Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of Oprozomib in Combination With Pomalidomide and Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma

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This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures. This format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (ICH E6).

Investigator's Agreement

I have read the attached protocol entitled A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of Oprozomib in Combination With Pomalidomide and Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma, dated **27 January 2021**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to one year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of investigator Date (DD Month YYYY)

1. Protocol Synopsis

Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of Oprozomib in Combination With Pomalidomide and Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma

Study Phase: 1b

Indication: Relapsed or Refractory Multiple Myeloma

Hypothesis:

At least one dose level of the formulations of oprozomib administered orally together with pomalidomide and dexamethasone is expected to achieve acceptable safety and tolerability in subjects with relapsed or refractory multiple myeloma.

Primary Objective:

- Identify the maximum tolerated dose (MTD) of oprozomib formulations in combination with pomalidomide and dexamethasone (OPomd) in subjects with relapsed or refractory multiple myeloma
- Evaluate the safety and tolerability of the OPomd combination in subjects with relapsed or refractory multiple myeloma

Secondary Objective(s):

- Characterize the pharmacokinetics (PK) of oprozomib
- Evaluate the efficacy of the OPomd combination according to International Myeloma Working Group (IMWG) uniform response criteria
- Identify the recommended formulation and Phase 3 dose (RP3D) of oprozomib in combination with pomalidomide and dexamethasone in subjects with relapsed or refractory multiple myeloma

Primary Endpoint:

- Determine the MTD for each formulation of oprozomib in combination with pomalidomide and dexamethasone as the dose that has the highest posterior probability of having a dose limiting toxicity (DLT) rate within the target toxicity interval (15% to 25%), while the posterior probability of excessive/unacceptable toxicity (> 25% to 100%) is < 40%
- Incidence of treatment-related, treatment-emergent adverse events and changes in laboratory test results

Secondary Endpoints:

- PK parameters of oprozomib including, but not limited to, maximum observed concentration (C_{max}), time to C_{max} (t_{max}), and the area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last})
- Overall response and best overall response according to the IMWG uniform response criteria, progression free survival (PFS), and duration of response (DOR)

[redacted]

Study Design:

This is a Phase 1b, multicenter, non-randomized, open-label, dose-exploration study of up to two formulations of oprozomib (an "immediate release" formulation [IR], and an "extended release gastro-retentive" formulation [GR]) administered according to a 2/7 schedule (two consecutive days per week), in combination with pomalidomide and dexamethasone in subjects with relapsed or refractory multiple myeloma. The evaluation of the different formulations will start with the IR (for the initial 1 to 2 dose levels) however, for most of the study the two oprozomib formulations will be tested in parallel.

The study will be conducted in two sequential parts:

- Part 1 – Evaluation of 2 formulations of oprozomib administered at 150 mg/day dose level in combination with dexamethasone (Od) only
- Part 2 – Evaluation of 2 formulations of oprozomib administered at increasing dose levels (dose escalation) in combination with pomalidomide and dexamethasone (OPomd)

Part 1 will test each formulation of oprozomib in combination with dexamethasone to evaluate the safety and tolerability of oprozomib in combination with dexamethasone at the starting dose level. Testing will begin with the IR formulation. If a dose modification of oprozomib is necessary, this will be decided based on analysis of emerging safety and PK data. Part 2 dose escalation will use the Bayesian 2-parameter logistic regression model with the new continual reassessment method (NCRM) applied to observed DLTs (Neuenschwander, 2008). Testing will begin with the IR formulation of oprozomib, and the starting dose level will be chosen based on the oprozomib dose determined during Part 1. All subjects will be treated during the first week only with a fixed, initial dose level of oprozomib. For all dosing days thereafter, the subjects will be treated with the appropriate dose level of oprozomib according to the dose escalation cohort being evaluated. It is anticipated that in Part 2, seven dose levels of oprozomib IR (between 150 mg and 300 mg/day, in increments of 25 mg) will be tested in combination with pomalidomide and dexamethasone. The number of dose levels, the increment of change as well as the minimum and maximum dose level of oprozomib to be tested may be adjusted during the study based on emerging safety and PK data. The application of the Bayesian algorithm will stop when the DLT rate of the recommended MTD has a probability within the target toxicity interval (15% to 25%) of $\geq 40\%$, an excessive/unacceptable interval (>25% to 100%) of $< 40\%$, and a minimum of 6 subjects have been treated at the MTD level or when the sample size reaches 36 subjects. In the event that evaluation of additional subjects is deemed necessary by the **d**ose **l**evel **r**eview team (DLRT), extra subjects may be enrolled. The testing of the GR formulation will start after the first one or two cohorts of IR have been evaluated. The starting dose for the GR formulation will be determined based on the safety and PK data observed in the first cohorts of the IR dose escalation, and it will be at least one dose level lower than the highest dose tested of the IR formulation. Once the MTDs are determined, the DLRT will review the available safety, efficacy, PK, and [redacted] data and recommend a formulation and a dose level for administration of oprozomib in the OPomd combination in future studies.

For additional details please refer to Section 6.1 and the Study Schema.

Sample Size: Approximately 64 DLT-evaluable subjects will be enrolled in this phase 1b study. In Part 1, at least 3 DLT-evaluable subjects will be enrolled for each of the oprozomib formulations. In Part 2, a Bayesian design will be applied to evaluate the oprozomib formulations (IR and GR) administered at increasing dose levels in combination with pomalidomide and dexamethasone. The maximum sample size for testing the IR formulation is set to 36 DLT-evaluable subjects. The anticipated sample size under the assumption of 11 cohorts evaluated for the GR formulation is 22 DLT-evaluable subjects.

Summary of Subject Eligibility Criteria:

Subjects ≥ 18 years of age with pathologically documented, definitively diagnosed, multiple myeloma disease relapsed or refractory after at least 2 prior lines of therapy. Prior therapeutic treatment or regimens must include lenalidomide and a proteasome inhibitor. Once consented to the study, subjects will undergo safety tests and provide a medical history to confirm they meet all requirements of the study.

For a full list of eligibility criteria, please refer to Section 7.1 and Section 7.2.

Investigational Product

Amgen Investigational Product Dosage and Administration:

Oprozomib will be administered orally according to a 2/7 schedule on days 1, 2, 8, 9, 15, 16, 22 and 23 of each 4 week cycle. Lansoprazole or another oral proton-pump inhibitor (PPI) is required (H2 antagonists are recommended if subject has intolerance or hypersensitivity to PPI) for the duration of treatment to prevent gastrointestinal (GI) toxicities. Oral hydration of 1.5 to 2 liters per 24 hours must be instituted in all subjects 24 hours prior to initiation of therapy for every cycle and continued throughout every day of oprozomib dosing.

The IR formulation of oprozomib will be supplied in two tablet strengths of 25 mg and 50 mg in bottles of 30 tablets stored at 5°C with desiccant, and it is recommended to be taken after a low fat meal. The GR formulation of oprozomib will be supplied in two tablet strengths of 25 mg and 100 mg in bottles of 30 tablets stored at 5°C with desiccant and is required to be taken immediately after a main meal that contains the highest calorie and fat content.

During Part 1, the initially tested dose level of oprozomib in combination with dexamethasone only, will be 150 mg/day for both formulations.

During Part 2, all subjects will be treated during the first week only, with a fixed, initial daily dose of oprozomib (currently 150 mg/day, but may be adjusted during the study based on emerging data), and for all dosing days thereafter with the appropriate dose level of oprozomib according to the dose escalation cohort evaluated. For the IR formulation, the currently anticipated dose levels to be tested are 150, 175, 200, 225, 250, 275 and 300 mg/day. The decision for the dose levels to be tested with the GR formulation will be based on information obtained from the Part 2 IR cohorts.

Non-investigational Product

Non-Amgen Non-investigational Product Dosage and Administration:

Dexamethasone is available as tablets containing 4 or 6 mg of dexamethasone drug substance for oral administration. All subjects will receive 20 mg of dexamethasone on each oprozomib dosing day. It is recommended that dexamethasone be taken with food or after meals. Additional product information is provided in the Dexamethasone Prescribing Information (Pfizer Laboratories, 2012).

Pomalidomide is available as a capsule containing 1, 2, 3, and 4 mg of pomalidomide drug substance for oral administration. Pomalidomide will be administered at a dose of 4 mg on days 1 to 21 of repeated 28-day cycles. In Part 1, pomalidomide may be added to the Od treatment regimen once the initial cohort in Part 2 establishes a first dose level of oprozomib as safe and tolerable in combination with pomalidomide and dexamethasone. In Part 2, all subjects will receive pomalidomide starting on day 1 of cycle 1. Pomalidomide may be taken with water. Inform subjects not to break, chew, or open the capsules. Pomalidomide may be taken with or without food. Anticoagulant or antiplatelet medication is recommended as prophylaxis for venous and arterial thromboembolism based on assessment of the subject's underlying risk factors. Additional product information is provided in the Pomalidomide Prescribing Information (**Pomalidomide U.S. Prescribing Information for United States; for other countries, see appropriate prescribing information**).

Procedures: After written informed consent has been obtained, all screening tests and procedures will be performed within 28 days of administration of the first dose of oprozomib (day 1), unless otherwise noted. Subjects will be seen in clinic where evaluations will be performed including physical examination, vital signs, clinical laboratory tests, ECGs, PK, and [redacted] sample collections. For a full list of study procedures, including the timing of each procedure and the Schedule of Assessments, please refer to Section 10.

Statistical Considerations:

The DLRT will hold dose level review meetings (DLRMs) to review data, monitor safety and make decisions on dose escalation/change.

Primary Analysis

The objectives of the primary analysis are to determine the MTD for each formulation of oprozomib in combination with pomalidomide and dexamethasone and further evaluate the safety and tolerability of the OPomd combination in subjects with relapsed or refractory multiple myeloma. In addition, this analysis will be used, as possible, to recommend the most appropriate oprozomib dose and formulation to be tested in future clinical trials in an OPomd combination, based on safety, tolerability, efficacy, PK and other available data from all the escalation cohorts.

The primary analysis will be based on subject data collected up to two months from the date of last subject enrollment. A Bayesian 2-parameter logistic regression model, the NCRM will be applied to observed DLTs to find MTDs for the oprozomib formulations (Neuenschwander, 2008). The prior distribution and the data available after each dose cohort are applied to the algorithm that computes the posterior distribution of the DLT rate at each dose level. The posterior probabilities of the estimated DLT rate at each dose to fall into target toxicity interval (15% to 25%) or excessive/unacceptable toxicity interval (> 25% to 100%) will be used in the dose escalation decision and the final determination of the MTD. Refer to study design section for a detailed description of the dose escalation method. The safety analyses will be based on the safety evaluable population, which is defined as all subjects who received any amount of the study treatment regimen oprozomib, dexamethasone and pomalidomide. Safety and tolerability will be assessed through summaries of study drug administration, DLTs, adverse events, changes in selected laboratory analytes, and vital signs by dose level.

The primary efficacy analysis will be performed in all subjects that received at least one cycle of OPomd and have baseline disease assessment and at least one post-baseline disease assessment. Both overall response rate and the best overall response will be summarized.

Final Analysis

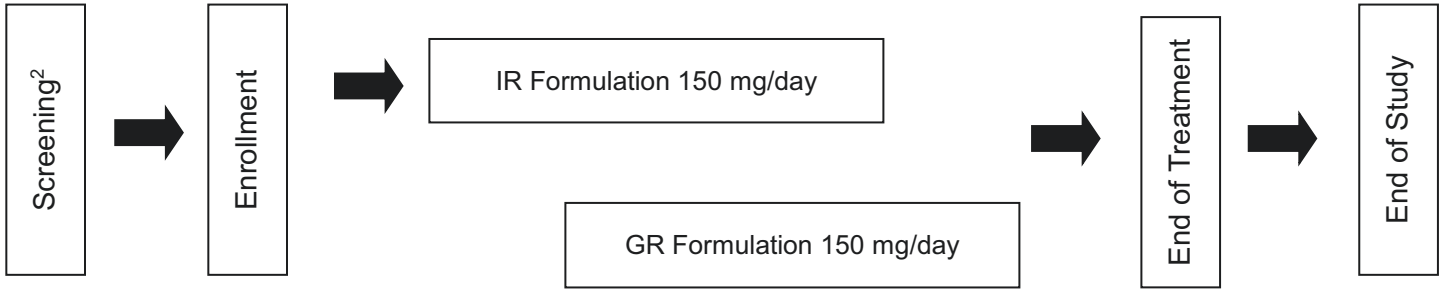
The objective of the final analysis is to provide an update on safety, tolerability and efficacy results. The final analysis will be based on subject data collected through study discontinuation or at the end of the study which includes the 30 day safety follow-up, whichever occurs first. The statistical methods used in the final analysis will be the same as those employed in the primary analysis, covering all study endpoints.

For a full description of statistical analysis methods, please refer to Section 13.

Sponsor: Amgen Inc.

2. Study Design and Treatment Schema

Part 1 – Oprozomib + Dexamethasone (Od) 2/7 Schedule[1]

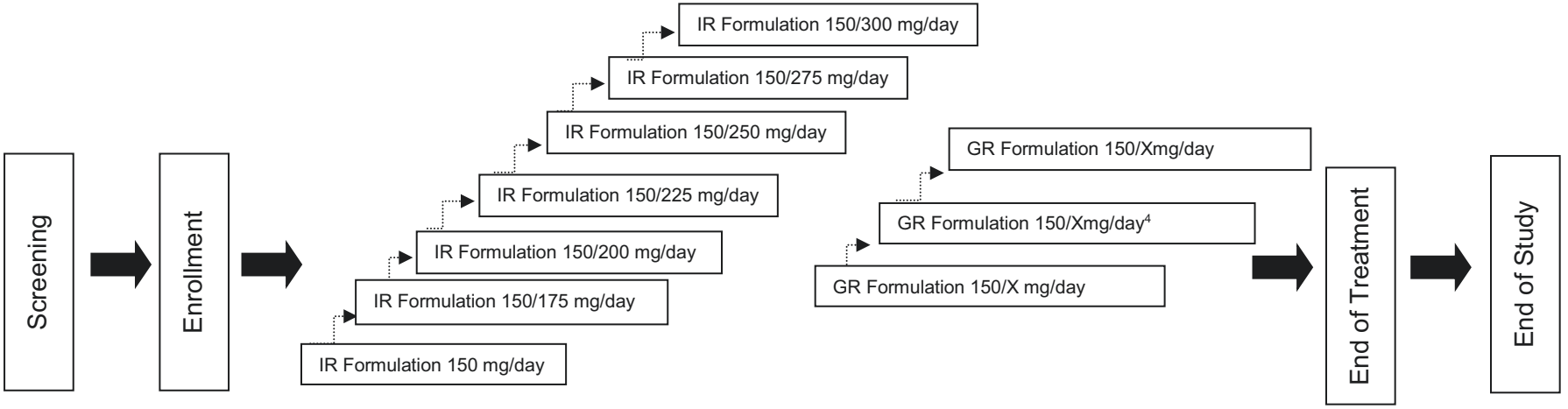


[1] The Part 1 subjects will be allowed to add pomalidomide to their treatment, once there is a dose level of oprozomib determined to be safe in combination with pomalidomide and dexamethasone (as determined by the first cohort in Part 2).

