but the subject will be followed until disease progression. In the Phase 3 portion of the study, subjects who permanently discontinue any or all components of study treatment for reasons other than progressive disease will continue the remaining study treatment, if any, and be followed for disease progression.	In the ~~Phase 1b~~ dose-escalation and dose-expansion portions of the study, subjects who permanently discontinue pomalidomide or oprozomib may continue on study. If both pomalidomide and oprozomib are permanently discontinued, study treatment will be discontinued but the subject will be followed until disease progression. ~~In the Phase 3 portion of the study, subjects who permanently discontinue any or all components of study treatment for reasons other than progressive disease will continue the remaining study treatment, if any, and be followed for disease progression.~~	Removed Phase 3 text to reflect what data was collected for the study
Section 10.2 (Pomalidomide Treatment Administration)	The starting dose of pomalidomide for the Phase 1b portion of the study is 4 mg once daily, orally, on Days 1–21 of repeated 28-day cycles until disease progression.	The starting dose of pomalidomide for th**is** study is 4 mg once daily, orally, on Days 1–21 of repeated 28-day cycles until disease progression.	The study is no longer divided into 2 parts
Section 10.4 (Dose Modification Guidelines)	Monotherapy with dexamethasone is not allowed in the Phase 1b dose-escalation and dose-expansion portions of the study. In the event that oprozomib or pomalidomide is permanently discontinued in Phase 3 only, dexamethasone may be continued.	Monotherapy with dexamethasone is not allowed in the ~~Phase 1b~~ dose-escalation and dose-expansion portions of the study. ~~In the event that oprozomib or pomalidomide is permanently discontinued in Phase 3 only, dexamethasone may be continued.~~	Removed Phase 3 text to reflect what data was collected for the study
Section 10.4.1 (Dose Reductions)	For the Phase 1b study, the initial cohort will start at an oprozomib dose level of 150 mg for the 5/14 schedule and 210 mg for the 2/7 schedule.	For th**is** study, the initial cohort will start at an oprozomib dose level of 150 mg for the 5/14 schedule and 210 mg for the 2/7 schedule.	The study is no longer divided into 2 parts

Section(s)	Changed from	Changed to	Rationale
Section 10.4.1 (Dose Reductions)	Modifications of the dose of oprozomib/placebo will occur in up to three 30-mg decrements down to a minimum dose of 150 mg.	Modifications of the dose of oprozomib~~/placebo~~ will occur in up to three 30-mg decrements down to a minimum dose of 150 mg.	Removed Phase 3 text to reflect what data was collected for the study
Section 10.4.1 (Dose Reductions)	For Parts 1 and 2 of the study, dose reduction levels for pomalidomide are provided in Table 11.	**The** dose reduction levels for pomalidomide are provided in Table 11.	Removed Phase 3 text to reflect what data was collected for the study
Section 10.4.1 (Dose Reductions)	In the event oprozomib or pomalidomide is permanently discontinued in Phase 3 only, dexamethasone may be continued.	~~In the event oprozomib or pomalidomide is permanently discontinued in Phase 3 only, dexamethasone may be continued.~~	Removed Phase 3 text to reflect what data was collected for the study
Section 10.5 (Definition of Dose-limiting Toxicity)	During the Phase 1b portion of the study, assessment of DLTs will occur during the 28-day period of Cycle 1 combination therapy.	During th**is** study, assessment of DLTs will occur during the 28-day period of Cycle 1 combination therapy.	The study is no longer divided into 2 parts.

Section(s)	Changed from	Changed to	Rationale
Section 11.3 (Disease Response Assessments)	The schedule of disease assessments for treated subjects is provided in Appendices A1, A2, B1, B2, C1, and C2. Disease response will be assessed by the investigator. Beginning with Cycle 1, assessments are to be completed at the end of every 4-week cycle for the first 18 months of study treatment, and then at the end of every other cycle (every 8 weeks), beginning with Month 20, for the remainder of study treatment and throughout long-term follow-up.	The schedule of disease assessments for treated subjects is provided in Appendices A1, A2, B1, and B2~~, C1, and C2~~. Disease response will be assessed by the investigator. Beginning with Cycle 1, assessments are to be completed at the end of every 4-week cycle for the first 18 months of study treatment, and then at the end of every other cycle (every 8 weeks), beginning with Month 20, for the remainder of study treatment ~~and throughout long-term follow-up~~.	Provide convenience for those on study treatment as study has completed its abbreviated report
Section 11.4.1 (Pharmacokinetic Measurements)	11.4.1.1 PHASE 1B DOSE ESCALATION AND EXPANSION In the Phase 1b dose-escalation and dose-expansion portions of the study, blood samples will be collected from all subjects from both schedules to measure plasma concentrations of oprozomib at 1 predose time point and up to 7 postdose time points on Day 1 of Cycle 1 and Cycle 2 (0.25, 0.5, 1, 2, 3, 4, and 6 hours postdose) and 1 predose time point on Day 2 of Cycle 1. Estimates of oprozomib PK parameters will be determined when possible. 11.4.1.2 Phase 3 In the Phase 3 portion of the study, samples will be collected from all subjects enrolled in the OPomd and the Pomd + placebo treatment arms. The plasma samples will be randomly obtained from each sampling window below on Day 1 of Cycle 1 and Cycle 3. The first postdose sampling window in Cycle 1 and Cycle 3 will be between 1 to 2.5 hours and the second postdose sampling window will be between 2.75 to 5 hours. Plasma samples from the OPomd arm will be analyzed for oprozomib concentrations (note the difference between sample collection and sample analysis). Population PK parameter estimates and variability in these estimates will be determined using a population-based analysis method.	~~11.4.1.1 PHASE 1B DOSE ESCALATION AND EXPANSION~~ In the ~~Phase 1b~~ dose-escalation and dose-expansion portions of the study, blood samples will be collected from all subjects from both schedules to measure plasma concentrations of oprozomib at 1 predose time point and up to 7 postdose time points on Day 1 of Cycle 1 and Cycle 2 (0.25, 0.5, 1, 2, 3, 4, and 6 hours postdose) and 1 predose time point on Day 2 of Cycle 1. Estimates of oprozomib PK parameters will be determined when possible. ~~11.4.1.2 Phase 3~~ ~~In the Phase 3 portion of the study, samples will be collected from all subjects enrolled in the OPomd and the Pomd + placebo treatment arms. The plasma samples will be randomly obtained from each sampling window below on Day 1 of Cycle 1 and Cycle 3. The first postdose sampling window in Cycle 1 and Cycle 3 will be between 1 to 2.5 hours and the second postdose sampling window will be between 2.75 to 5 hours. Plasma samples from the OPomd arm will be analyzed for oprozomib concentrations (note the difference between sample collection and sample analysis). Population PK parameter estimates and variability in these estimates will be determined using a population-based analysis method.~~	Removed Phase 3 text to reflect what data was collected for the study