[2] The estimated study duration for a participant is 12 months, approximately 4 weeks for screening and 10 months of treatment. 30 days after the last dose of oprozomib, the subject will return to the clinic for a safety follow-up visit.

Study Design and Treatment Schema

Part 2 – Oprozomib + Pomalidomide + Dexamethasone (Opomd) 2/7 Schedule[1]



[1] All subjects will be treated during the first week only, with a fixed, initial dose level of oprozomib (150 mg/day). For all dosing days thereafter the subjects will be treated with the appropriate dose level of oprozomib according to the dose escalation cohort evaluated.

[2] The evaluation of different formulations will start with IR (for the initial 1 to 2 dose levels) however, during the study, the two oprozomib formulations will be tested in parallel. The initial dose of the GR formulation will be determined by the data generated during the first cohorts of IR formulation escalation.

3. Study Glossary

Abbreviation or Term	Definition/Explanation
ADCC	antibody-dependent cytotoxic T-cell activity
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{inf}	AUC from time 0 to the time extrapolated to infinity
AUC_{last}	area under the curve until the last measurable concentration
BCRP	breast cancer-resistant protein
B/L	baseline
BLR	Bayesian Logistic Regression
BUN	blood urea nitrogen
C_{max}	maximum observed concentration
CR	complete response
CrCl	creatinine clearance
CT	computed tomography
CT-L	chymotrypsin-like
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug induced liver injury
DLRM	dose level review meeting
DLRT	dose level review team
DLT	dose limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
End of study for individual subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of treatment	Last day of protocol specified treatment
End of study (primary completion)	defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint(s)
End of study (end of trial)	defined as when the last subject is assessed or receives an intervention for evaluation in the study; if the study includes multiple parts (eg, safety follow-up or survival assessment), the end of study would include these additional parts

Abbreviation or Term	Definition/Explanation
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
FDA	Food and Drug Administration
GCP	good clinical practice
GI	gastrointestinal
GR	gastro-retentive
HBV	hepatitis B virus
HBcAb	hepatitis B core antibody
HCV	hepatitis C virus
HepBsAg	hepatitis B surface antigen
HepCAb	hepatitis C antibody
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IPIM	investigational product instruction manual
IR	immediate release
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
IMWG	International Myeloma Working Group
LDH	lactate dehydogenase
LSP	Lactation Surveillance Program
MDRD	modification of diet in renal disease
mg	milligram
MGUS	monoclonal gammopathy of undetermined clinical significance
mLRRMM	**m**illiliter refractory multiple myeloma
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NASH	nonalcoholic steatohepatitis
NCCN	National Comprehensive Cancer Network
NCRM	new continual reassessment method
Od	oprozomib in combination dexamethasone
ODex	**oprozomib in combination with dexamethasone**
OPomd	oprozomib in combination with pomalidomide and dexamethasone
OPZ	**oprozomib**
ORR	overall response rate

Abbreviation or Term	Definition/Explanation
OS	overall survival (OS)
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
[redacted]	
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PO	per os – by mouth
PPI	proton pump inhibitor
PR	partial response
PSP	Pregnancy Surveillance Program
PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cell
RP3D	recommended formulation and Phase 3 dose
SAE	serious adverse event
sCR	stringent complete response
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline (E6)). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study day 1	defined as the first day that protocol specified investigational product(s)/protocol-required therapies is/are administered to the subject
SPEP	serum protein electrophoresis
$t_{1/2}$	terminal elimination half-life
TBIL	total bilirubin
TLS	tumor lysis syndrome
T_{max}	time when maximum plasma concentration is reached
ULN	upper limit of normal
UPEP	urine protein electrophoresis
US	United States
VGPR	very good partial response
WBC	white blood cell

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4. OBJECTIVES

4.1 Primary

- Identify the maximum tolerated dose (MTD) of oprozomib formulations in combination with pomalidomide and dexamethasone (OPomd) in subjects with relapsed or refractory multiple myeloma
- Evaluate the safety and tolerability of the OPomd combination in subjects with relapsed or refractory multiple myeloma

4.2 Secondary

- Characterize the pharmacokinetics (PK) of oprozomib
- Evaluate the efficacy of OPomd according to International Myeloma Working Group (IMWG) uniform response criteria
- Identify the recommended formulation and recommended formulation and Phase 3 dose (RP3D) of oprozomib in combination with pomalidomide and dexamethasone in subjects with relapsed or refractory multiple myeloma

5. BACKGROUND AND RATIONALE

5.1 Multiple Myeloma Background

Multiple myeloma is a neoplastic plasma-cell disorder that is characterized by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, monoclonal protein in the blood or urine and associated organ dysfunction (Palumbo and Anderson, 2011). Multiple myeloma accounts for almost 2% of all cancers and 20% of hematologic malignancies. The disease is slightly more common in males and African Americans (Siegel, 2015). Multiple myeloma remains an incurable cancer, although recent improved understanding of pathogenesis of myeloma has led to the development of new treatments and improved survival (Smith and Yong, 2013).

Myeloma arises from an asymptomatic premalignant proliferation of monoclonal plasma cells that are derived from post–germinal center B cells. Multistep genetic and micro-environmental changes lead to the transformation of these cells into a malignant neoplasm. Myeloma is thought to evolve most commonly from a monoclonal gammopathy of undetermined clinical significance (MGUS) that progresses to smoldering myeloma and ultimately to symptomatic myeloma.

The uncontrolled growth of myeloma cells has many consequences, including skeletal destruction, bone marrow failure, increased plasma volume and viscosity, suppression of normal immunoglobulin production, and renal insufficiency (Durie, 2011).

Symptomatic (active) disease should be treated immediately and the age of the patient guides the treatment strategy. Current data support the initiation of a three-drug regimen induction therapy (eg., bortezomib, thalidomide and dexamethasone) plus hematopoietic stem cell transplantation for patients under the age of 65 years who do not have substantial heart, lung, renal, or liver dysfunction. Autologous stem cell transplantation with a reduced-intensity conditioning regimen should be considered for older patients or those with coexisting conditions. Conventional therapy combined with thalidomide, lenalidomide, or bortezomib should be administered in patients older than 65 years of age. Less intensive approaches that limit toxic effects or prevent treatment interruption that would reduce the intended treatment effect should be considered in patients over 75 years of age or in younger patients with coexisting conditions. Biologic age, which may differ from chronologic age and the presence of coexisting conditions should determine treatment choice and drug dose (Palumbo and Anderson, 2011).

Despite advances in the management of multiple myeloma as described, relapse is inevitable in almost all patients. Recurrence of myeloma is typically more aggressive with each relapse, leading to the development of treatment-refractory disease, which is associated with a shorter survival (Dimopoulos, 2014). More treatment options are still warranted. Treatment of relapsed or refractory multiple myeloma (RRMM) presents a special therapeutic challenge, due to the heterogeneity of disease at relapse and the absence of clear biological based recommendations regarding the choice of salvage therapies at various time points of disease progression. With increasing recognition of the inherent clonal heterogeneity and genomic instability of the plasma cells influencing both inherent and acquired therapeutic resistance, the identification of the optimal choice and sequence of therapies has become critical. Several new agents and targets are currently under development and show considerable promise. Along with carfilzomib and pomalidomide that were approved by US FDA in 2012 and 2013 respectively, four additional agents including daratumumab, elotuzumab, ixazomib and panobinostat were approved by the US FDA for RRMM in 2015. Next generation proteasome inhibitors (PIs) (marizomib and oprozomib) and other molecularly targeted therapies directed at specific cell signaling pathways (including PI3K/AKT/mTOR inhibitors, Hsp90 inhibitors, cell cycle inhibitors, kinesin spindle protein inhibitors) are currently in development.

Even newer approaches such as monoclonal antibodies targeting CD138, and others have also demonstrated promising anti-myeloma activity (Nooka, 2015).

5.2 Oprozomib Background

Oprozomib is a potent, selective, and irreversible oral tripeptide epoxyketone inhibitor of the chymotrypsin-like (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).

Exposure to oprozomib was associated with potent pro-apoptotic activity across a broad panel of tumor-derived cell lines in culture. The anti-tumor efficacy of oprozomib has been further shown in several mouse models of both solid (colorectal adenocarcinoma, non-small cell lung carcinoma) and hematologic (multiple myeloma, non-Hodgkin lymphoma) tumors, where its activity was equivalent to carfilzomib (Zhou, 2009).

Refer to Section 4 of the Oprozomib IB for additional information related to the physical, chemical, and pharmaceutical properties and formulations.

5.2.1 Pharmacokinetics

5.2.1.1 Nonclinical Pharmacokinetics

Oprozomib was orally bioavailable in plasma following solution administration in mice, rats and dogs. Upon single oral administrations of oprozomib in solution to mice (20 and 40 mg/kg), rats (10 to 40 mg/kg), and dogs (6 to 15 mg/kg), plasma concentrations of oprozomib rapidly reached a t_{max} of 2 to 18 minutes and were rapidly cleared with a half-life ($t_{1/2}$) of 9 to 47 minutes. The plasma clearance of oprozomib in these species was much higher than hepatic blood flow, indicating that oprozomib, upon entering the systemic circulation, was largely cleared by extrahepatic mechanisms.

Oprozomib formulations used in previous clinical studies included Oprozomib in Capsules and Oprozomib Tablets. Female beagle dogs were given a single administration of Oprozomib in Capsules at 10 mg/kg or Oprozomib Tablets at 10 mg/kg. The plasma exposure was essentially equivalent with both formulations, with a trend towards increased dose-normalized AUC_{last} and maximum observed concentration (C_{max}) exposure for tablets and no differences in t_{max}.

Oprozomib is classified as a substrate of the p-glycoprotein (P-gp) efflux transporter, but not the breast cancer-resistant protein (BCRP) transporter in vitro. Furthermore, oprozomib is a weak, time-dependent inhibitor of human cytochrome P450 (CYP) 3A4/5 (CYP3A4/5) in vitro and reduced the enzymatic activities and mRNA expression of

CYP1A2, CYP2B6, and CYP3A4 in human hepatocytes. Details of oprozomib nonclinical PK are summarized in the Oprozomib Investigator's Brochure.

In this study, two new formulations will be evaluated: an immediate release (IR) formulation (with intended in vitro release of 80% within 30 min) and a gastro-retentive (GR) formulation. Preliminary results in female beagle dogs given the IR formulation suggest that the exposures were comparable to Oprozomib in Capsules and Oprozomib Tablets. Additionally, preliminary results in female beagle dogs suggest that the GR formulation displayed a slow release plasma concentration profile as expected with lower peak (C_{max}) and total (area under the concentration-time curve [AUC]) exposures relative to the IR formulation.

5.2.1.2 Clinical Pharmacokinetics

The clinical PK of different oral formulations of oprozomib has been investigated in subjects with solid tumors and hematologic malignancies. The PK of oprozomib has been reported in 4 studies: 2 studies administering oprozomib as a single agent (Studies 2009-003, 2011-001), 1 study administering oprozomib in combination with dexamethasone (2012-001), and 1 study administering oprozomib in combination with pomalidomide and dexamethasone (OPZ007). Oprozomib was rapidly absorbed and cleared following oral administration of Oprozomib in Capsules and Oprozomib Tablets (with intended in vitro release greater than or equal to 75% of the total dose of oprozomib over 8 hours). In general, a trend toward increasing oprozomib exposure, as assessed by AUC_{last} and C_{max}, with increasing dose was observed. High PK variability of oprozomib between subjects and within subjects was observed in the studies conducted. [redacted]. Based on the results from a clinical drug-drug interaction study on the effect of oprozomib on midazolam, a CYP3A4 substrate, it is not expected that oprozomib will cause a relevant decrease in metabolism of CYP3A4 substrates (Ou et al, 2018). Details of oprozomib clinical PK and the drug-drug interaction study findings are summarized below and in the Oprozomib IB.

Study 2009-003 is a completed phase 1, open-label, dose escalation study designed to evaluate the MTD, safety, tolerability and PK of Oprozomib in Capsules in subjects with advanced refractory or recurrent solid tumors. PK was characterized in 25 subjects administered Oprozomib in Capsules orally once daily on Days 1, 2, 3, 4, and 5 of a 14-day cycle (5/14 schedule). The doses ranged from 30 to 180 mg. Oprozomib was

rapidly absorbed with a t_{max} of 0.900 to 2.29 hours and was cleared with a $t_{1/2}$ of 0.49 to 1.62 hours following single dose administration under fasting conditions.

Study 2011-001 is a phase 1b/2, open-label, dose escalation study designed to evaluate the MTD, safety, tolerability and efficacy of oprozomib in subjects with hematologic malignancies. As of January 2016, PK has been characterized following once daily oral administration of Oprozomib Tablets in 32 subjects on a 5/14 schedule and 30 subjects on a 2/7 schedule. The doses ranged from 150 to 270 mg on the 5/14 schedule and 150 to 330 mg on the 2/7 schedule (oprozomib administered on Day 1 and 2 every 7 days). Oprozomib was rapidly absorbed under fasting conditions with a t_{max} of 1.3 to 2.2 hours, and was cleared with a $t_{1/2}$ of 0.52 to 2.1 hours following a single dose administration. Study 2012-001 is an ongoing phase 1b/2, open-label, dose escalation study designed to evaluate the MTD, safety, tolerability, and efficacy of oprozomib and dexamethasone in patients with relapsed and/or refractory multiple myeloma. As of January 2015, PK has been characterized following once daily oral administration of oprozomib tablets in 16 subjects on a 5/14 schedule and 19 subjects on a 2/7 schedule. The doses ranged from 180 to 210 mg on the 5/14 schedule and 210 to 300 mg on the 2/7 schedule. Oprozomib was rapidly absorbed under fasted conditions with a median t_{max} of 1 to 2 hours and was cleared with a median $t_{1/2}$ of 0.60 to 1.4 hours.

Study OPZ007 is an ongoing phase 1b study designed to determine the MTD, RP3D, safety, tolerability and progression-free survival of OPomd in subjects with primary refractory or relapsed and refractory multiple myeloma (Shah et al, 2015). As of October 2015, PK has been characterized following once daily administration of Oprozomib Tablets in 3 patients given 150 mg oprozomib on the 5/14 schedule and 8 and 10 patients given 210 and 240 mg oprozomib, respectively, on the 2/7 schedule. Preliminary results demonstrated that the PK of oprozomib when given in combination with pomalidomide and dexamethasone was generally consistent with other oprozomib studies. Oprozomib was absorbed with a median t_{max} of 1.0 to 4.0 hours and was cleared with a median $t_{1/2}$ of 0.449 to 0.894 hours.

Study OPZ009 is a phase 1, clinical drug-drug interaction study designed to assess the effect of oprozomib on the PK of midazolam, a CYP3A4 substrate, in subjects with advanced malignancies (Ou et al, 2018; Tsimberidou et al, 2016). Patients received 300 mg oprozomib tablets on Days 1, 2, 8, and 9 of two consecutive 14-day cycles. Midazolam was administered as a single 2 mg dose alone during a baseline visit prior to the start of oprozomib administration and 1 hour following oprozomib on cycle 1, day 1

and cycle 2, day 2. There was no change in midazolam area under the plasma concentration-time curve from time 0 to time infinity (AUC_{inf}) following multiple oprozomib dosing and only a 14% mean increase in midazolam C_{max}. Following a single oprozomib dose, a minimal mean increase of 28% and 33% in midazolam AUC and C_{max}, respectively, was observed. Based on these results, it is not expected that oprozomib will cause a relevant decrease in metabolism of CYP3A4 substrates. A product label review of CYP3A4 substrates given concomitantly with oprozomib demonstrating that dose adjustments were not required for the weak inhibitory potential observed in the OPZ009 study provides additional evidence that there is no clinically relevant drug-drug interaction of oprozomib with CYP3A4 substrates.

5.3 Risk Assessment

Important identified risks to human subjects with the use of oprozomib include diarrhea, nausea, vomiting, abdominal pain, GI hemorrhage, constipation, fatigue, hypophosphatemia, dehydration, tumor lysis syndrome, decreased appetite, anemia, thrombocytopenia, infection (pneumonia, sepsis, and urinary tract infection), hypotension, acute renal failure and syncope (the last three only secondary to diarrhea and dehydration).

Please refer to Section 7 of the Oprozomib IB for a description of important potential risks, which include posterior reversible encephalopathy syndrome (PRES).

5.4 Non-Amgen Non-investigational Medicinal Product Background

5.4.1 Pomalidomide

Pomalidomide is an analogue of thalidomide that displays greater anti-proliferative and immunomodulatory activity compared with the parent drug, and similar antiangiogenic activity (Bartlett, 2007; Payvandi, 2004). Pomalidomide has also been shown to stimulate antibody-dependent cytotoxic T-cell activity (ADCC) (Bartlett, 2007). In combination with dexamethasone, it is indicated for patients with multiple myeloma who have received at least two prior therapies (including a proteasome inhibitor and lenalidomide), and have demonstrated disease progression on the last drug taken.

Additional product information is provided in the Pomalidomide Prescribing Information (**Pomalidomide U.S. Prescribing Information for United States; for other countries, see appropriate prescribing information**).

5.4.2 Dexamethasone

Dexamethasone is a synthetic adrenocortical steroid and it is indicated in combination with pomalidomide for the treatment of multiple myeloma. Additional product information is provided in the Dexamethasone Prescribing Information (Pfizer Laboratories, 2012).

5.5 Rationale

5.5.1 Rationale for Targeting the Proteasome

The proteasome is a multi-catalytic proteinase complex that is responsible for maintaining the cellular physiology of normal and transformed cells through degradation of a wide variety of protein substrates. 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.

Subsequently, proteasome inhibitors have been shown to have antiproliferative, proapoptotic, and antiangiogenic 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).

5.5.2 Rationale for the Use of Pomalidomide and Dexamethasone

Pomalidomide administered in combination with dexamethasone reflects a current standard of care (National Comprehensive Cancer Network [NCCN] category 1 option) in the treatment of relapsed and refractory multiple myeloma (NCCN Guidelines Version 3, 2016). Pomalidomide was approved by the U.S. Food and Drug Administration (FDA) and by the European Commission in 2013. In the U.S., pomalidomide, in combination with dexamethasone, is indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval of pomalidomide by the European Commission, for use in combination with dexamethasone, is for the treatment of patients with relapsed and refractory multiple myeloma that have received at least two prior therapies and have demonstrated disease progression on the last drug taken.

5.5.3 Rationale for the Evaluation of Oprozomib in Combination With Pomalidomide and Dexamethasone

Relapsed/refractory multiple myeloma remains a significant unmet medical need. Current standard of care, pomalidomide plus low-dose dexamethasone, provides limited improvement over disease progression with an observed median PFS of less than 4 months, and a median overall survival (OS) of approximately one year (**Additional product information is provided in the Pomalidomide Prescribing Information: Pomalidomide U.S. Prescribing Information for United States; for other countries, see appropriate prescribing information**).

Preliminary safety, efficacy and PK of oprozomib in combination with pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma are undergoing evaluation in the context of a phase 1b study (Study OPZ007), and data generated to date supports further evaluation of the triplet combination. In the ongoing study, patients received at least 2 prior regimens and at least 2 consecutive prior cycles of bortezomib together with lenalidomide or thalidomide. Patients received oprozomib orally once daily on either a 5/14 schedule or on a 2/7 schedule of 28-day cycles. In the 5/14 schedule, 4 patients received oprozomib 150 mg/day and in the 2/7 schedule 17 and 10 patients received oprozomib 210 mg/day and 240 mg/day respectively. Patients received also pomalidomide (starting dose 4 mg) on days 1 to 21 and dexamethasone 20 mg on days 1, 2, 8, 9, 15, 16, 22, 23 of each cycle. Thirty-one patients were enrolled in the study by 26 October 2015. The MTD was not reached on either schedule; the 2/7 schedule at 210 mg/day dose of oprozomib was chosen for the expansion cohort in this study based on the safety and efficacy data available. The most common Grade $\geq$ 3 adverse events observed in the study were anemia and diarrhea (with 47% and 11%, respectively, in the 2/7 210 mg/day cohort). A partial response or better was reported in 2 patients (50%) in the 5/14 schedule and in 17 patients (63%) in the 2/7 schedule. With the dose of 210 mg/day of oprozomib administered on a 2/7 schedule the combination was similarly active (71% overall response rate [ORR]), and even in a highly refractory patient population: 4 of 5 CFZ-refractory patients in this group achieved $\geq$ partial response (PR). The pharmacokinetics of oprozomib when given in combination with pomalidomide and dexamethasone were generally consistent with other oprozomib studies. The authors concluded that the initial results suggest that the combination of OPomd has encouraging anti-myeloma activity and is generally well tolerated (Shah et al, ASH 2015).

In the present new study, two new formulations of oprozomib (IR and GR) in combination with pomalidomide and dexamethasone, will be evaluated in an effort to further optimize safety and PK parameters of this triplet regimen.

5.5.4 Rationale for the Starting Dose and Schedule

5.5.4.1 Oprozomib

In the ongoing Phase 1b study evaluating oprozomib in combination with pomalidomide and dexamethasone, 1 dose limiting toxicity (DLT) (a Grade 3 gastric hemorrhage with severe erosive gastritis by endoscopic diagnosis), was reported among subjects treated with 210 mg using the 2/7 schedule. Four DLTs were reported in two subjects using the 5/14 schedule and an oprozomib dose of 150 mg/day. The DLTs included Grade 3 mucositis and Grade 3 rash in one subject, and Grade 3 abdominal distention and Grade 3 impaired cognitive function in another subject. While the MTD was not defined using either schedule, the maximum administered dose for the 2/7 schedule of oprozomib was 240 mg and a 210 mg dose of oprozomib administered on a 2/7 schedule was chosen for the expansion cohort based on the available safety and efficacy data.

Early development of oprozomib included also single-agent evaluation using a 2/7 schedule. 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. One DLT of Grade 3 orthostatic hypotension was reported in the 300 mg cohort, therefore 300 mg was declared the MTD.

In study number 2011-001 (a phase 1b/2 study of single-agent oprozomib in patients with hematologic malignancies), oprozomib 150/180 mg was administered as monotherapy on days 1-5 of a 14 day cycle (5/14 schedule). Subjects received oprozomib at a dose of 150 mg in cycle 1 and at a dose of 180 mg starting in cycle 2 and thereafter. Among the 23 subjects enrolled in this group, reports of Grade 3 or greater GI adverse events were limited to a report of Grade 3 diarrhea in 1 subject (4%) (Vij et al 2015).

Based on above data, in the present study the starting IR and GR oprozomib dose is proposed to be 150 mg/day (may be adjusted as per emerging data). The 150 mg/day dose level is 150 mg below the previous single agent MTD of 300 mg/day and 60 mg below the recommended expansion dose of 210 mg/day in the ongoing Phase 1b OPomd combination study. This is also the anticipated “initial dose level” of oprozomib to be administered to all subjects during the first week of treatment only, regardless of

what dose level will be administered onwards. The 2/7 schedule was preferred over 5/14 due to efficacy and tolerability.

Two formulations, Oprozomib in Capsules and Oprozomib Tablets have been characterized previously in subjects. The PK of Oprozomib in Capsules has been characterized at doses of 30 to 180 mg in patients given oprozomib as a single agent (Study 2009-003). Following single dose administration of the capsules, oprozomib was rapidly absorbed with a t_{max} of 0.900 to 2.29 hours and was cleared with a $t_{1/2}$ of 0.49 to 1.62 hours. Mean observed C_{max} and AUC_{last} ranged from 223 to 1320 ng/mL and 290 to 1610 ng·hr/mL, respectively. The PK of Oprozomib Tablets has also been characterized at doses of 150 to 330 mg in two studies in subjects given oprozomib either as a single agent (Study 2011-001) or in combination with dexamethasone (Study 2012-001). Mean observed C_{max} and AUC_{last} for oprozomib ranged from 594 to 1890 ng/mL and 1050 to 3820 ng·hr/mL, respectively.

The rate and extent of exposure of the IR formulation in the current study is expected to be similar to that of the Oprozomib in Capsules. The IR formulation, at the doses planned, is not predicted to exceed the exposures observed in the dose range with Oprozomib Tablets in previous studies. Similarly, the GR formulation, at the doses planned in this study, is not expected to exceed the exposures observed with Oprozomib Tablets in previous studies. The PK will be assessed after each dose cohort to monitor the actual concentrations and variability following administration.

5.5.4.2 Step-up Dosing

A stepped-up dosing regimen has been tested in rats. Oprozomib was tolerated following oral administration of 30 mg/kg twice weekly for the first week with an increase in dose of 50 mg/kg in the second week and thereafter on the same schedule. Rats did not tolerate oprozomib when given 50 mg/kg orally at the same schedule continuously from the first dose. A stepped-up dosing regimen using oprozomib as monotherapy underwent preliminary evaluation using both the 2/7 and 5/14 schedules in subjects with relapsed/refractory multiple myeloma. Subjects received a reduced dose of OPZ during cycle 1 (150 and 240 mg/day, respectively) followed by a higher dose of OPZ during cycles 2 and beyond (180 and 300 mg/day, respectively). Preliminary data indicate that the incidence of Grade 3 or greater nausea, vomiting and diarrhea may be improved with the use of a step-up dosing regimen. These data are consistent with findings with improved tolerability with step-up intravenous dosing of carfilzomib and support the

concept that a step-up dosing regimen may improve tolerability in subjects given oprozomib orally.

5.5.4.3 Pomalidomide

Pomalidomide will be administered at the approved dose of 4 mg given orally once daily on Days 1 to 21 of repeated 28-day cycles.

Approval of pomalidomide was based on the Phase 2 Study MM002 (Jagannath, 2012). A total of 221 subjects were randomized. The safety and efficacy of pomalidomide 4 mg, once daily for 21 of 28 days, until disease progression, were evaluated alone and in combination with dexamethasone (40 mg/day given only on Days 1, 8, 15, and 22 of each 28-day cycle for patients aged 75 years or younger, or 20 mg/day given only on Days 1, 8, 15, and 22 of each 28-day cycle for subjects aged greater than 75 years. The 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%). 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%).

The MM003 Study (San Miguel 2013) was a phase 3 multi-center, randomized, open-label study of pomalidomide in combination with low-dose dexamethasone which was compared to high-dose dexamethasone alone in adult patients with relapsed and refractory multiple myeloma, who had received at least two prior treatment regimens, including lenalidomide and bortezomib, and demonstrated disease progression on or within 60 days of the last therapy. A total of 455 subjects were enrolled in the trial including 302 in pomalidomide/low-dose dexamethasone arm and 153 in the high-dose dexamethasone arm. Subjects in the pomalidomide/low-dose dexamethasone arm received 4 mg of pomalidomide orally on Days 1 to 21 of each 28-day cycle. A dexamethasone dose of 40 mg was administered once per day on Days 1, 8, 15 and 22 of a 28-day cycle. Patients > 75 years of age started treatment with 20 mg dexamethasone using the same schedule. Dexamethasone 40 mg in the high-dose arm was administered once per day on Days 1 through 4, 9 through 12, and 17 through 20 of a 28-day cycle. Patients > 75 years of age started treatment with 20 mg dexamethasone using the same schedule. Pomalidomide/low-dose dexamethasone significantly

extended median PFS (4.0 vs. 1.9 months, HR = 0.48, P < .0001) and OS (12.7 vs. 8.1 months, HR = 0.74, P < .0285) vs. high dose dexamethasone. The ORR was 31% for pomalidomide/low-dose dexamethasone vs. 10% for high-dose dexamethasone (P < .0001). The most frequent Grade 3/4 adverse events (AEs) for pomalidomide/low-dose dexamethasone vs. high-dose dexamethasone were neutropenia (48% vs. 16%), anemia (33% vs. 37), and thrombocytopenia (22% vs. 26%).

5.5.4.4 Dexamethasone

Dexamethasone will be administered at a dose of 20 mg orally on Days 1, 2, 8, 9, 15, 16, 22 and 23 of repeating 28-day cycles. This regimen provides a total weekly dose consistent with the dosing used in the MM003, MM002 and other clinical trials (Lacy et al, 2011), and is the dexamethasone dosing regimen used in the ongoing Phase 1b study of oprozomib in combination with pomalidomide and dexamethasone.