Section(s)	Changed from	Changed to	Rationale
Section 11.4.2 (Pharmacodynamic Measurements)	In the Phase 1b dose-escalation and dose-expansion portions of the study, blood samples for the quantitation of proteasome inhibition by oprozomib will be collected from all subjects for both schedules at 1 predose time point, up to 2 postdose time points (4 and 6 hours postdose) on Day 1 of Cycle 1 and Cycle 2, and 1 predose timepoint on Day 2 of Cycle 1. These timepoints are also specified in the Laboratory Manual. Blood samples for PDn analyses will not be collected in Phase 3.	In the ~~Phase 1b~~ dose-escalation and dose-expansion portions of the study, blood samples for the quantitation of proteasome inhibition by oprozomib will be collected from all subjects for both schedules at 1 predose time point, up to 2 postdose time points (4 and 6 hours postdose) on Day 1 of Cycle 1 and Cycle 2, and 1 predose timepoint on Day 2 of Cycle 1. These timepoints are also specified in the Laboratory Manual. ~~Blood samples for PDn analyses will not be collected in Phase 3.~~	Removed Phase 3 text to reflect what data was collected for the study
Section 11.4.3 (Genomic Measurements)	Analysis of genomic biomarkers that may predict for response and resistance following treatment with proteasome inhibitors will be conducted for all subjects from all phases of the study who consent to optional genomic biomarker analysis.	Analysis of genomic biomarkers that may predict for response and resistance following treatment with proteasome inhibitors will be conducted for all subjects **in** the study who consent to optional genomic biomarker analysis.	Removed Phase 3 text to reflect what data was collected for the study
Section 11.4.3 (Genomic Measurements)	Bone marrow aspirate or biopsy collection does not need to be repeated if previously completed within 45 days prior to Cycle 1 Day 1 dosing, and for Phase 3 only, if it was processed at the central laboratory. Additional bone marrow samples for biomarkers may be collected at disease progression (End of Study Treatment due to PD or Long-Term Follow-Up) from all subjects who consent.	Bone marrow aspirate or biopsy collection does not need to be repeated if previously completed within 45 days prior to Cycle 1 Day 1 dosing~~, and for Phase 3 only, if it was processed at the central laboratory~~. Additional bone marrow samples for biomarkers may be collected at disease progression (End of Study Treatment due to PD ~~or Long-Term Follow-Up~~) from all subjects who consent.	Provide convenience for those on study treatment as study has completed its abbreviated report
Section 11.5 (Patient-reported Outcomes Assessments	Beginning with Cycle 1, HRQoL/PRO assessments are to be completed at the beginning of every cycle prior to drug administration through End of Study Treatment/Early Discontinuation visit during the dose-expansion portion of the trial, and at the beginning of every cycle prior to drug administration through End of Study Treatment/Early Discontinuation visit and then every 12 weeks during the long-term follow-up in the Phase 3 portion of the study.	Beginning with Cycle 1, HRQoL/PRO assessments are to be completed at the beginning of every cycle prior to drug administration through End of Study Treatment/Early Discontinuation visit during the dose-expansion portion of the trial, and at the beginning of every cycle prior to drug administration through End of Study Treatment/Early Discontinuation visit ~~and then every 12 weeks during the long-term follow-up in the Phase 3 portion of the study.~~	Removed Phase 3 text to reflect what data was collected for the study

Section(s)	Changed from	Changed to	Rationale
Section 12 (Study and Study Treatment Discontinuation)	*New text added*	Any subject who withdraws without PD will **no longer** be followed with long-term assessments every 4 weeks through 18 months on study, and then every 8 weeks thereafter, beginning with Month 20, until progression or initiation of next therapy **under Amendment 3**.	Provide convenience for those on study treatment as study has completed its abbreviated report
Section 12.1 (Study Treatment Discontinuation)	For both parts of the study, subjects may withdraw from study treatment at any time.	For th**is** study, subjects may withdraw from study treatment at any time.	Study is no longer divided into 2 parts
Section 12.1 (Study Treatment Discontinuation)	Part 1 Phase 1b Dose Escalation and Expansion Only	~~Part 1 Phase 1b Dose Escalation and Expansion Only~~	Study is no longer divided into 2 parts
Section 12.3 (Long-term Follow-up	After completion of the End of Study Treatment visit, subjects will be followed for disease progression, OS, and quality of life (QOL).	After completion of the End of Study Treatment visit, subjects will be followed for ~~disease progression,~~ OS~~, and quality of life (QOL)~~.	Provide convenience for those on study treatment as study has completed its abbreviated report

Section(s)	Changed from	Changed to	Rationale
Section 12.3 (Long-term Follow-up	• For subjects who have not progressed at end of study treatment, disease response assessments will be performed every 4 weeks through 18 months on study, and then every 8 weeks thereafter, beginning with Month 20, until progression or initiation of next therapy	• For subjects who have not progressed at end of study treatment, disease response assessments will **no longer** be performed every 4 weeks through 18 months on study, and then every 8 weeks thereafter, beginning with Month 20, until progression or initiation of next therapy **under Amendment 3**	Provide convenience for those on study treatment as study has completed its abbreviated report
Section 12.3 (Long-term Follow-up)	Quality of Life • For Phase 3 only, in long-term follow-up, QOL questionnaires will be collected from subjects (regardless of disease status) every 12 weeks.	~~Quality of Life~~ • ~~For Phase 3 only, in long-term follow-up, QOL questionnaires will be collected from subjects (regardless of disease status) every 12 weeks.~~	Removed Phase 3 text to reflect what data was collected for the study
Section 12.4 (Study Treatment)	• The DMC recommends termination of the Phase 3 portion of the study	• ~~The DMC recommends termination of the Phase 3 portion of the study~~	Removed Phase 3 text to reflect what data was collected for the study

Section(s)	Changed from	Changed to	Rationale
Section 13.5 (Serious Adverse Event Reporting and Documentation Requirements)	Onyx Drug Safety must be notified of the occurrence of any SAE within 24 hours of the investigator, designee, or site personnel's knowledge of the event. The SAE will be reported by completing and submitting the SAE report form through the EDC system. In the event that the EDC system is not available, paper SAE report forms may be used to report the SAE to Onyx Drug Safety. Please refer to the SAE Reporting Guidelines in the study reference manual. Follow-up reports must be submitted in a timely fashion as additional information becomes available.	**Amgen Global Patient** Safety must be notified of the occurrence of any SAE within 24 hours of the investigator, designee, or site personnel's knowledge of the event. The SAE will be reported by completing and submitting the SAE report form through the EDC system. In the event that the EDC system is not available, paper SAE report forms may be used to report the SAE to **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 Contingency Report Form (see Appendix N) 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 off line 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 off line, then the site can report this information on a paper Serious Adverse Event Report Form (see Appendix N).** **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 event data to Amgen Global Patient Safety within 24 hours of receipt of the information.**	Update safety reporting language with latest template.

Section 13.6 (Pregnancy Reporting)	Pregnancy occurring in a female subject, or in a male subject's partner, while enrolled in this clinical trial through 30 days after the subject's last dose of study drug, although not considered an SAE, must be reported to Onyx Drug Safety on a Pregnancy Reporting Form within 24 hours of the investigator, designee, or site personnel learning of the event. If the subject is pregnant, all study treatment must be discontinued immediately and the pregnancy must be reported to the investigator and sponsor within 24 hours. In the event of a pregnancy in the partner of a male subject, the pregnant partner will be asked to complete an authorization form prior to the collection of any pregnancy data. If such authorization is provided by the partner, the investigator will follow the pregnancy of the male subject's partner until completion or termination of the pregnancy. Any abnormal maternal, fetal, or neonatal outcomes must be reported to Onyx Drug Safety as a follow-up on the Pregnancy Reporting Form within the same time parameters as stated above for report of a pregnancy. If the outcome of the pregnancy meets an SAE criterion (e.g., spontaneous abortion, stillbirth, neonatal death, or fetal or neonatal congenital anomaly), the investigator will report the SAE through the EDC system. A fetus exposed to study drug by a parent (female subject or male subject's partner) will be followed until a minimum of 12 weeks after birth. Follow-up may be extended at the discretion of the Onyx study medical monitor. All findings inclusive of SAEs will be reported to Onyx Drug Safety within 24 hours of the investigator, designee, or site personnel learning of the event. Subject to the parents' continuing authorization, SAEs that may occur in these infants will be reported to Onyx Drug Safety.	Pregnancy occurring in a female subject, or in a male subject's partner, while enrolled in this clinical trial through 30 days after the subject's last dose of study drug, although not considered an SAE, must be reported to **Amgen Global Patient** Safety on a**n Amgen** Pregnancy **Notification Worksheet (Appendix O)** within 24 hours of the investigator, designee, or site personnel learning of the event. If the subject is pregnant, all study treatment must be discontinued immediately and the pregnancy must be reported to the investigator and sponsor within 24 hours. **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 O). 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).**	Update pregnancy reporting language with latest template.