5.5.5 Clinical Experience – Phase 1

As of the 21 August 2020 data cutoff date, Study 20160104 had enrolled 54 subjects with RRMM: 36 with the IR formulation and 18 with the GR formulation. Forty-five enrolled subjects were evaluable for efficacy, with 9 subjects in combination with dexamethasone and 23 subjects with pomalidomide and dexamethasone. Preliminary results demonstrated anti-tumor activity in RRMM, with 20 of 28 evaluable subjects having a PR or better with the IR formulation and 3 of 8 having a PR or better with GR formulation in combination with pomalidomide and dexamethasone.

A total of 6 DLTs were observed. For the GR formulation, 1 subject with the 150 mg GR formulation in the Opomd group experienced grade 4 neutropenia and subsequently developed febrile neutropenia (reported as separate DLT events). The DLRM recommended to escalate to 200 mg; one DLT was observed (grade 4 thrombocytopenia). For the IR formulation, 1 DLT was observed with the 150 mg dose and the 200 mg dose, and 2 DLTs were observed with the 250 mg dose across both the ODex and OPomd groups. A summary of DLTs is provided in Table 1.

Table 1. Subject Incidence of Dose-limiting Toxicities (DLT) During DLT Evaluation Period by Preferred Term in Descending Order of Frequency (DLT-Evaluable Analysis Set)

	Non-roll Over Subjects										
	ODex 2/7 Schedule			OPomd 2/7 Schedule							
Preferred Term	IR 150 mg/day (N = 5) n (%)	GR 150 mg/day (N = 8) n (%)	ODex 2/7 Total (N = 13) n (%)	IR 150 mg/day (N = 4) n (%)	GR 150 mg/day (N = 4) n (%)	IR 200 mg/day (N = 8) n (%)	GR 200 mg/day (N = 5) n (%)	IR 225 mg/day (N = 10) n (%)	IR 250 mg/day (N = 8) n (%)	OPomd 2/7 Total (N = 39) n (%)	Total Subjects (N = 52) n (%)
Number of subjects reporting DLTs	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (25.0)	1 (12.5)	1 (20.0)	0 (0.0)	2 (25.0)	6 (15.4)	6 (11.5)
Lipase increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	2 (5.1)	2 (3.8)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (2.6)	1 (1.9)
Acute kidney injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	1 (1.9)
Febrile neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	1 (1.9)
Neutrophil count decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	1 (1.9)
Thrombocytopenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (2.6)	1 (1.9)

2/7 schedule = every week on 2 consecutive days; GR = Extended release gastro-retentive formulation; IR = Immediate Release formulation; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of subjects in the analysis set; n = Number of subjects with observed data; ODex = Oprozomib in combination with dexamethasone; OPomd = Oprozomib in combination with pomalidomide and dexamethasone.
Note: Coded using MedDRA version 23.0. Reporting Period: Inception to data cutoff date: 02 December 2019. Snapshot date: 21 August 2020.
Source: Table 12-2 as presented in 20160104 Clinical Study Report, data snapshot date of 21 August 2020.

A total of 52 subjects were included in the safety analysis set. Overall, 51 of the 52 subjects (98.1%) treated with oprozomib (12 subjects [92.3%] in the ODex group [N = 13] and 39 subjects [100.0%] in the OPomd group [N = 39]) reported at least 1 treatment-emergent adverse event during the primary analysis period. The most common treatment-emergent adverse events (> 50%) were nausea, vomiting, and diarrhea; 14 subjects (26.9%, 1 subject [7.7%] in the ODex group and 13 subjects [33.3%] in the OPomd group) who received oprozomib reported at least one grade ≥ 3 gastrointestinal disorder event during the primary analysis period. Grade ≥ 3 adverse events were reported for 45 subjects (86.5%) (10 subjects [76.9%] in the ODex group and 35 subjects [89.7%] in the OPomd group). A summary of adverse events is provided in Table 2. Summary of Subject Incidence of Treatment-Emergent Adverse Events (Safety Analysis Set).

Table 2. Summary of Subject Incidence of Treatment-Emergent Adverse Events (Safety Analysis Set)

	Non-roll Over Subjects										
	ODex 2/7 Schedule			OPomd 2/7 Schedule							
	IR 150 mg/day (N = 5) n (%)	GR 150 mg/day (N = 8) n (%)	ODex 2/7 Total (N = 13) n (%)	IR 150 mg/day (N = 4) n (%)	GR 150 mg/day (N = 4) n (%)	IR 200 mg/day (N = 8) n (%)	GR 200 mg/day (N = 5) n (%)	IR 225 mg/day (N = 10) n (%)	IR 250 mg/day (N = 8) n (%)	OPomd 2/7 Total (N = 39) n (%)	Total Subjects (N = 52) n (%)
All treatment-emergent adverse events	4 (80.0)	8 (100.0)	12 (92.3)	4 (100.0)	4 (100.0)	8 (100.0)	5 (100.0)	10 (100.0)	8 (100.0)	39 (100.0)	51 (98.1)
Grade ≥ 2	4 (80.0)	8 (100.0)	12 (92.3)	4 (100.0)	4 (100.0)	8 (100.0)	5 (100.0)	10 (100.0)	8 (100.0)	39 (100.0)	51 (98.1)
Grade ≥ 3	3 (60.0)	7 (87.5)	10 (76.9)	4 (100.0)	4 (100.0)	8 (100.0)	5 (100.0)	8 (80.0)	6 (75.0)	35 (89.7)	45 (86.5)
Grade ≥ 4	1 (20.0)	1 (12.5)	2 (15.4)	3 (75.0)	2 (50.0)	1 (12.5)	4 (80.0)	0 (0.0)	1 (12.5)	11 (28.2)	13 (25.0)
Serious adverse events	2 (40.0)	2 (25.0)	4 (30.8)	2 (50.0)	4 (100.0)	6 (75.0)	4 (80.0)	3 (30.0)	4 (50.0)	23 (59.0)	27 (51.9)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (25.0)	2 (25.0)	1 (20.0)	0 (0.0)	1 (12.5)	6 (15.4)	6 (11.5)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (2.6)	1 (1.9)
Treatment-related treatment-emergent adverse events	4 (80.0)	8 (100.0)	12 (92.3)	4 (100.0)	4 (100.0)	8 (100.0)	5 (100.0)	10 (100.0)	8 (100.0)	39 (100.0)	51 (98.1)
Grade ≥ 2	2 (40.0)	6 (75.0)	8 (61.5)	4 (100.0)	3 (75.0)	7 (87.5)	4 (80.0)	9 (90.0)	7 (87.5)	34 (87.2)	42 (80.8)
Grade ≥ 3	1 (20.0)	4 (50.0)	5 (38.5)	4 (100.0)	3 (75.0)	6 (75.0)	1 (20.0)	5 (50.0)	5 (62.5)	24 (61.5)	29 (55.8)
Grade ≥ 4	0 (0.0)	1 (12.5)	1 (7.7)	3 (75.0)	2 (50.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (12.5)	7 (17.9)	8 (15.4)
Serious adverse events	0 (0.0)	1 (12.5)	1 (7.7)	1 (25.0)	2 (50.0)	2 (25.0)	1 (20.0)	1 (10.0)	1 (12.5)	8 (20.5)	9 (17.3)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (25.0)	2 (25.0)	1 (20.0)	0 (0.0)	1 (12.5)	6 (15.4)	6 (11.5)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (2.6)	1 (1.9)

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Footnotes and abbreviations are on the last page of the table.

Table 2. Summary of Subject Incidence of Treatment-Emergent Adverse Events (Safety Analysis Set)

	Non-roll Over Subjects										
	ODex 2/7 Schedule			OPomd 2/7 Schedule							
	IR 150 mg/day (N = 5) n (%)	GR 150 mg/day (N = 8) n (%)	ODex 2/7 Total (N = 13) n (%)	IR 150 mg/day (N = 4) n (%)	GR 150 mg/day (N = 4) n (%)	IR 200 mg/day (N = 8) n (%)	GR 200 mg/day (N = 5) n (%)	IR 225 mg/day (N = 10) n (%)	IR 250 mg/day (N = 8) n (%)	OPomd 2/7 Total (N = 39) n (%)	Total Subjects (N = 52) n (%)
All treatment-emergent disease-related events	1 (20.0)	1 (12.5)	2 (15.4)	0 (0.0)	0 (0.0)	1 (12.5)	2 (40.0)	0 (0.0)	1 (12.5)	4 (10.3)	6 (11.5)
Grade ≥ 2	1 (20.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	1 (12.5)	3 (7.7)	4 (7.7)
Grade ≥ 3	1 (20.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	0 (0.0)	2 (5.1)	3 (5.8)
Grade ≥ 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (2.6)	1 (1.9)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (2.6)	1 (1.9)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (2.6)	1 (1.9)

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2/7 schedule = every week on 2 consecutive days; AE = adverse event; CRF = case report form; GR = extended release gastro-retentive formulation; IR = immediate release formulation; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of subjects in the analysis set; n = Number of subjects with observed data; ODex = oprozomib in combination with dexamethasone; OPomd = oprozomib in combination with pomalidomide and dexamethasone; TEAE = treatment-emergent adverse event.

Note: For subjects with multiple events, only the worst severity grade is reported. (TEAEs) are defined as AEs starting on or after first dose of investigational product as determined by the flag indicating if the adverse event started before the first dose on the events CRF and up to and including 30 days after the last dose of investigational product or the End of the Study date, whichever is earlier. Coded using MedDRA version 23.0. Reporting Period: Inception to data cutoff date: 02 December 2019. Snapshot date: 21 August 2020. Dose reductions due to an adverse event were reported for a total of 14 subjects (See Table 14-5.12 as presented in 20160104 Clinical Study Report, data snapshot date of 21 August 2020).

Source: Table 12-3 as presented in 20160104 Clinical Study Report, data snapshot date of 21 August 2020.

5.6 Clinical Hypothesis

At least one dose level of the formulations of oprozomib administered orally together with pomalidomide and dexamethasone is expected to achieve acceptable safety and tolerability in subjects with relapsed or refractory multiple myeloma.

6. EXPERIMENTAL PLAN

6.1 Study Design

This is a Phase 1b, multicenter, non-randomized, open-label, dose-exploration study of up to two formulations of oprozomib (an IR formulation and a GR formulation) administered orally in combination with pomalidomide and dexamethasone in subjects with relapsed or refractory multiple myeloma. The evaluation of the different formulations will start with the IR (for the initial 1 to 2 dose levels) however, for most of the study the two oprozomib formulations will be tested in parallel.

Throughout the study, oprozomib will be administered according to a 2/7 schedule (ie, every week on 2 consecutive days). All subjects will be treated during the first week only with a fixed, initial dose of oprozomib (currently 150 mg/day, which may be adjusted during the study based on emerging data). For all dosing days thereafter the subjects will be treated with the appropriate dose level of oprozomib according to the dose escalation cohort evaluated. During the initial DLT window (Days 1 through 28), subjects will be assessed for DLTs. DLTs are defined in Section 9.2.1.4. Dosing will continue until evidence of progressive disease (PD) defined by IMWG, the subject becomes intolerant to the treatment, signs and symptoms of clinical progression are evident as determined by the principal investigator, or the subject withdraws consent.

The study will be conducted in two sequential parts:

Part 1 – Evaluation of 2 oprozomib formulations administered at a currently anticipated 150 mg/day dose level in combination with dexamethasone (Od) only.

Part 2 – Evaluation of 2 oprozomib formulations administered at different increasing dose levels (dose escalation) in combination with pomalidomide and dexamethasone (OPomd).

Part 1 will test a sample size of 3 subjects per each formulation of oprozomib. If 1 of the initial 3 evaluable subjects experiences a DLT, then 3 additional evaluable subjects will be enrolled. If 2 or more of the evaluable subjects experience a DLT (eg, 33% or higher with 6 evaluable subjects), then the dose level of 150 mg/day of that particular oprozomib formulation will be determined to be non-tolerable and a second Part 1 cohort will be enrolled to test a decreased dose of oprozomib in combination with

dexamethasone. The reduced dose of oprozomib used in subsequent cohorts will be determined based on analysis of emerging safety and PK data from the initial cohort.

Part 2 dose escalation will use the Bayesian 2-parameter logistic regression model with the new continual reassessment method (NCRM) applied to observed DLTs (Neuenschwander, 2008). For the IR formulation, the starting dose level will be determined based on the oprozomib dose exploration in Part 1 (150 mg/day if ≤ 1 DLT is seen at this dose level with the Od combination). It is anticipated that seven dose levels of oprozomib (between 150 mg/day and 300 mg/day, in increments of 25 mg) will be tested in combination with pomalidomide and dexamethasone. One or more cohorts (of at least 2 subjects) may be enrolled at each dose level of oprozomib, depending on the toxicity observed. The dose level review team (DLRT) will review the safety data and dose level recommended by the algorithm after every cohort has completed the DLT period. The starting dose for the GR formulation will be determined based on the safety and PK data observed in the first cohorts of the IR dose escalation, and it will be at least one dose level lower than the highest dose tested of the IR formulation. This strategy will potentially reduce the sample size needed to define the MTD and therefore, the anticipated sample size is 22 DLT-evaluable subjects for the GR formulation dose escalation.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 13.1.1.

6.2 Number of Sites

The study will be conducted at approximately 20 sites in the US and internationally. Sites that do not enroll subjects into an open cohort within 4 months of site initiation may be closed.

6.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”. Subjects with relapsed or refractory multiple myeloma are eligible for this study. The eligibility criteria are defined in Section 7.1 and Section 7.2.

Approximately 64 DLT-evaluable subjects will be enrolled in the study. In Part 1, each formulation will be tested in a cohort of at least 3 DLT-evaluable subjects. In Part 2 (dose escalation), a Bayesian design will be applied to evaluate the oprozomib formulations administered at different increasing dose levels in combination with

pomalidomide and dexamethasone. The maximum sample size for testing the IR formulation is set to 36 DLT-evaluable subjects. The anticipated sample size for the GR formulation is 22 DLT-evaluable subjects. The rationale for the number of subjects required is detailed in Section 13.2.

6.4 Replacement of Subjects

Subjects that are not DLT-evaluable will be replaced. In order to be DLT-evaluable, a subject would receive the doses of study treatment as specified below during the 28 day DLT window:

- All planned doses of oprozomib be received
- 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

If the subject discontinues the treatment or misses a dose of oprozomib for reasons other than DLT before completion of the DLT window, the DLRT will decide if the subject is DLT-evaluable and will make the final decision on subject replacement.

6.5 Estimated Study Duration

The average duration of the study is anticipated to be approximately 28 months which includes 10 months of protocol treatment period. The average enrollment period is 18 months and could range from 13 months to 23 months based on the MTD dose level and the shape of dose toxicity curve.