		• **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 13.5. 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 O). 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.** **Collection of Lactation Information** • **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 P) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.**	

Section(s)	Changed from	Changed to	Rationale
		• **Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 22.** **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 14.1 (Study Endpoints)	14.1.1 PART 1: PHASE 1B DOSE ESCALATION AND DOSE EXPANSION PORTIONS OF THE STUDY (BY SCHEDULE)	~~14.1.1 PART 1: PHASE 1B DOSE ESCALATION AND DOSE EXPANSION PORTIONS OF THE STUDY (BY SCHEDULE)~~	The study is no longer divided into 2 parts
Section 14.1.1 (Primary Endpoints) – previously Section 14.1.1. 1 in Amendment 2	14.1.1 PRIMARY ENDPOINTS-PART 1	14.1.1 PRIMARY ENDPOINTS-~~PART 1~~	The study is longer divided into 2 parts
Section 14.1.2 (Secondary Endpoints) – previously Section 14.1.1. 2 in Amendment 2	14.1.2 SECONDARY ENDPOINTS-PART 1	14.1.2 SECONDARY ENDPOINTS-~~PART 1~~	The study is no longer divided into 2 parts
Section 14.1.3 (Exploratory Endpoints) – previously Section 14.1.1. 3 in Amendment 2	14.1.3 EXPLORATORY ENDPOINTS-PART 1	14.1.3 EXPLORATORY ENDPOINTS-~~PART 1~~	The study is no longer divided into 2 parts

Section 14.1.2 (Part 2: Randomized Phase 3 Portion of the Study)	14.1.2 PART 2: RANDOMIZED PHASE 3 PORTION OF THE STUDY 14.1.2.1 Primary Endpoint-Part 2 • Progression-free survival, defined as time from randomization to the earlier of disease progression determined by ORCA according to the IMWG-URC, or death due to any cause. 14.1.2.2 Secondary Endpoints-Part 2 • Overall survival defined as time from randomization to death due to any cause • Overall response, defined as the best response of sCR, CR, VGPR, or PR as determined by ORCA according to the IMWG-URC • Clinical benefit, defined as the best response of MR or better, as determined by ORCA according to the IMWG-URC and modified EBMT criteria • Duration of response, defined as the time from the first evidence of confirmed PR or better to disease progression, as determined by ORCA according to the IMWG-URC, or death due to any cause • Improvement in renal function, as defined by an increase in GFR of at least 10 mL/min • Improvement in hemoglobin, as defined by an increase of at least 2 g/dL • Adverse events and laboratory abnormalities graded according to NCI-CTCAE, Version 4.03 • Vital signs and clinical laboratory results during and following study drug administration • Bone pain and the impact of bone pain measured with the BPI-SF • Change over time in the global health status/QoL scale of the EORTC QLQ-C30 • Change over time in the disease symptoms subscale of the EORTC QLQ-MY20	~~14.1.2 PART 2: RANDOMIZED PHASE 3 PORTION OF THE STUDY~~ ~~14.1.2.1 Primary Endpoint-Part 2~~ • ~~Progression-free survival, defined as time from randomization to the earlier of disease progression determined by ORCA according to the IMWG-URC, or death due to any cause.~~ ~~14.1.2.2 Secondary Endpoints-Part 2~~ • ~~Overall survival defined as time from randomization to death due to any cause~~ • ~~Overall response, defined as the best response of sCR, CR, VGPR, or PR as determined by ORCA according to the IMWG-URC~~ • ~~Clinical benefit, defined as the best response of MR or better, as determined by ORCA according to the IMWG-URC and modified EBMT criteria~~ • ~~Duration of response, defined as the time from the first evidence of confirmed PR or better to disease progression, as determined by ORCA according to the IMWG-URC, or death due to any cause~~ • ~~Improvement in renal function, as defined by an increase in GFR of at least 10 mL/min~~ • ~~Improvement in hemoglobin, as defined by an increase of at least 2 g/dL~~ • ~~Adverse events and laboratory abnormalities graded according to NCI-CTCAE, Version 4.03~~ • ~~Vital signs and clinical laboratory results during and following study drug administration~~ • ~~Bone pain and the impact of bone pain measured with the BPI-SF~~ • ~~Change over time in the global health status/QoL scale of the EORTC QLQ-C30~~ • ~~Change over time in the disease symptoms subscale of the EORTC QLQ-MY20~~	Removed Phase 3 text to reflect what data was collected for the study

Section(s)	Changed from	Changed to	Rationale
	• Change over time in neurotoxicity symptoms measured by the FACT/GOG-Ntx4 score (Version 4) • Change over time in health status assessed by EQ-5D-5L • Population based PK parameters including, but not limited to, area under the plasma concentration time curve (AUC) and C_{max}, determined for OPomd subjects 14.1.2.3 Exploratory Endpoints-Part 2 • Progression-free survival and overall response, as determined by the investigator according to the IMWG-URC • Duration of response, defined as the time from the first evidence of confirmed PR or better to disease progression as determined by the investigator according to the IMWG-URC or death due to any cause • Clinical benefit as determined by the investigator according to the IMWG-URC and modified EBMT criteria • Duration of clinical benefit (DOCB), defined as the time from first evidence of MR or better to disease progression or death due to any cause, as determined by ORCA and the investigator according to the IMWG-URC and modified EBMT criteria • Genomic biomarkers that may be correlated with antitumor activity and resistance following treatment with proteasome inhibitors • Neuropathy events (defined as Grade 2 or higher peripheral neuropathy) • Change over time in all domains of the EORTC QLQ-C30 and EORTC QLQ-MY20 (excluding the global health scale and disease symptoms subscale, respectively)	~~• Change over time in neurotoxicity symptoms measured by the FACT/GOG-Ntx4 score (Version 4)~~ ~~• Change over time in health status assessed by EQ-5D-5L~~ ~~• Population based PK parameters including, but not limited to, area under the plasma concentration time curve (AUC) and C_{max}, determined for OPomd subjects~~ ~~14.1.2.3 Exploratory Endpoints-Part 2~~ ~~• Progression-free survival and overall response, as determined by the investigator according to the IMWG-URC~~ ~~• Duration of response, defined as the time from the first evidence of confirmed PR or better to disease progression as determined by the investigator according to the IMWG-URC or death due to any cause~~ ~~• Clinical benefit as determined by the investigator according to the IMWG-URC and modified EBMT criteria~~ ~~• Duration of clinical benefit (DOCB), defined as the time from first evidence of MR or better to disease progression or death due to any cause, as determined by ORCA and the investigator according to the IMWG-URC and modified EBMT criteria~~ ~~• Genomic biomarkers that may be correlated with antitumor activity and resistance following treatment with proteasome inhibitors~~ ~~• Neuropathy events (defined as Grade 2 or higher peripheral neuropathy)~~ ~~• Change over time in all domains of the EORTC QLQ-C30 and EORTC QLQ-MY20 (excluding the global health scale and disease symptoms subscale, respectively)~~	

Section(s)	Changed from	Changed to	Rationale
Section 14.3 (Data Monitoring Committee)	In Part 1 of the study, safety will be monitored by a CSRC for both the Phase 1b dose-escalation and dose-expansion portions of the study. In the Phase 3 portion of the study, no formal efficacy interim analyses are planned for the PFS primary endpoint. An interim analysis of OS, the key secondary endpoint, is planned at the time of primary analysis of PFS. Details of the efficacy monitoring plan for OS are described in Section 14.5.2.2. Overall survival may be evaluated by the DMC in their ongoing safety review during the course of the study. As the objective of this evaluation is not to declare OS efficacy before the planned efficacy interim and final analyses of OS, alpha level will not be adjusted for these reviews. An independent DMC will be convened for the Phase 3 portion of the study and will act in an advisory capacity to the sponsor with respect to safeguarding the interests of study subjects, assessing interim safety and efficacy (OS secondary only) data, and for monitoring the overall conduct of the study. To enhance the integrity of the study, the DMC may also formulate recommendations relating to the selection, recruitment, and retention of subjects, management of subjects, improving adherence to protocol treatment, and the procedures for data management and quality control. The DMC will meet to review safety data on a periodic basis, but no less frequently than approximately every 6 months. The initial meeting should occur within 3 months after approximately 30 subjects are enrolled in the Phase 3 portion of the study. Unplanned safety review meetings of the DMC may be called at any time by the sponsor or the DMC Chair if additional review of safety data is warranted. The membership criteria and other details of the DMC will be described in the DMC Charter.	In th**is** study, safety will be monitored by a CSRC for both the dose-escalation and dose-expansion portions of the study.	Removed Phase 3 text to reflect what data was collected for the study

Section(s)	Changed from	Changed to	Rationale
Section 14.5.1.1 (Safety Population)	All subjects receiving any amount of study treatment (oprozomib, placebo, pomalidomide, or dexamethasone) will be included in safety analyses. In the Phase 3 portion of the study, subjects will be included in the treatment group corresponding to the actual treatment received.	All subjects receiving any amount of study treatment (oprozomib, ~~placebo,~~ pomalidomide, or dexamethasone) will be included in safety analyses. ~~In the Phase 3 portion of the study, subjects will be included in the treatment group corresponding to the actual treatment received.~~	Removed Phase 3 text to reflect what data was collected for the study
Section 14.5.1.2 (Efficacy Population)	Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study For Part 1 of the study, the efficacy population is equivalent to the safety population. Part 2: Randomized Phase 3 Portion of the Study For the Phase 3 portion of the study, the efficacy population will include all randomized subjects as randomized, i.e., according to the intent to treat (ITT) principle.	For th**is** study, the efficacy population is equivalent to the safety population.	Removed Phase 3 text to reflect what data was collected for the study
Section 14.5.2 (Efficacy Analyses)	All efficacy analyses will be presented separately for Part 1 and Part 2 of the study. 14.5.2.1 Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study	~~All efficacy analyses will be presented separately for Part 1 and Part 2 of the study.~~ ~~14.5.2.1 Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study~~	Removed Phase 3 text to reflect what data was collected for the study

<table>
<tr>
<td>Section 14.5.2 (Efficacy Analyses)</td>
<td>
14.5.2.2 Part 2: Randomized Phase 3 Portion of the Study
Unless otherwise noted, all primary and secondary efficacy analyses will include all randomized subjects analyzed according to the ITT principle (Section 14.5.1), i.e., subjects will be analyzed by the treatment assigned at randomization.
Primary Efficacy Analysis
The primary efficacy endpoint for the Phase 3 portion of the study is PFS, defined as the time from randomization to the earlier of disease progression or death due to any cause. Disease progression will be determined using the IMWG-URC (Appendix D). Response and disease progression will be determined using a validated computer algorithm (ORCA) as well as by local investigators. The primary analysis of PFS will be based on ORCA-assessed outcomes. The PFS outcomes assessed by the investigators will serve as a supportive analysis of the primary analysis of PFS.
For purposes of calculating PFS, the start date for PD is the date at which progression is first observed. The duration of PFS will be right censored according to the conventions described in Table 18.
Table 18 Date of Progression or Censoring for Progression free Survival
<table>
<tr><th>Situation</th><th>Date of Progression or Censoring</th><th>Outcome</th></tr>
<tr><td>No baseline disease assessments</td><td>Date of randomization</td><td>Censored</td></tr>
<tr><td>No postbaseline disease assessments and alive</td><td>Date of randomization + 1 day</td><td>Censored</td></tr>
<tr><td>New anticancer treatment started before documentation of PD or death</td><td>Date of last disease assessment prior to start of a new anticancer treatment</td><td>Censored</td></tr>
</table>
</td>
<td>
~~14.5.2.2 Part 2: Randomized Phase 3 Portion of the Study~~
~~Unless otherwise noted, all primary and secondary efficacy analyses will include all randomized subjects analyzed according to the ITT principle (Section 14.5.1), i.e., subjects will be analyzed by the treatment assigned at randomization.~~
~~Primary Efficacy Analysis~~
~~The primary efficacy endpoint for the Phase 3 portion of the study is PFS, defined as the time from randomization to the earlier of disease progression or death due to any cause. Disease progression will be determined using the IMWG-URC (Appendix D). Response and disease progression will be determined using a validated computer algorithm (ORCA) as well as by local investigators. The primary analysis of PFS will be based on ORCA-assessed outcomes. The PFS outcomes assessed by the investigators will serve as a supportive analysis of the primary analysis of PFS.~~
~~For purposes of calculating PFS, the start date for PD is the date at which progression is first observed. The duration of PFS will be right censored according to the conventions described in Table 18.~~
~~Table 18 Date of Progression or Censoring for Progression free Survival~~
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<tr><th>~~Situation~~</th><th>~~Date of Progression or Censoring~~</th><th>~~Outcome~~</th></tr>
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<tr><td>~~New anticancer treatment started before documentation of PD or death~~</td><td>~~Date of last disease assessment prior to start of a new anticancer treatment~~</td><td>~~Censored~~</td></tr>
</table>
</td>
<td>Removed Phase 3 text to reflect what data was collected for the study</td>
</tr>
</table>

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	~~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	~~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 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	~~Death before first disease assessment~~	~~Date of death~~	~~Progressed~~	

PD = progressive disease.

The primary analysis of PFS will be conducted when 157 PFS events have occurred.

The primary inferential comparison between treatment groups for PFS will be based on the stratified log-rank test at an overall 0.025 (1-sided) significance level using randomization stratification factors as strata:

- Age: < 75 years versus ≥ 75 years
- Number of prior therapies: 2 versus 3 or more
- Carfilzomib status: carfilzomib naïve/sensitive versus carfilzomib-refractory. Carfilzomib-sensitive multiple myeloma patients are defined as having had previously achieved a PR or greater with therapy that includes carfilzomib (or carfilzomib monotherapy), and did not experience PD until more than 60 days after their last dose of carfilzomib.
  Carfilzomib-refractory multiple myeloma is defined as disease that is nonresponsive while on primary or

~~PD = progressive disease.~~

~~The primary analysis of PFS will be conducted when 157 PFS events have occurred.~~

~~The primary inferential comparison between treatment groups for PFS will be based on the stratified log-rank test at an overall 0.025 (1-sided) significance level using randomization stratification factors as strata:~~