6.5.1 Study Duration for Subjects

The estimated study duration for a participant is 12 months, approximately 4 weeks for screening and 10 months of treatment. However, this may be longer or shorter depending on the subject's disease, ability to tolerate study treatment and/or willingness to participate in the study. Approximately 30 days after the last dose of oprozomib, the subject will return to the clinic for a safety follow-up (EOS) visit.

6.5.2 End of Study

The end of study for a subject occurs when a subject discontinues study treatment and completes the EOS visit. The date the final safety assessment or procedure is performed is considered the end of study. The safety follow-up or EOS visit will occur 30 to 37 days after the last administration of study treatment. A subject is considered to have completed the study if they complete an EOS visit.

Primary Completion: is defined as the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary

analysis. The primary analysis will occur when target enrollment is complete and each subject either completes 2 months on study or withdraws from the study. Subjects who are still active at the time of the primary analysis may continue on study treatment until disease progression, study withdrawal, death, or intolerance to study treatment is observed.

End of Study: is defined as the time when the last subject is assessed or receives an intervention for evaluation in the study. Once achieved, the final analysis will occur.

7. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). Before any study-specific activity/procedure, the appropriate written informed consent must be obtained (see Section 14.1).

7.1 Inclusion Criteria

101 Subject has provided informed consent prior to initiation of any study-specific activities/procedures

102 Age ≥ 18 years old at the time of signing the informed consent

103 Subject must have a pathologically documented, definitively diagnosed, multiple myeloma relapse, or refractory progressive disease after at least 2 lines of therapy for multiple myeloma (see Appendix D and Appendix F for further details). Prior therapeutic treatment or regimens must include a proteasome inhibitor and lenalidomide

104 Subject must be willing and able to undergo bone marrow aspirate per protocol (with or without bone marrow biopsy per institutional guidelines)

105 Measurable disease (assessed within 28 days prior to day 1), as indicated by one or more of the following:

- Serum M-protein ≥ 0.5 g/dL
- Urine M-protein ≥ 200 mg/24 hours
- In subjects without detectable serum or urine M-protein: serum Free Light Chain (sFLC) ≥ 10 mg/dL (≥ 100 mg/L) and an abnormal sFLC ratio

106 Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2

107 Hematological function, as follows, without transfusion support:

- Absolute neutrophil count ≥ 1.0 X 10^9/L
- Platelet count ≥ 75 X 10^9/L (in patients with < 50% of bone marrow nucleated cells were plasma cells) or ≥ 50 X 10^9/L (in patients with ≥ 50% of bone marrow nucleated cells were plasma cells) without transfusion or growth factor support

- Hemoglobin > 8 g/dL (> 80 g/L) Use of erythropoietic stimulating factors and red blood cell (RBC) transfusions per institutional guidelines is allowed, however most recent RBC transfusion must not be within 7 days prior to obtaining screening hemoglobin

108 Coagulation function as follows: PT/INR and PTT < 1.5 x Institutional Upper Limit of Normal (ULN)

109 Renal function as follows: estimated glomerular filtration rate based on Modification of Diet in Renal Disease calculation (MDRD) > 30 mL/min/1.73 m^2

110 Hepatic function, as follows: AST and ALT < 3 x ULN, Total bilirubin < 1.5 x ULN (except subjects with Gilbert's syndrome)

7.2 Exclusion Criteria

201 Currently receiving treatment in another investigational device or drug study, or less than 28 days or 5 half-lives whichever is shorter since ending treatment on another investigational device or drug study(s)

202 Previously received an allogeneic stem cell transplant and the occurrence of one or more of the following:

- received the transplant within 6 months prior to study day 1
- received immunosuppressive therapy within the last 3 months prior to study day 1
- having signs or symptoms of acute or chronic graft-versus-host disease

203 Autologous stem cell transplant < 90 days prior to study day 1

204 Multiple myeloma with IgM subtype

205 POEM syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)

206 Plasma cell leukemia (> 2.0 $X10^9$/L circulating plasma cells by standard differential)

207 Waldenstrom's macroglobulinemia

208 Amyloidosis

209 Requirement for plasmapheresis during the screening period

210 Dexamethasone at cumulative doses of greater than 160 mg or equivalent within 21 days prior to study day 1 is not allowed. Use of topical or inhaled steroids is acceptable

211 History of other malignancy, except:

- Malignancy treated with curative intent and with no known active disease present for ≥ 1 year before study day 1 and felt to be at low risk for recurrence by the treating physician
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated cervical carcinoma in situ without evidence of disease

- Adequately treated breast ductal carcinoma in situ without evidence of disease
- Prostatic intraepithelial neoplasia without evidence of prostate cancer
- Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ

212 Evidence of a bleeding diathesis

213 Current use of therapeutic doses of anticoagulation unless agreed upon by the investigator and the Amgen Medical Monitor. Please note: thromboprophylaxis is recommended with pomalidomide treatment

214 Myocardial infarction within 6 months of study day 1, symptomatic congestive heart failure (New York Heart Association $>$ class II).

215 Infection requiring anti-infective treatments (oral or intravenous) within 2 weeks of study day 1.

216 Hepatitis B and C based on the following results:

- Positive for hepatitis B surface antigen (HBsAg) (indicative of chronic hepatitis B or recent acute hepatitis B)
- Negative HBsAg and positive for hepatitis B core antibody: hepatitis B virus DNA by polymerase chain reaction (PCR) is necessary. Detectable hepatitis B virus DNA suggests occult hepatitis B
- Positive Hepatitis C virus antibody (HCVAb): hepatitis C virus RNA by PCR is necessary. Detectable hepatitis C virus RNA suggests chronic hepatitis C

217 History of clinically significant GI hemorrhage (Grade $\geq$ 2) in the 6 months prior to study day 1, unless agreed upon by the investigator and the Amgen Medical Monitor

218 Known positive results for Human Immunodeficiency Virus (HIV)

219 Unresolved toxicities from prior anti-tumor therapy, defined as not having resolved to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 Grade 1, or to levels dictated in the eligibility criteria with the exception of Grade 2 peripheral neuropathy, alopecia or toxicities from prior anti-tumor therapy that are considered irreversible (defined as having been present and stable for $>$ 4 weeks may be allowed if they are not otherwise described in the exclusion criteria AND there is agreement to allow by both the investigator and the Amgen Medical Monitor)

220 Anti-tumor therapy (chemotherapy, antibody therapy, molecular targeted therapy, or investigational agent) within 28 days or 5 half-lives whichever is shorter prior to study day 1.

221 Prior systemic radiation therapy must have been completed at least 28 days before study day 1. Prior focal radiotherapy completed at least 14 days before study day 1

222 Major surgery within 28 days prior to study day 1

223 Females of reproductive potential who are unwilling to use two methods of contraception, one highly effective and one additional effective contraception

method while on study through 30 days after receiving the last dose of study drug. Males unwilling to always use latex or synthetic condom during any sexual contact with females of reproductive potential while on study through 90 days after receiving the last dose of study drug. Acceptable highly effective methods of birth control are defined:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence
- Males must also refrain from donating sperm for at least 90 days after the last dose of oprozomib

224 Female who is breastfeeding or who plans to breastfeed while on study through 30 days after receiving the last dose of study drug

225 Female with a positive pregnancy test

226 Female planning to become pregnant while on study through 30 days after receiving the last dose of study drug

227 Known hypersensitivity to any immunomodulatory drugs (IMiDs) or their formulation excipients, including rash

228 Known hypersensitivity or intolerance to dexamethasone or its formulation excipients

229 Prior exposure to oprozomib

230 History or evidence of any other clinically significant disorder, condition or disease that, in the opinion of the investigator or Amgen medical monitor, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

231 Prior use of pomalidomide if subjects required pomalidomide dose reduction or pomalidomide discontinuation due to toxicity

232 Subjects known to have any of the following disorders will be excluded unless agreed upon by the investigator and the Amgen Medical Monitor:

- Galactosemia (deficiency in galactose-1-phosphate-uridylyltransferase or UDP-galactose-4-epimerase or galactokinase; Fanconi-Bickel-Syndrome)
- hereditary lactase deficiency
- glucose-galactose malabsorption

8. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material (see Section 14.2).

All subjects must personally sign and date the IRB/IEC approved informed consent form (ICF) before commencement of study-specific procedures. Each subject who signs the informed consent enters into the screening period for the study and receives a unique subject identification number before any study procedures are performed. The subject identification number will be assigned manually. 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 unique study identification number will consist of 11 digits. The first 3 digits will represent the last 3 digits of the protocol number (eg, 104). The next 5 digits will represent the country code and site number (eg, 66001) and will be identical for all subjects at the site. The next 3 digits will be assigned in sequential order as subjects are screened (eg, 001, 002, 003). For example, the first subject to enter screening at site 66001 will receive the number 10466001001, and the second subject at the same site will be 10466001002. The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

All screening tests and procedures should be performed within 28 days prior to study day 1, unless otherwise indicated. All blood and urine samples collected for screening assessments will be submitted and analyzed by the local laboratory. Time permitting, screening laboratory assessments used to determine subject eligibility may be repeated once (up to a total of 2 times during the 28 day screening period), if necessary.

Subjects who do not meet eligibility criteria within the 28 day screening period will not be eligible for enrollment. Subjects may be re-screened up to 2 additional times at the

discretion of the investigator. The subject must be re-consented if a re-screening attempt occurs outside of the 28 day screening period. Subjects who are deemed ineligible will be documented as screen failures.

An Amgen representative will notify the site in writing when a cohort is open to screen and enroll subjects. Subjects may be eligible to enroll once all screening tests and procedures are completed and results indicate that all eligibility criteria are met. A site representative will complete and send the enrollment eligibility worksheet to Amgen. The eligibility worksheet should be completed and emailed to the Amgen representative at least 3 days prior to the planned day of first dose. The Amgen representative will acknowledge receipt of the paperwork and send confirmation of the cohort and dose level assignment for the subject.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria and the subject takes the first dose of IP. The investigator is to document this decision and date, in the subject's medical record and in the enrollment electronic case report form (eCRF).

Adverse Events are to be collected for a subject once they are enrolled in the study.

8.1 Treatment Assignment

The treatment assignment will include the cohort number and dose level in which subjects will be enrolled. The treatment assignment date is to be documented in the subject's medical record and on the enrollment eCRF.

9. TREATMENT PROCEDURES

9.1 Classification of Product

The Amgen investigational product used in this study is oprozomib.

The non-Amgen non-investigational products used in this study include: pomalidomide and dexamethasone.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of oprozomib, pomalidomide and dexamethasone.

9.2 Investigational Product

All investigational product(s) will be self-administered. A diary will be provided for subjects to record their adherence to the oral medication. Time of meal intake will be

recorded on subject diary for dosing days at home. For purposes of this protocol, "study treatment" refers to any combination of oprozomib, pomalidomide and dexamethasone.

9.2.1 Oprozomib Investigational Product

Oprozomib will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. Oprozomib is formulated as:

1. Immediate release (IR) formulation: oral solid dosage form in strengths of 25 and 50 mg. Both strengths are presented as round tablets with a non-functional white film coating. The tablets will be packaged in 75 cc high-density, polyethylene bottles with desiccant and closed with heat inductions seals and polypropylene child resistant closures. Each bottle will contain 30 tablets.
2. Extended release gastro-retentive (GR) formulation: oral solid dosage form in strengths of 25 mg and 100 mg. Both strengths are presented as oval tablets with a non-functional white film coating. The tablets will be packaged in 75 cc high-density, polyethylene bottles with desiccant and closed with heat induction seals and polypropylene child resistant closures. Each bottle will contain 30 tablets.

9.2.1.1 Dosage, Administration, and Schedule

Oprozomib will be administered orally on days 1, 2, 8, 9, 15, 16, 22, and 23 of each 4 week cycle. It is recommended that oprozomib IR be taken after a low fat meal. The oprozomib GR formulation must be taken immediately after a main meal that contains the highest calorie and fat content. Subjects are to be informed not to break, chew, or crush the oprozomib tablets. Oprozomib tablets should be swallowed whole. Lansoprazole or another oral PPI is required (H2 antagonists are recommended if subject has intolerance or hypersensitivity to PPI) for the duration of treatment to prevent GI toxicities. Oral hydration of 1.5 to 2 liters per 24 hours must be instituted in all subjects 24 hours prior to initiation of therapy for every cycle and continued throughout every day of oprozomib dosing. Throughout the study, oprozomib will be administered according to a 2/7 schedule i.e, every week on 2 consecutive days.

During Part 1, the initial tested dose level of oprozomib in combination with dexamethasone only, is anticipated to be 150 mg/day for both formulations.

During Part 2, all subjects will be treated during the first week only with a fixed, initial daily dose of oprozomib (currently 150 mg/day), and for all dosing days thereafter with the appropriate dose level of oprozomib according to the dose escalation cohort evaluated. For the IR formulation, the anticipated dose levels to be tested are 150, 175, 200, 225, 250, 275, and 300 mg/day. The starting dose of the GR formulation will be determined based on the safety and PK data observed in the first cohorts of the IR dose

escalation, and it will be at least one dose level lower that the highest dose tested of the IR formulation. Once there is a first dose level of oprozomib determined to be safe in combination with pomalidomide and dexamethasone (as determined by the first cohort in Part 2), the Part 1 subjects will be allowed to add pomalidomide to their treatment at that particular dose level. Once the oprozomib RP3D and the preferred formulation is identified, all subjects continuing the study in Parts 1 and 2 will be allowed to switch to the oprozomib RP3D and the recommended formulation. Subjects with clinical benefit may be able to switch formulation to **GR at 150 mg that is cleared by the DLRM** if agreed upon by the investigator and the Amgen medical monitor.

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

The effects of overdose of oprozomib are not known.

9.2.1.2 Dose-cohort Study Escalation and Stopping Rules

Part 1

Part 1 of the study (Od) will test a sample size of at least 3 subjects per each formulation of oprozomib. If 1 of the initial 3 evaluable subjects experiences a DLT, then 3 additional evaluable subjects will be enrolled. If 2 or more of the evaluable subjects experience a DLT (eg, 33% or higher with 6 evaluable subjects), then the dose level of 150 mg/day of that particular oprozomib formulation will be determined to be non-tolerable, and a second Part 1 cohort will be enrolled to test a decreased dose of oprozomib in combination with dexamethasone. The reduced dose of oprozomib used in subsequent cohorts will be determined based on analysis of emerging safety and PK data of the initial cohort.