- ~~Age: < 75 years versus ≥ 75 years~~
- ~~Number of prior therapies: 2 versus 3 or more~~
- ~~Carfilzomib status: carfilzomib naïve/sensitive versus carfilzomib-refractory. Carfilzomib-sensitive multiple myeloma patients are defined as having had previously achieved a PR or greater with therapy that includes carfilzomib (or carfilzomib monotherapy), and did not experience PD until more than 60 days after their last dose of carfilzomib.~~
  ~~Carfilzomib-refractory multiple myeloma is defined as disease that is nonresponsive while on primary or~~

	salvage therapy that includes carfilzomib, or that progresses on or within 60 days of last therapy. The hazard ratio between the 2 treatment arms will be estimated using a stratified Cox proportional hazards model. The distribution of PFS, including medians, will be summarized descriptively using the Kaplan- Meier method for each treatment group. The 95% CIs for median and other quartiles of PFS will be constructed using the method of Brookmeyer and Crowley (1982). Duration of follow-up for PFS will be estimated by the reverse Kaplan-Meier method of Schemper (1996). Secondary Efficacy Analyses Overall survival is defined as the time from randomization to death due to any cause. Subjects who are alive or lost to follow-up as of the data analysis cutoff date will be right censored. The censoring date will be determined from the subject's last known date alive. Final analysis of OS will be performed when 211 deaths have occurred. Two hundred and eleven (211) deaths will provide 75% power to detect a 32% decrease in the risk of OS for OPomd versus Pomd (HR = 0.68) at the 1-sided 0.025 level of significance. Under exponential distribution, 23.5 months versus 16 months is assumed for median OS for the OPomd and Pomd arms, respectively. The assumed median OS of 16 months for the Pomd group is based on a Phase 2 study of pomalidomide/dexamethasone (Jagannath 2012). Under these assumptions, and assuming 10% lost to follow-up for OS at 60 months, 211 deaths are expected to occur approximately 56 months after the study starts. The interim analysis for OS will occur at the time of the primary analysis of PFS. The primary analysis of PFS is anticipated to occur approximately 14 months after the first subject is randomized. Approximately 30% of the total number of death events is expected at the time of the primary PFS analysis. The interim and final analysis of OS will be performed using an O'Brien-Fleming group	~~salvage therapy that includes carfilzomib, or that progresses on or within 60 days of last therapy.~~ ~~The hazard ratio between the 2 treatment arms will be estimated using a stratified Cox proportional hazards model.~~ ~~The distribution of PFS, including medians, will be summarized descriptively using the Kaplan- Meier method for each treatment group. The 95% CIs for median and other quartiles of PFS will be constructed using the method of Brookmeyer and Crowley (1982). Duration of follow-up for PFS will be estimated by the reverse Kaplan-Meier method of Schemper (1996).~~ ~~Secondary Efficacy Analyses~~ ~~Overall survival is defined as the time from randomization to death due to any cause. Subjects who are alive or lost to follow-up as of the data analysis cutoff date will be right censored. The censoring date will be determined from the subject's last known date alive.~~ ~~Final analysis of OS will be performed when 211 deaths have occurred. Two hundred and eleven (211) deaths will provide 75% power to detect a 32% decrease in the risk of OS for OPomd versus Pomd (HR = 0.68) at the 1-sided 0.025 level of significance. Under exponential distribution, 23.5 months versus 16 months is assumed for median OS for the OPomd and Pomd arms, respectively. The assumed median OS of 16 months for the Pomd group is based on a Phase 2 study of pomalidomide/dexamethasone (Jagannath 2012). Under these assumptions, and assuming 10% lost to follow-up for OS at 60 months, 211 deaths are expected to occur approximately 56 months after the study starts.~~ ~~The interim analysis for OS will occur at the time of the primary analysis of PFS. The primary analysis of PFS is anticipated to occur approximately 14 months after the first subject is randomized. Approximately 30% of the total number of death events is expected at the time of the primary PFS analysis. The interim and final analysis of OS will be performed using an O'Brien-Fleming group~~	

sequential monitoring plan. The monitoring plan will include an upper boundary for benefit constructed using a false-positive error rate of 0.025 (Table 19). The Lan-Demets alpha spending function approach will be used to adjust the O'Brien-Fleming boundary if the actual interim analysis does not correspond to the projected information time.

Table 19O'Brien-Fleming Monitoring Boundary for Benefit

Information Fraction	Death Events	Study Month	Boundary (Reject H_o)	1-Sided Significance Level	Alpha Spent
30%	63	14	3.929	0.000042	0.000
100%	211	56	1.96	0.025	0.025

Statistical analyses conducted for OS will be identical to those described for PFS. In addition to the key secondary endpoint of OS, inferential testing will be conducted for ORR, CBR, improvement in renal function, improvement in hemoglobin, change over time in QLQ-MY20 total scale, and change over time in QLQ-C30 total scale.

Inferential testing of primary and selected secondary endpoints will be performed against an overall 1-sided significance level of 0.025 in accordance with a closed testing procedure (CTP). The CTP will be used to account for inflation of the overall type 1 error rate due to hypothesis testing of multiple endpoints.

The CTP will be structured as follows: If the null hypothesis for the primary efficacy endpoint of PFS is rejected at the 1-sided 0.025 level of significance, then testing of the aforementioned secondary endpoints will proceed in a sequential step down manner.

~~sequential monitoring plan. The monitoring plan will include an upper boundary for benefit constructed using a false-positive error rate of 0.025 (Table 19). The Lan-Demets alpha spending function approach will be used to adjust the O'Brien-Fleming boundary if the actual interim analysis does not correspond to the projected information time.~~

~~Table 19O'Brien-Fleming Monitoring Boundary for Benefit~~

~~Information Fraction~~	~~Death Events~~	~~Study Month~~	~~Boundary (Reject H_o)~~	~~1-Sided Significance Level~~	~~Alpha Spent~~
~~30%~~	~~63~~	~~14~~	~~3.929~~	~~0.000042~~	~~0.000~~
~~100%~~	~~211~~	~~56~~	~~1.96~~	~~0.025~~	~~0.025~~

~~Statistical analyses conducted for OS will be identical to those described for PFS. In addition to the key secondary endpoint of OS, inferential testing will be conducted for ORR, CBR, improvement in renal function, improvement in hemoglobin, change over time in QLQ-MY20 total scale, and change over time in QLQ-C30 total scale.~~

~~Inferential testing of primary and selected secondary endpoints will be performed against an overall 1-sided significance level of 0.025 in accordance with a closed testing procedure (CTP). The CTP will be used to account for inflation of the overall type 1 error rate due to hypothesis testing of multiple endpoints.~~

~~The CTP will be structured as follows: If the null hypothesis for the primary efficacy endpoint of PFS is rejected at the 1-sided 0.025 level of significance, then testing of the aforementioned secondary endpoints will proceed in a sequential step down manner.~~