After all DLT-evaluable subjects within a cohort have completed the DLT window, the DLRT will convene to review all available study data, including data collected after the initial DLT window, demographics, study treatment administration, medical history, concomitant medications, adverse events, clinical tests, vital signs, laboratory results and PK/[redacted] information. The DLRT will make all dose and/or schedule change decisions.

Part 2

The dose escalation design will use the Bayesian 2-parameter logistic regression model, the NCRM applied to observed DLTs (Neuenschwander, 2008).

For the IR formulation, the starting dose level is 150 mg/day (2/7 schedule); the maximum and the minimum planned dose levels are 300 mg/day and 150 mg/day, respectively. Dose levels and escalation and de-escalation increments may be adjusted based on data generated in the study. One or more cohorts of at least 2 subjects may be enrolled at each dose level, depending on the toxicity observed. In accord with NCRM, the relationship between dose and the probability of DLT will be updated as additional subject safety information becomes available. After all subjects enrolled at the starting dose level are DLT-evaluable, the Bayesian Logistic Regression (BLR) model will be updated, and the NCRM will recommend the next dose level from the updated probabilities for target toxicity interval and excessive/unacceptable toxicity interval. The next cohort (eg. the Dose Level 2 or continuation of Dose Level 1) will be the dose with the highest posterior probability of having a toxicity rate in the target toxicity interval, which is defined as 15% to 25%, and will be subject to the constraint that the probability of excessive/unacceptable toxicity, which is defined as $>$ 25% to 100%, is less than 40%. The DLRT will review the safety data and dose level recommended by the algorithm after every cohort has completed the DLT period. The DLRT will decide to expand the cohort at the current dose level, advance to the next dose level, or de-escalate to a lower dose level, based on the available data. Dose level skipping will be allowed in dose escalation decisions with a maximum increment of 50 mg/day. The NCRM will continue to assign subjects to subsequent dose levels based on the cumulative DLT data, until either the DLT rate of the recommended MTD has a probability of within the target toxicity interval (15%-25%) $\geq$ 40%, an excessive/unacceptable interval (>25%-100%) $<$ 40%, and a minimum of 6 subjects have been treated at the candidate MTD or the predetermined maximum sample size of 36 DLT-evaluable subjects is reached, whichever comes first.

The starting dose level of the GR formulation will be determined by the DLRT and based on the DLTs and adverse events observed in the first cohorts of the IR dose escalation and it will be at least one dose level lower than the highest dose tested of the IR formulation. This strategy will potentially reduce the sample size needed to find the MTD for the GR formulation and is currently anticipated to be 22 DLT-evaluable subjects.

The DLRT will review the available safety, efficacy and PK / [redacted] data and recommend a formulation and dose of OPomd for further clinical testing.

The DLRT may request additional reviews or recommend modifying or suspending the study if safety concerns arise during the study. In the event that a need to modify or

suspend the study is identified, this information will be communicated to investigators immediately.

Refer to Section 13.3.2 for additional details regarding the DLRT.

Dose Exploration Stopping Rules

The DLRT may consider Part 2 dose exploration complete if one of the following rules is met:

- A total of 58 DLT-evaluable subjects have been enrolled of which 22 are anticipated for the GR formulation, or
- MTDs are identified for the IR and the GR formulations

9.2.1.3 Other Rules for Holding Enrollment

- If DLTs occur in the first 2 subjects treated with OPomd, enrollment will be held to allow DLRT review and adjustment of the algorithm.
- If there is a study drug-related Grade 5 toxicity, enrollment will be held to allow DLRT review and further decision.

The DLRT will discuss such cases to decide whether to resume enrollment.

9.2.1.4 Dose Limiting Toxicities

A DLT will be defined as any of the events described below occurring in a subject during the DLT window, and regarded by the investigators and/or Amgen medical monitor to be related to study treatment. The DLT window will be the initial 28 days of study treatment. The DLT window may be extended to assess events starting within the window in case the DLT definition is time dependent (neutropenia or thrombocytopenia, see below). Any adverse event occurring outside the DLT window that is determined by the investigator to be possibly related to the investigational product, which is seen more frequently or is more severe than expected or is persistent despite appropriate management, can be determined to be a DLT upon unanimous decision by the DLRT after review of the adverse event and all available safety data. The CTCAE version 4.03 will be used to assess the severity of toxicities/adverse events. Study drug-related is defined as a reasonable likelihood of clinical causality based on a temporal relationship, biology, de-challenge improvement and that the adverse event was not likely explained by the subject's clinical state, underlying disease, concomitant medication, or study/non-study procedure.

- Any toxicity that does not meet the criteria for DLT and requires permanent discontinuation of oprozomib treatment in cycle 1 will be considered a DLT

- A delay in ability to receive Day 1 dose of cycle 2 due to a hematologic or non-hematologic drug-related toxicity persisting beyond 14 days from cycle 1 Day 28 will be considered a DLT
- For non-hematologic toxicities, any ≥ Grade 3 toxicity will be considered a DLT with exceptions as described below:
  - Grade 3 asymptomatic electrolyte abnormalities, with exception of hypophosphatemia as below, will not be considered a DLT
  - Asymptomatic Grade 3 hypophosphatemia that does not resolve within 24 hours will be considered a DLT.
  - Grade 3 nausea, vomiting and diarrhea will not be considered a DLT unless persisting longer than 3 days despite optimal supportive care (please refer to the diagram Guidelines for Oprozomib and Pomalidomide Dose Modifications and Treatments for details)
  - 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
- For hematologic toxicities:
    - Grade 4 neutropenia will be considered a DLT if absolute neutrophil count (ANC) < 0.5 x 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 x 10^9/L)
  - Thrombocytopenia will be considered a DLT if:
    - Grade 4 lasting ≥ 7 days, or
    - Grade ≥ 3 with clinically significant bleeding (≥ Grade 2) or requiring platelet transfusion.
    - Grade 4 anemia is not considered a DLT

9.3 Non-Amgen Non-investigational Products

9.3.1 Non-Amgen Non-investigational Product Pomalidomide

9.3.1.1 Dosage, Administration, and Schedule

Pomalidomide is available as a capsule containing 1, 2, 3, or 4 mg of pomalidomide drug substance for oral administration. Additional product information is provided in the Pomalidomide Prescribing Information (**Pomalidomide U.S. Prescribing Information for United States; for other countries, see appropriate prescribing information**). Pomalidomide will be administered at a dose of 4 mg on days 1 to 21 of repeated 28-day cycles. Pomalidomide may be taken with or without food. Pomalidomide may be taken with water. Subjects are to be informed not to break, chew, or open the capsules. Aspirin (or other anticoagulant or antiplatelet medication such as clopidogrel bisulfate,

low-molecular-weight heparin, or warfarin) is recommended as prophylaxis for venous and arterial thromboembolism based on assessment of the subject's underlying risk factors (refer to the Pomalidomide Prescribing Information [**Pomalidomide U.S. Prescribing Information for United States; for other countries, see appropriate prescribing information**]). In Part 1, pomalidomide may be added to the treatment once there is a first dose level of oprozomib determined to be safe in combination with pomalidomide and dexamethasone (as determined by the first cohort in Part 2). In Part 2, all subjects will receive pomalidomide on day 1 of cycle 1.

Subjects who permanently discontinue pomalidomide may continue on study on oprozomib and dexamethasone.

9.3.1.2 Dose-cohort Study Escalation and Stopping Rules

Dose reduction levels for pomalidomide are provided in Table 3. Dose adjustments should, in general, follow the instructions provided in the Pomalidomide Prescribing Information 2013 (**Pomalidomide U.S. Prescribing Information for United States; for other countries, see appropriate prescribing information**). Where Pomalidomide is not available in 1 or 2 mg, sites are allowed to modify the dose of pomalidomide based on local prescribing standards.

Table 3. Dose Decrements for Pomalidomide

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

9.3.2 Non-Amgen Non-investigational Product Dexamethasone

Dexamethasone, a synthetic adrenocortical steroid, is available as tablets containing 4 or 6 mg of dexamethasone drug substance for oral administration. All subjects will receive 20 mg of dexamethasone on each oprozomib dosing day. For subjects over 75 years old, after the first cycle and at the investigator's discretion, dexamethasone can be reduced to 10 mg. It is recommended that dexamethasone be taken with food or after meals. If taken together with oprozomib IR formulation, a low fat meal is recommended. If taken together with oprozomib GR formulation, a main meal that contains the highest calorie and fat content is required. Subjects must be advised to take meals prior to dosing.

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

9.3.2.1 Dose-cohort Study Escalation and Stopping Rules

Dose reduction levels for dexamethasone are provided in Table 4.

Table 4. Dose Decrements for Dexamethasone

Nominal Dose	Reduced Dexamethasone Doses	
	First Dose Reduction	Second Dose Reduction
20 mg	12 mg	8 mg
10 mg[a]	8 mg	4 mg

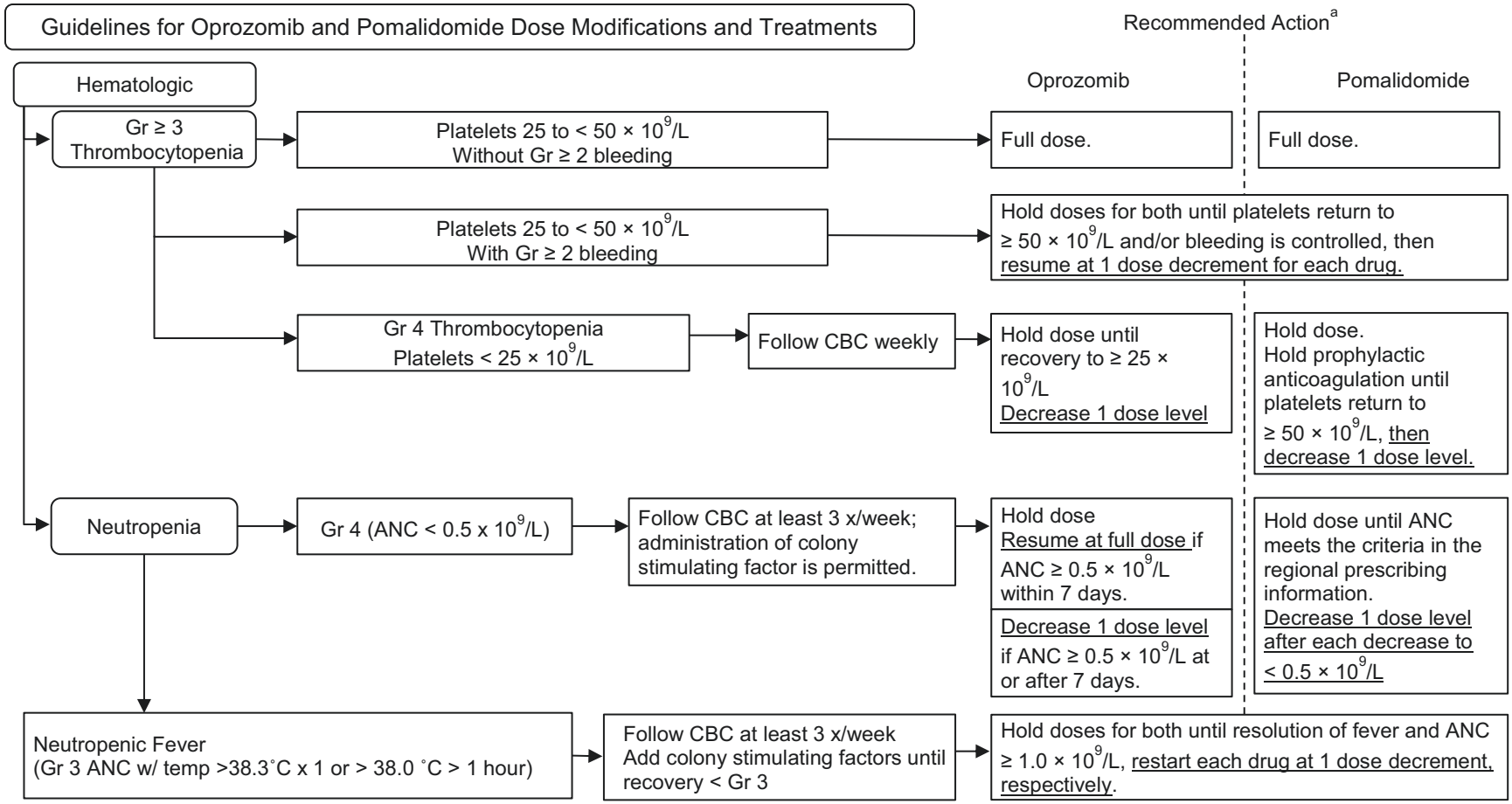
[a] For subjects over 75 years old, after the first cycle and at the investigator's discretion, dexamethasone can be reduced to 10 mg

9.3.2.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

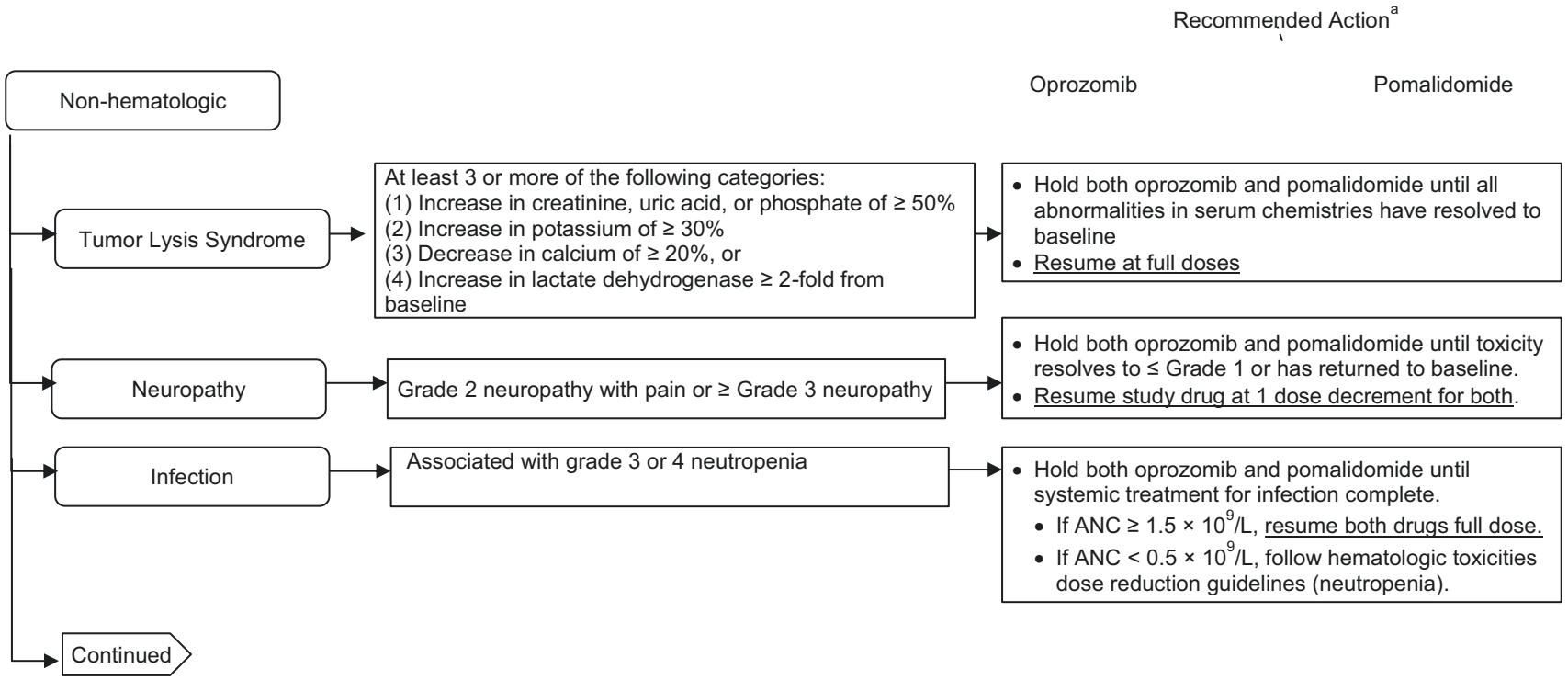
If any dose of pomalidomide, oprozomib or dexamethasone is reduced during the previous cycle, the reduced dose level will be continued on day 1 of the next cycle. If the reduced dose level is well tolerated for a complete cycle, the subject may, at the investigator's discretion, be re-challenged with the dose level prior to the reduction at the start of the next cycle unless the subject experiences a GI hemorrhage.