	Testing of selected secondary efficacy endpoints will continue, provided the null hypothesis for each previously tested endpoint is rejected. Otherwise, no further testing will be done. The sequential order in which efficacy endpoints will be tested is as follows: • PFS • OS • ORR • CBR • Improvement in renal function • Improvement in hemoglobin • Change over time in QLQ-C30 global health scale • Change over time in QLQ-MY20 disease symptoms subscale Overall response rate will be estimated based on the proportion of subjects in each treatment group who achieve sCR, CR, VGPR, or PR as their best response across the entire treatment duration. The inferential comparison between treatment groups for this endpoint will be made using the Cochran-Mantel Haenszel chi-square test, stratified by the randomization stratification factors. Approximate 95% CIs will be calculated by treatment group for the true ORR. An estimate of the common odds ratio for overall response will be provided as a measure of the relative treatment effect. The odds ratio (and 95% CI) will be estimated using the Mantel-Haenszel method. The Pomd group will serve as the reference treatment group in the calculation of the odds ratio. Clinical benefit rate will be estimated based on the proportion of subjects in each group who achieve sCR, CR, VGPR, PR, or MR, and will be analyzed in the same manner as described previously for ORR. Improvement in renal function is defined as an increase in GFR of ≥ 10 mL/min.	~~Testing of selected secondary efficacy endpoints will continue, provided the null hypothesis for each previously tested endpoint is rejected. Otherwise, no further testing will be done. The sequential order in which efficacy endpoints will be tested is as follows:~~ ~~• PFS~~ ~~• OS~~ ~~• ORR~~ ~~• CBR~~ ~~• Improvement in renal function~~ ~~• Improvement in hemoglobin~~ ~~• Change over time in QLQ-C30 global health scale~~ ~~• Change over time in QLQ-MY20 disease symptoms subscale~~ ~~Overall response rate will be estimated based on the proportion of subjects in each treatment group who achieve sCR, CR, VGPR, or PR as their best response across the entire treatment duration. The inferential comparison between treatment groups for this endpoint will be made using the Cochran-Mantel Haenszel chi-square test, stratified by the randomization stratification factors. Approximate 95% CIs will be calculated by treatment group for the true ORR. An estimate of the common odds ratio for overall response will be provided as a measure of the relative treatment effect. The odds ratio (and 95% CI) will be estimated using the Mantel-Haenszel method. The Pomd group will serve as the reference treatment group in the calculation of the odds ratio.~~ ~~Clinical benefit rate will be estimated based on the proportion of subjects in each group who achieve sCR, CR, VGPR, PR, or MR, and will be analyzed in the same manner as described previously for ORR.~~ ~~Improvement in renal function is defined as an increase in GFR of ≥ 10 mL/min.~~	

	Improvement in hemoglobin is defined as an increase of ≥ 2 g/dL. Incidence of improvement in renal function and improvement in hemoglobin will be analyzed in the same manner as described previously for ORR. Duration of response and DOCB will be summarized for each treatment group by Kaplan-Meier method; however, no formal inferential comparisons will be made for these endpoints, as responders constitute a nonrandom subset of the ITT population. Quality of life will be assessed by the European Organization for Research and Treatment (EORTC) 30-item QLQ-C30 test and by the 20-item QLQ-MY20 module specifically designed to address the quality of life for those with multiple myeloma (Appendix E). The primary constructed scales from the QLC-C30 are: • Global Health Status/QoL • Physical Functioning, Role Functioning • Emotional Functioning • Cognitive Functioning • Social Functioning Nine additional scales can be derived: Fatigue, Nausea and Vomiting, Pain, Dyspnoea, Insomnia, Appetite Loss, Constipation, Diarrhea, and Financial Difficulties. The QLQ-MY20 EORTC questionnaire was developed to assess the quality of life in cancer subjects with multiple myeloma. The QLQ-MY20 includes 20 items assessing disease symptoms, side effects of treatment, body image, and future perspective. There are 3 multi-item scales (Disease Symptoms Scale, Side Effects of Treatment Scale, and Future Perspective Scale) and 1 single-item scale (Body Image). Scoring procedures are similar for both questionnaires and can be found in the EORTC QLQ-C30 Scoring Manual, Version 3. The analysis and reporting of all QOL data will be performed using the ITT population.	~~Improvement in hemoglobin is defined as an increase of ≥ 2 g/dL.~~ ~~Incidence of improvement in renal function and improvement in hemoglobin will be analyzed in the same manner as described previously for ORR.~~ ~~Duration of response and DOCB will be summarized for each treatment group by Kaplan-Meier method; however, no formal inferential comparisons will be made for these endpoints, as responders constitute a nonrandom subset of the ITT population.~~ ~~Quality of life will be assessed by the European Organization for Research and Treatment (EORTC) 30-item QLQ-C30 test and by the 20-item QLQ-MY20 module specifically designed to address the quality of life for those with multiple myeloma (Appendix E). The primary constructed scales from the QLC-C30 are:~~ ~~• Global Health Status/QoL~~ ~~• Physical Functioning, Role Functioning~~ ~~• Emotional Functioning~~ ~~• Cognitive Functioning~~ ~~• Social Functioning~~ ~~Nine additional scales can be derived: Fatigue, Nausea and Vomiting, Pain, Dyspnoea, Insomnia, Appetite Loss, Constipation, Diarrhea, and Financial Difficulties.~~ ~~The QLQ-MY20 EORTC questionnaire was developed to assess the quality of life in cancer subjects with multiple myeloma. The QLQ-MY20 includes 20 items assessing disease symptoms, side effects of treatment, body image, and future perspective. There are 3 multi-item scales (Disease Symptoms Scale, Side Effects of Treatment Scale, and Future Perspective Scale) and 1 single-item scale (Body Image).~~ ~~Scoring procedures are similar for both questionnaires and can be found in the EORTC QLQ-C30 Scoring Manual, Version 3. The analysis and reporting of all QOL data will be performed using the ITT population.~~	

Section(s)	Changed from	Changed to	Rationale
	Changes over time in QLQ-C30 global health status scores will be compared between treatment groups using a restricted maximum likelihood-based linear mixed model for repeated measures data under the missing at random assumption. Formal inferential testing will not be performed for the QOL subscales of EORTC QLQ-C30 and QLQ-MY20 (except for disease symptoms subscale). Instead, the analysis of these endpoints will be descriptive only and considered exploratory. Details of the analyses and the impact and handling of missing data in analyses will be addressed in the SAP.	~~Changes over time in QLQ-C30 global health status scores will be compared between treatment groups using a restricted maximum likelihood-based linear mixed model for repeated measures data under the missing at random assumption. Formal inferential testing will not be performed for the QOL subscales of EORTC QLQ-C30 and QLQ-MY20 (except for disease symptoms subscale). Instead, the analysis of these endpoints will be descriptive only and considered exploratory. Details of the analyses and the impact and handling of missing data in analyses will be addressed in the SAP.~~	

Section 14.5.3 (Safety Analysis)	The safety population will be used in all safety analyses (see Section 14.5.1.1). Results of safety analyses will be presented separately for Part 1 and Part 2 of the study. Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study For the Phase 1b portion of the study, safety data will be summarized for each cohort and for the pooled cohorts. Safety will be assessed through summaries of DLTs, AEs, changes in laboratory test results, ECGs, vital signs, and oprozomib, pomalidomide, and dexamethasone exposure. Part 2: Randomized Phase 3 Portion of the Study For the Phase 3 portion of the study, safety data will be summarized grouped according to treatment actually received. Treatment-emergent AEs are defined as AEs that start on or after the first day study treatment is administered and within 30 days of the last administration of study treatment or before start of subsequent anticancer treatment (whichever occurs first). Treatment-emergent AEs will be summarized by the number and percentage of subjects who experienced the event, according to system organ class and preferred term. A subject experiencing multiple instances of the same AE will be counted once within each system organ class and similarly counted once within each preferred term. Adverse event incidence rates may also be calculated based on other measures of subject exposure (e.g., total number of treatment cycles administered). Adverse events will also be summarized by NCI-CTCAE Version 4.03 severity grade and by relationship to each study drug. For AEs not adequately addressed by NCI-CTCAE Version 4.03, the severity grading described in Table 17 may be used. Additional summaries may also be provided for SAEs and events resulting in the permanent discontinuation of therapy. All AEs will be included in individual subject listings. Incidence, severity, and duration of specific signs and symptoms indicative of neuropathy and other neurotoxicities will be assessed. The appropriate terms in these categories	The safety population will be used in all safety analyses (see Section 14.5.1.1). For th**is** study, safety data will be summarized for each cohort and for the pooled cohorts. Safety will be assessed through summaries of DLTs, AEs, changes in laboratory test results, ECGs, vital signs, and oprozomib, pomalidomide, and dexamethasone exposure.	Removed Phase 3 text to reflect what data was collected for the study