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 Amgen study medical monitor permits the subject to resume therapy.

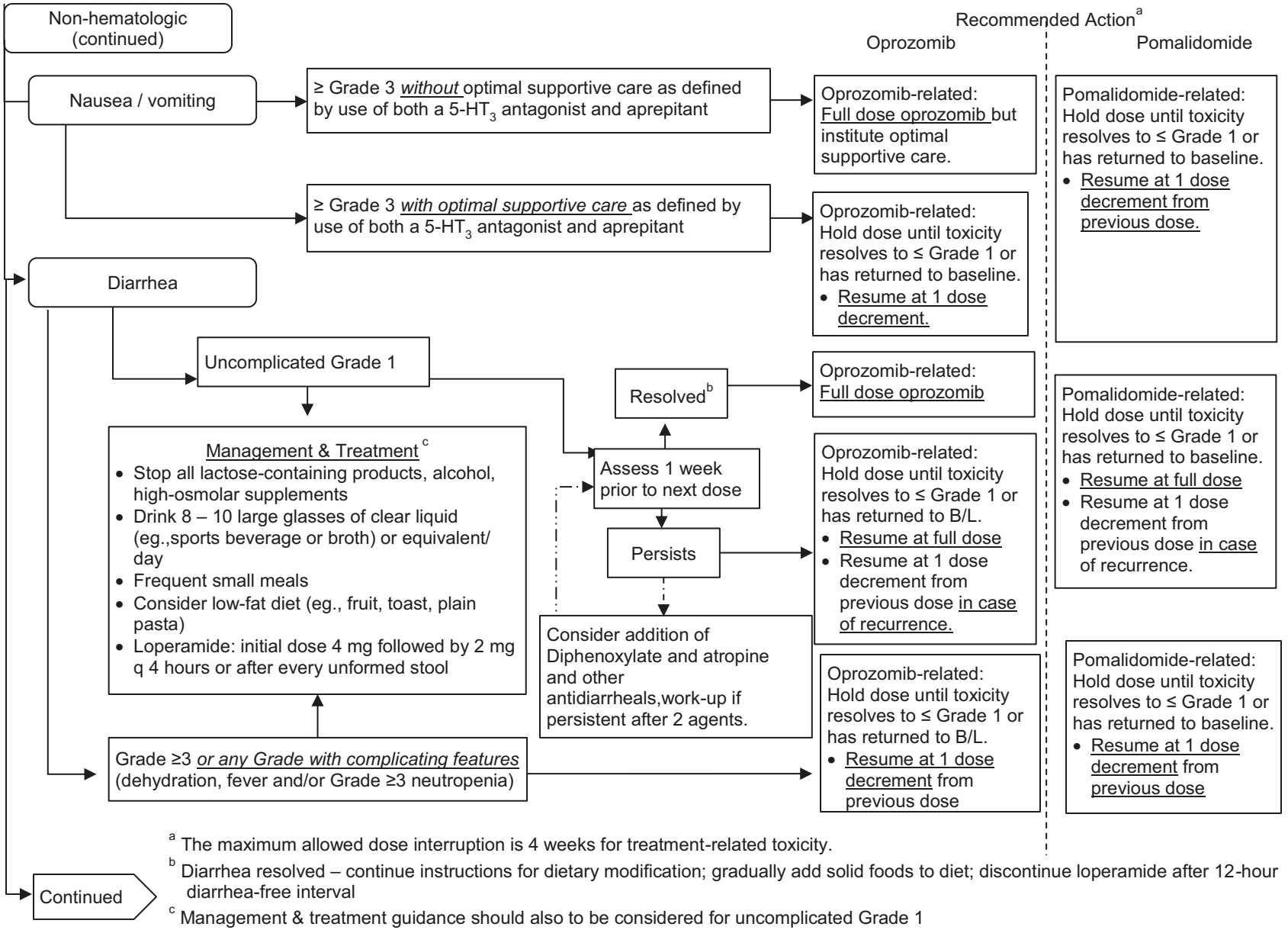
Dexamethasone will be permanently discontinued after 2 dose reductions for either nominal dose in the event of additional dexamethasone-related toxicity. At the investigator's discretion, dexamethasone may be tapered prior to complete discontinuation according to institutional practice. If dexamethasone dosing is permanently stopped due to toxicity in accordance with the dose modification guidelines described in Table 5, the subject may continue to receive oprozomib and pomalidomide, and will 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. In the event pomalidomide is permanently discontinued, oprozomib in combination with dexamethasone may be continued. Similarly, if oprozomib is discontinued, pomalidomide and dexamethasone may be continued. Please see the diagram Guidelines for Oprozomib and Pomalidomide Dose Modifications and Treatments.



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



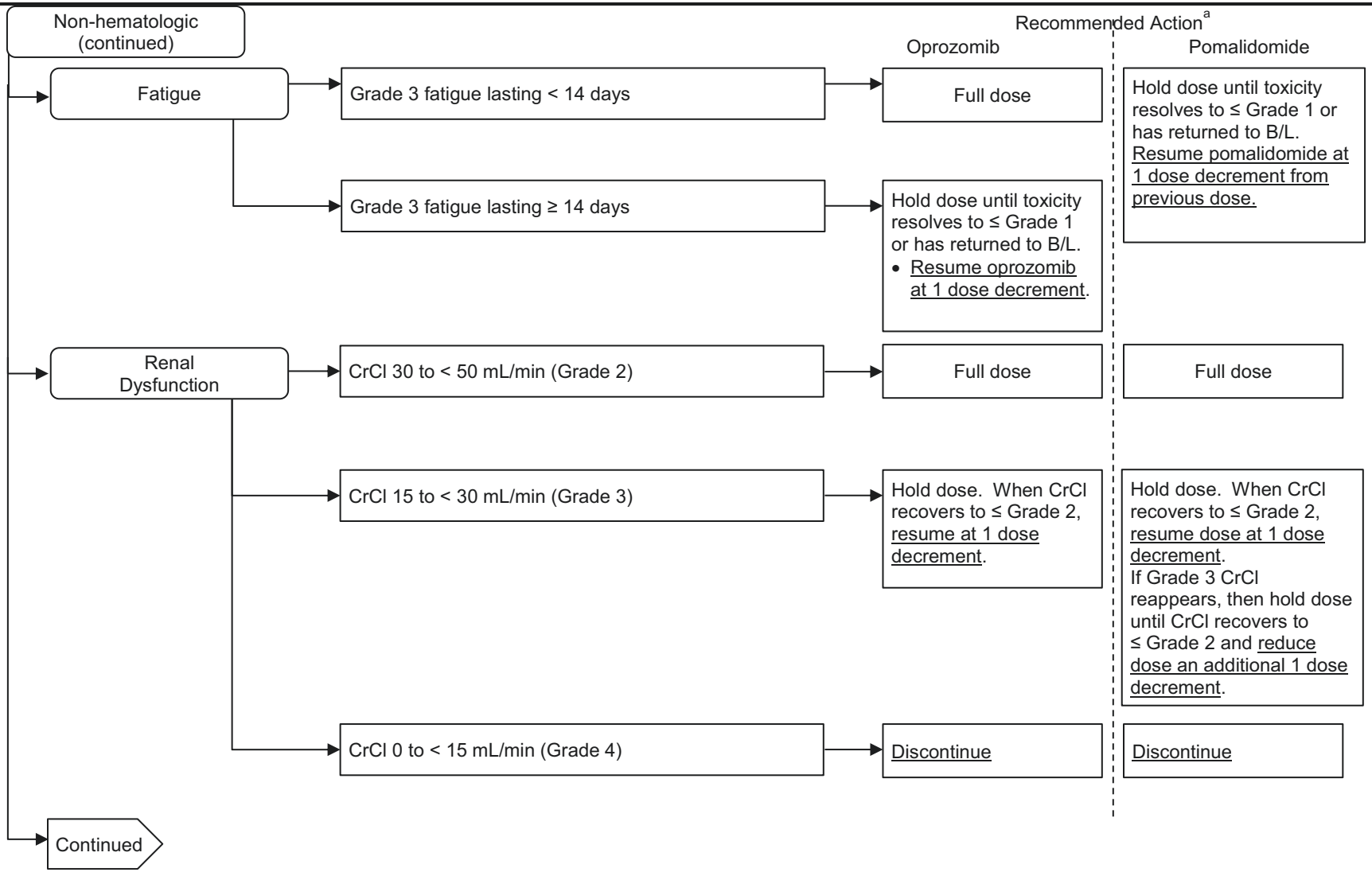
[a] The maximum allowed dose interruption is 4 weeks for treatment-related toxicity.



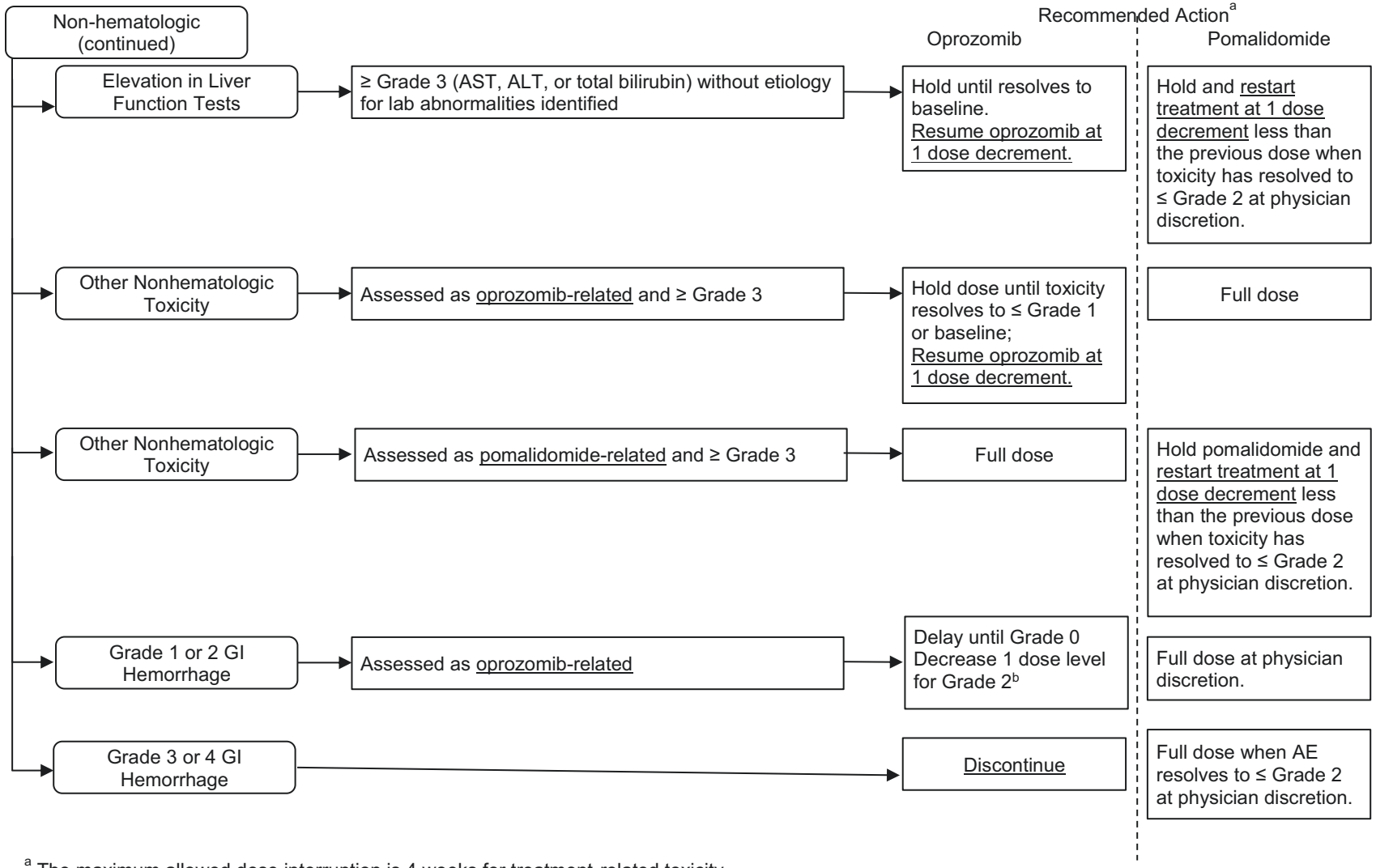
[a] The maximum allowed dose interruption is 4 weeks for treatment-related toxicity.

[b] Diarrhea resolved – continue instructions for dietary modification; gradually add solid foods to diet; discontinue loperamide after 12-hour diarrhea-free interval

[c] Management & treatment guidance should also to be considered for uncomplicated Grade 1



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



[a] The maximum allowed dose interruption is 4 weeks for treatment-related toxicity.
[b] Subjects who experience Grade 1 or 2 GI hemorrhage may be re-challenged following discussion and agreement between the Amgen Medical Monitor and investigator.