Section(s)	Changed from	Changed to	Rationale
	will be codified and analyses performed to provide a subject incidence of those with the relevant events. Laboratory parameters will be summarized using descriptive statistics, by postdose shifts in toxicity grades of laboratory parameters relative to baseline, changes from baseline, and data listings of clinically significant abnormalities. The changes in hematology, chemistry, and other laboratory values will be summarized descriptively for each scheduled and unscheduled protocol assessment time point. Changes will be calculated relative to the values collected at baseline and on the first day of each cycle of treatment. The incidence of Grade 3 and 4 hematological toxicities (including neutropenia, thrombocytopenia, and anemia) will be provided by treatment cycle and across all treatment cycles. The use of blood transfusions (platelets, RBC) and/or growth factor support will be summarized. Subject listings of all laboratory data collected during the study will be presented. Laboratory values outside normal limits will be identified in the subject listings. Vital sign results (systolic and diastolic blood pressure, pulse, respiration, and temperature) and ECGs will be summarized descriptively.		
Section 14.5.5 (Pharmacokinetic Analyses)	Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study In the Phase 1b Dose-Escalation and Dose-Expansion portions of the study, blood samples will be collected from all subjects for determination of plasma concentrations of oprozomib at 1 predose time point and up to 7 postdose time points on Day 1 of Cycle 1 and Cycle 2 (0.25, 0.5, 1, 2, 3, 4, and 6 hours postdose) and 1 predose time point on Day 2 of Cycle 1 for both schedules.	~~Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study~~ In the ~~Phase 1b~~ Dose-Escalation and Dose-Expansion portions of the study, blood samples will be collected from all subjects for determination of plasma concentrations of oprozomib at 1 predose time point and up to 7 postdose time points on Day 1 of Cycle 1 and Cycle 2 (0.25, 0.5, 1, 2, 3, 4, and 6 hours postdose) and 1 predose time point on Day 2 of Cycle 1 for both schedules.	The study is no longer divided into 2 parts

Section(s)	Changed from	Changed to	Rationale
Section 14.5.5 (Pharmacokinetic Analyses)	Part 2: Randomized Phase 3 Portion of the Study In Phase 3, population PK of oprozomib will be characterized in the OPomd regimen. The population modeling program will be used to fit a nonlinear mixed effects model to estimate PK parameters including C_{max}, AUC, clearance, the inter- and intrasubject variability, and the population variability in the parameter estimates. The sparse sampling concentrations obtained from subjects in this study and results from other oprozomib studies with intensive sampling will be used in the development of a structural model. The best model will be evaluated by goodness-of-fit statistics and reduction in the objective function and posterior predictive checks. Subject characteristics such as age, gender, body weight, body surface area (BSA), and race will be included in the model to identify potential covariates affecting PK of oprozomib. Potential correlations of relevant PK parameters with dose, safety or efficacy outcomes, and other covariates may be explored.	~~Part 2: Randomized Phase 3 Portion of the Study~~ ~~In Phase 3, population PK of oprozomib will be characterized in the OPomd regimen. The population modeling program will be used to fit a nonlinear mixed effects model to estimate PK parameters including C_{max}, AUC, clearance, the inter- and intrasubject variability, and the population variability in the parameter estimates. The sparse sampling concentrations obtained from subjects in this study and results from other oprozomib studies with intensive sampling will be used in the development of a structural model. The best model will be evaluated by goodness-of-fit statistics and reduction in the objective function and posterior predictive checks. Subject characteristics such as age, gender, body weight, body surface area (BSA), and race will be included in the model to identify potential covariates affecting PK of oprozomib. Potential correlations of relevant PK parameters with dose, safety or efficacy outcomes, and other covariates may be explored.~~	Removed Phase 3 text to reflect what data was collected for the study
Section 14.7 (Determination of Sample Size)	Part 1: Phase 1b Dose-Escalation and Dose-Expansion Portions of the Study A total enrollment of approximately 82 subjects is planned for Part 1 of the study. During the Part 1 Phase 1b dose-escalation portion of the study, approximately 21 subjects are expected to be enrolled for each schedule.	A total enrollment of approximately 82 subjects is planned for th**is** study. During the dose-escalation portion of the study, approximately 21 subjects are expected to be enrolled for each schedule.	The study is no longer divided into 2 parts
Section 14.7 (Determination of Sample Size)	A minimum of 20 additional subjects are planned for enrollment and treatment for 1 or both schedules at the sponsor's discretion at the RP3D during the Phase 1b dose-expansion portion of Part 1 of the study.	A minimum of 20 additional subjects are planned for enrollment and treatment for 1 or both schedules at the sponsor's discretion at the RP3D during the ~~Phase 1b~~ dose-expansion portion of ~~Part 1~~ of the study.	The study is no longer divided into 2 parts

<table>
<tr><th>Section(s)</th><th>Changed from</th><th>Changed to</th><th>Rationale</th></tr>
<tr><td>Section 14.7 (Determination of Sample Size)</td><td>Part 2: Randomized Phase 3 Portion of the Study
For the Phase 3 portion of the study, 157 PFS events are required to detect a 45.7% reduction in the risk of PFS (HR = 0.543) with 95% power and a 1-sided significance level of 0.025. Enrollment of 270 subjects (2:1 OPomd versus Pomd, respectively) is consistent with reaching the required 157 events in approximately 14 months, assuming an enrollment rate of approximately 22 subjects per month, a 5% drop-out rate at 18 months, and a median PFS of 3.8 and 7 months for Pomd and OPomd, respectively.
Therefore, the total planned enrollment will be approximately 352 subjects for the entire study.</td><td>~~Part 2: Randomized Phase 3 Portion of the Study~~
~~For the Phase 3 portion of the study, 157 PFS events are required to detect a 45.7% reduction in the risk of PFS (HR = 0.543) with 95% power and a 1-sided significance level of 0.025. Enrollment of 270 subjects (2:1 OPomd versus Pomd, respectively) is consistent with reaching the required 157 events in approximately 14 months, assuming an enrollment rate of approximately 22 subjects per month, a 5% drop-out rate at 18 months, and a median PFS of 3.8 and 7 months for Pomd and OPomd, respectively.~~
~~Therefore, the total planned enrollment will be approximately 352 subjects for the entire study.~~</td><td>Removed Phase 3 text to reflect what data was collected for the study</td></tr>
<tr><td>Appendix A1 (Schedule of Study Assessments – Long-term Follow-up column)
Appendix A2 (Schedule of Study Assessments – Long-term Follow-up column)
Appendix B1 (Schedule of Study Assessments – Long-term Follow-up column)
Appendix B2 (Schedule of</td><td><table><tr><th>Visit</th><th>Long-term Follow-up</th></tr><tr><td>SPEP/UPEP/Serum FLC Immunofixation[n]</td><td>X</td></tr><tr><td>Skeletal Survey[o]</td><td>X</td></tr><tr><td>Plasmacytoma Evaluation[p]</td><td>X</td></tr><tr><td>Bone Marrow Aspirate and FISH Analyses[q,</td><td>X</td></tr></table></td><td><table><tr><th>Visit</th><th>Long-term Follow-up</th></tr><tr><td>SPEP/UPEP/Serum FLC Immunofixation[n]</td><td>~~X~~</td></tr><tr><td>Skeletal Survey[o]</td><td>~~X~~</td></tr><tr><td>Plasmacytoma Evaluation[p]</td><td>~~X~~</td></tr><tr><td>Bone Marrow Aspirate and FISH Analyses[q,</td><td>~~X~~</td></tr></table></td><td>Provide convenience for those on study treatment as study has completed its abbreviated report</td></tr>
</table>

Section(s)	Changed from	Changed to	Rationale
Study Assessments – Long-term Follow-up column)			
Appendix A1 (Schedule of Study Assessments – footnote b) Appendix A2 (Schedule of Study Assessments – footnote b) Appendix B1 (Schedule of Study Assessments – footnote b) Appendix B2 (Schedule of Study Assessments – footnote b)	*New text added*	All other physical examinations will be limited physical examinations **only if clinically indicated**.	Provide convenience for those on study treatment as study has completed its abbreviated report
Appendix A1 (Schedule of Study Assessments – footnote c) Appendix A2 (Schedule of Study Assessments – footnote c)	*New text added*	Neurological assessments (BPNS and if applicable record AEs with CTCAE grading) will be performed at Screening and on Day 1 of every cycle starting from Cycle 2 **if clinically indicated** and at the End of Study Treatment/Early Discontinuation (See Appendix M).	Provide convenience for those on study treatment as study has completed its abbreviated report

Section(s)	Changed from	Changed to	Rationale
Appendix B1 (Schedule of Study Assessments – footnote c) Appendix B2 (Schedule of Study Assessments – footnote c)			
Appendix A1 (Schedule of Study Assessments – footnote f) Appendix A2 (Schedule of Study Assessments – footnote f) Appendix B1 (Schedule of Study Assessments – footnote f) Appendix B2 (Schedule of Study Assessments – footnote f)	For Cycle 2, vital signs are required. For Cycles 3 and higher, vital signs are required...	For Cycle 2, **if clinically indicated,** vital signs are required. For Cycles 3 and higher, **if clinically indicated,** vital signs are required...	Provide convenience for those on study treatment as study has completed its abbreviated report
Appendix A1 (Schedule of Study Assessments – footnote g)	*New text added*	Perform ECG approximately within 1 hour before (predose) and approximately 1 hour after (postdose) administration of oprozomib for Cycles 1, 2, 3, 4, 6, 8, 12, 18, 24 and then every 6 months **solely if clinically indicated**, until progression or unacceptable toxicity. Perform standard ECG	Provide convenience for those on study treatment as

Section(s)	Changed from	Changed to	Rationale
Appendix A2 (Schedule of Study Assessments – footnote g) Appendix B1 (Schedule of Study Assessments – footnote g) Appendix B2 (Schedule of Study Assessments – footnote g)		assessment at Screening and End of Study Treatment/Early Discontinuation visit.	study has completed its abbreviated report
Appendix A1 (Schedule of Study Assessments – footnote i) Appendix A2 (Schedule of Study Assessments – footnote i) Appendix B1 (Schedule of Study Assessments – footnote i) Appendix B2 (Schedule of Study Assessments – footnote i)	*New text added*	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), done locally **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 A1 (Schedule of Study Assessments – footnote j) Appendix A2 (Schedule of Study Assessments – footnote j) Appendix B1 (Schedule of Study Assessments – footnote j) Appendix B2 (Schedule of Study Assessments – footnote j)	*New text added*	Day 1 samples for laboratory analyses can be drawn within 72 hours prior to dosing on Day 1 for all subsequent cycles after Cycle 1 **only if clinically indicated**.	Provide convenience for those on study treatment as study has completed its abbreviated report
Appendix A1 (Schedule of Study Assessments – footnote l) Appendix A2 (Schedule of Study Assessments – footnote l) Appendix B1 (Schedule of Study Assessments – footnote l)	*New text added*	Coagulation tests, done locally **if clinically indicated**, and includes the following: Prothrombin time, activated partial thromboplastin time, and international normalized ratio.	Provide convenience for those on study treatment as study has completed its abbreviated report

Section(s)	Changed from	Changed to	Rationale
Appendix B2 (Schedule of Study Assessments – footnote l)			
Appendix A1 (Schedule of Study Assessments – footnote o) Appendix A2 (Schedule of Study Assessments – footnote o) Appendix B1 (Schedule of Study Assessments – footnote o) Appendix B2 (Schedule of Study Assessments – footnote o)	For subjects who did not progress during treatment with bone lesions present at Baseline, skeletal survey will continue to be measured every 4 weeks as clinically indicated (every 28 days ± 4 days) until PD. During long-term follow-up, skeletal survey evaluation should be performed as clinically indicated.	[p] For subjects who did not progress during treatment with bone lesions present at Baseline, skeletal survey will **no longer be required**. During long-term follow-up, skeletal survey evaluation **will also no longer be required**.	Provide convenience for those on study treatment as study has completed its abbreviated report
Appendix A1 (Schedule of Study Assessments – footnote p) Appendix A2 (Schedule of Study Assessments – footnote p)	For subjects with plasmacytoma at Baseline and did not progress during treatment, plasmacytoma will continue to be measured every 4 weeks as clinically indicated (every 28 days ± 4 days) until PD. During long-term follow-up, plasmacytoma evaluation should be performed as clinically indicated.	For subjects with plasmacytoma at Baseline and did not progress during treatment, plasmacytoma will **no longer be required**. During long-term follow-up, plasmacytoma evaluation **will also no longer be required**.	Provide convenience for those on study treatment as study has completed its abbreviated report

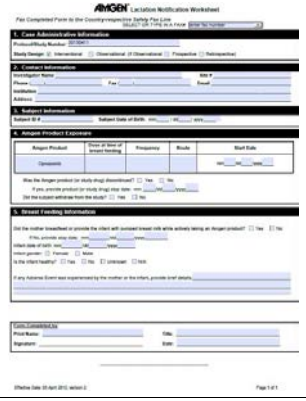
Section(s)	Changed from	Changed to	Rationale
Appendix B1 (Schedule of Study Assessments – footnote p) Appendix B2 (Schedule of Study Assessments – footnote p)			
Appendix A1 (Schedule of Study Assessments – footnote q) Appendix A2 (Schedule of Study Assessments – footnote q) Appendix B1 (Schedule of Study Assessments – footnote q) Appendix B2 (Schedule of Study Assessments – footnote q)	Bone marrow aspirate will also be collected at disease progression (may be collected at End of Study Treatment/Early Discontinuation due to PD or during Long-Term Follow-Up) for subjects who consent to optional genomic biomarker analysis.	Bone marrow aspirate will also be collected at disease progression **if clinically indicated** (may be collected at End of Study Treatment/Early Discontinuation due to PD**; it will no longer be required** during Long-**t**erm Follow-**u**p) for subjects who consent to optional genomic biomarker analysis.	Provide convenience for those on study treatment as study has completed its abbreviated report

Appendix C1 (Schedule of Study Assessments) – entire appendix deleted			Removed Phase 3 text to reflect what data was collected for the study

Appendix C2 (Schedule of Study Assessments) – entire appendix deleted			Removed Phase 3 text to reflect what data was collected for the study

Section(s)	Changed from	Changed to	Rationale
Appendix N (Example Electronic Serious Adverse Event Contingency Report Form)		**APPENDIX N Example Electronic Serious Adverse Event Contingency Report Form** 	Provide updated adverse event reporting form.

Section(s)	Changed from	Changed to	Rationale
			
Appendix O (Example Amgen Pregnancy Notification Worksheet)		**APPENDIX O EXAMPLE AMGEN PREGNANCY NOTIFICATION WORKSHEET** 	Provide updated pregnancy reporting worksheet.

Section(s)	Changed from	Changed to	Rationale
Appendix P (Example Amgen Lactation Notification Worksheet)		**APPENDIX P EXAMPLE AMGEN LACTATION NOTIFICATION WORKSHEET** 	Provide updated lactation reporting worksheet.