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

- To initiate a new cycle of pomalidomide, the ANC must meet the criteria in the regional prescribing information. If toxicities continue to occur after dose reductions down to 1 mg, 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 Amgen medical monitor. No more than 3 dose reductions will be permitted for an individual subject on study and additional reductions may be managed by schedule change. If toxicity continues, oprozomib should be discontinued.

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

- Non-treatment-related events: If the toxicity resolves to ≤ Grade 1 or baseline and the toxicity is not treatment-related, oprozomib may be restarted at the same dose level
- If 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 after discussion with the Amgen medical monitor
- If required by continued or recurrent toxicity, a second or third dose reduction of oprozomib may be permitted after discussion with Amgen medical monitor. No more than 3 will be permitted for an individual subject on study and additional reductions may be managed by schedule change. If toxicity continues, oprozomib should be discontinued.
- Subjects who develop Grade 3 or 4 GI hemorrhage should not be re-challenged with oprozomib. Oprozomib should be permanently discontinued. Endoscopy should be strongly considered for any subject with GI hemorrhage.

Guidelines for dexamethasone dose modifications and treatment are summarized in Table 5.

Table 5. 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 H2 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.
	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 H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone permanently.
	Acute pancreatitis	Permanently discontinue dexamethasone.
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.

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Table 5. Guidelines for Dexamethasone-Related Toxicity

Body System	Symptom	Recommended Action
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.

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9.4 Management and Prophylaxis of Additional Adverse Events of Interest

9.4.1 Herpes Zoster Infection

Valacyclovir or an equivalent antiviral is recommended for the duration of treatment to decrease the risk of reactivation of Herpes zoster.

9.4.2 Gastrointestinal Toxicities

Lansoprazole or another oral PPI is required (H2 antagonists are recommended if subject has intolerance or hypersensitivity to PPI) for the duration of treatment with oprozomib to prevent GI toxicities. In an earlier clinical study (Study 2011-001) the PK exposure of oprozomib (assessed by AUC_{last} and C_{max}) was compared in subjects (n = 21) receiving PPIs versus subjects (n=45) not receiving PPIs. In this preliminary analysis, PPI did not appear to have any effect on the PK exposure of oprozomib.

Subjects who experience grade 3 or 4 GI hemorrhage during the study will not be re-challenged with oprozomib. Subjects who experience grade 1 or 2 GI hemorrhage may be re-challenged following discussion and agreement between the Amgen Medical Monitor and investigator.

It is strongly recommended that subjects be premedicated with a 5-HT3 antagonist, such as ondansetron or granisetron, prior to each dose of oprozomib and then as needed to prevent nausea and vomiting. Additional antiemetics may be used per investigator discretion.

For subjects developing any grade of diarrhea, loperamide (Imodium) is strongly recommended at the first onset of symptoms. Other antidiarrheal agents may be used if necessary.

9.4.3 Pancreatitis

Evaluate abdominal pain (particularly ≥ Grade 3 in severity) with nausea, vomiting, and diarrhea with testing of amylase/lipase levels and abdominal imaging, as clinically indicated.

9.4.4 Thrombosis

Aspirin (or other anticoagulant or antiplatelet medication such as clopidogrel bisulfate, low-molecular-weight heparin, or warfarin) is recommended as prophylaxis for venous and arterial thromboembolism based on assessment of the subject's underlying risk factors (refer to the Pomalidomide Prescribing Information [**Pomalidomide U.S. Prescribing Information for United States; for other countries, see appropriate prescribing information**] for more information).

9.4.5 Tumor Lysis Syndrome (TLS)

Oral hydration of 1.5–2 liters per 24 hours must be instituted in all subjects 24 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 (ie, for multiple myeloma: Durie-Salmon or International Staging System Stage II/III, or rapidly increasing M-protein or light chains) or compromised renal function (creatinine clearance [CrCl] < 50 cc/min). These subjects may be at elevated risk for TLS and should be closely monitored. Uric acid levels should be normalized prior to initiation of treatment, if appropriate.

Subjects with laboratory abnormalities prior to dosing that are consistent with lysis of tumor cells must not receive the scheduled dose prior to institution of the aforementioned preventive measures. Evidence of lysis of tumor cells is defined by abnormalities in at least 3 of the following 4 categories:

1. Increase in LDH increase ≥ 2 fold from baseline ULN;
2. Increases in serum creatinine, uric acid, or phosphorus ≥ 50%;
3. Potassium increase ≥ 30%;
4. Calcium decrease from baseline of ≥ 20% in the absence of concomitant bisphosphonate therapy (Sezer, 2006).

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 same dose level. The Amgen medical monitor should be consulted if there is a treatment delay > 4 weeks.

All cases of TLS must be reported to Amgen as an SAE as outlined in Section 12.2.2.2.

9.4.6 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.

- 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 to 8 ounce glasses of fluids in the 24 hours prior to dosing and on every day of oprozomib dosing.
- Fluid status should be evaluated and maintained at 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.
- Evaluate and confirm there is no occult bleeding.
- In addition, vital signs monitoring may be extended beyond the time periods specified in the Schedule of Assessments.

9.5 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (eg, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBIL]) or international normalized ratio [INR]) or signs/symptoms of hepatitis may meet the criteria for withholding of investigational product. Withholding is either permanent or

conditional depending upon the clinical circumstances discussed below (as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009).

9.5.1 Criteria for Permanent Withholding of Study Treatment due to Potential Hepatotoxicity

Study treatment should be permanently withheld and the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

Increased AST or ALT from the relevant baseline value as specified below:

Baseline AST or ALT value	AST or ALT evaluation
< ULN	> 3X ULN

AND

TBIL > 2 x ULN or INR > 1.5

AND

No other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or elevated TBIL values include, but are not limited to:

- Hepatobilliary tract disease
- Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, Cytomegalovirus, Herpes Simplex Virus, Varicella, Toxoplasmosis, and Parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs including herbal and dietary supplements, plants, and mushrooms
- Hereditary disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic Steatohepatitis (NASH) or other "fatty liver disease"
- Non-hepatic causes (eg, rhabdomyolisis, hemolysis)

9.5.2 Criteria for Conditional Withholding of Study Treatment due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent withholding of study treatment outlined above and with no underlying liver disease and normal transaminases and TBIL at baseline or subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for conditional withholding of study treatment:

- Elevation of either AST or ALT according to the following schedule:

Baseline AST or ALT value	AST or ALT elevation
Any	> 8x ULN at any time
Any	> 5x ULN but < 8x ULN for ≥ 2 weeks
Any	> 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule
Any	> 3x ULN with clinical signs or symptoms that is consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice, rash or eosinophilia (> 5%).

- OR: TBIL > 3x ULN at any time
- OR: ALP > 8x ULN at any time

Study treatment should be withheld pending investigation into alternative causes of DILI. If study treatment is withheld, the subject should be followed according to recommendations in Appendix A for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBIL is discovered and the laboratory abnormalities resolve to normal or baseline.

9.5.3 Criteria for Rechallenge of Study Treatment After Potential Hepatotoxicity

The decision to rechallenge the subject should be discussed and agreed upon unanimously by the subject, investigator, and Amgen. Subjects who clearly meet the criteria for permanent discontinuation (ie, no definite alternative cause for the laboratory abnormalities was discovered as described in Section 9.5.1) should never be rechallenged. If signs or symptoms recur with rechallenge, then oprozomib should be permanently discontinued.

9.6 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 9.9.

Concomitant therapies are to be collected from informed consent through the EOS. Collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

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 30 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 H), Pomalidomide Education and Counseling Guidance Document (Appendix I), and Pomalidomide Information Sheet for Subjects Enrolled in Clinical Research Studies (Appendix J).

Females of reproductive potential must have 2 negative pregnancy tests before initiating study treatment. The first test should be performed within 10 to 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 90 days 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 90 days 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 90 days after discontinuing treatment.

9.7 Tobacco Restrictions

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

9.8 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s) or device(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product.

Any product complaint(s) associated with an investigational product(s) or non-investigational product(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

9.9 Excluded Treatments, Medical Device Use, and/or Procedures During Study Period

Drug interactions may occur with concomitant use of certain medications with pomalidomide. Refer to the Pomalidomide Prescribing Information for current guidance on dosing restriction or adjustment recommendations.

Glucocorticoid therapy that exceeds a cumulative dose of 160 mg of dexamethasone is not permitted within 21 days prior to enrollment. During the study, glucocorticoid therapy (in addition to dexamethasone) is only permitted upon discussion with the Amgen 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.

Treatment with drugs associated with increased risk of GI hemorrhage should be based on an assessment of underlying risks.

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 and 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. Study procedures required at EOS should be done.

10. STUDY PROCEDURES

10.1 Schedule of Assessments

Table 6. Schedule of Assessments

Schedule of Assessments																																																			
	Screen		Treatment																																																EOS[19]
Cycles			1																												2				3						4				5				6 and beyon		
Days[1]	-28	-14	1				2			8								9		15		22							23		1		15		1				15		1		15		1				1		
Hours (relative to dosing)			Pre	0	1-3	4-6	Pre	0	4	Pre	0	0.5	1	2	4	6	8	Pre	0	Pre	0	Pre	0	0.5	1	2	4	6	Pre	0	Pre	0	Pre	0	Pre	0	1-3	4-6	Pre	0	Pre	0	Pre	0	Pre	0	1-3	4-6	Pre	0	
GENERAL AND SAFETY ASSESSMENT																																																			
Informed Consent	X																																																		
Clinical Evaluation[2]	X		X				X			X								X		X		X							X		X		X		X				X		X		X		X				X		X
Vital Signs[3]	X		X				X			X								X		X		X							X		X		X		X				X		X		X		X				X		X
12-lead ECG[4]	X		X[4]							X[4]			X[4]																		X[4]																				X
ECHO or MUGA[5]	X																																																		
Peripheral Neuropathy Assessment[6]	X		X																												X				X						X				X				X		X
Concomitant Medication Review	←																																																		→
Adverse Event Review	←																																																		→
LABORATORY ASSESSMENT AND DOSING																																																			
Oprozomib and Dexamethasone Dosing[7]				X				X			X								X[7]		X		X							X		X		X		X				X		X		X		X				X	
Pomalidomide Dosing[8]				X				X			X								X		X											X		X		X				X		X		X		X				X	
Oprozomib PK[9]			X		X	X[17]				X		X	X	X	X	X	X	X				X		X	X	X	X	X	X						X		X	X[17]							X		X	X[17]			
Safety Lab Tests[10]		X	X				X			X								X		X		X							X		X		X		X				X		X		X		X				X		X
Pregnancy Test[11]		X	X							X										X		X									X				X						X				X				X		X
Hepatitis Serology[12]	X																																																		
SPEP/UPEP/sFLC	X		X																												X				X						X				X				X		X
Immunofixation[13]	X																																																		
Quantitative Ig[14]	X																																																		
Beta-2 Microglobulin			X																																																
Bone Marrow, FISH[15]	X																																																		
[redacted]																																																			
IMAGING ASSESSMENTS																																																			
Plasmacytoma[17]	X																																																		
Bone Lesions[18]	X																																																		

Footnotes defined on next page

1 Visit windows: A +/-1 day window is allowed for C1D8, C1D15, C1D22, C2D15, C3D15 and C4D15, however study treatment dosing must occur on two sequential days. Starting with C2, there is a +/-2 day window for D1 of every cycle.
2 Clinical evaluation will include: physical exam with a neurologic assessment, ECOG status and weight. At screening only: medical and surgical history and height.
3 Vital signs (blood pressure, respiratory rate, heart rate, temperature) will be collected after the subject has rested for at least 5 minutes.
4 ECG will be performed after subject has rested for approximately 5 minutes in the supine position; ECG performed in triplicate (approximately 30 seconds apart and run consecutively, interval between tracings should not be greater than 60 seconds) at all timepoints, reporting PR, QRS, QT, QTc, RR interval. Subjects receiving 270 mg or higher dose of oprozomib IR formulation in combination with pomalidomide and dexamethasone, must have ECG done 1 and 2 hours after oprozomib doses on Cycle 1 Day 1, Cycle 1 Day 8 and Cycle 2 Day 1. After cycle 2, ECGs are only required if clinically indicated, unless specified on the SOA. If interval prolongation > 480 msec occurs (and is a 30 msec increase above baseline), subject's serum potassium, magnesium, calcium and phosphorus should be measured immediately and replaced if needed.
5 Required at screening only.
6 Refer to Appendix G for the evaluation tool. The site will enter the score to each question on the eCRF and the total score will be derived in electronic database.
7 Each complete cycle will be 4 weeks (28 days duration) comprising 8 dose administrations of oprozomib and dexamethasone: days 1, 2, 8, 9, 15, 16, 22 and 23. It is recommended that oprozomib IR be taken after a low fat meal. The GR formulation must be taken immediately after a main meal that contains the highest calorie and fat content. Dexamethasone may be taken at the same time as oprozomib. On PK collection days, the time of meal intake will be recorded on the eCRF. Subjects must be advised to take meals prior to dosing.
8 Pomalidomide will be administered on Days 1 to 21 of each 4 week cycle and may be taken with or without food. Once there is a first dose level of oprozomib determined to be safe in combination with pomalidomide and dexamethasone (as determined by the first cohort in Part 2), the Part 1 subjects will be allowed to add pomalidomide to their treatment at that particular dose level.
9 PK samples should be collected at the exact nominal time point as noted. The permitted time windows for PK postdose collection C1D8 and C1D22 are: ± 5 minutes for the 0.5 and 1 hour time points, ± 10 minutes for the 2 hour time point and ± 20 minutes thereafter. The C1D8 8 hour post dose, the C1D9 pre-dose and C1D23 pre-dose PK collections will occur only for the subjects taking the GR formulation.
10 Safety lab tests will include chemistry, hematology, coagulation and urinalysis. If acceptable screening laboratory assessments are within 48 hours of study day 1, the pre-dose laboratory assessments do not need to be obtained. If a subject has a grade 3 hypophosphatemia, a repeat phosphate level test within 24 hours is required to rule out DLT.
11 Females of childbearing potential only: Serum pregnancy test performed at screening; urine or serum pregnancy test at all other timepoints. See Section 9.6
12 All subjects will be tested for HBsAG, antiHBcAb, and HCVAb. If HBsAg is negative and HBcAb is positive, test HBV DNA by PCR. If HCVAb is positive, test HCV RNA by PCR.
13 Immunofixation is done at screening and is required at next assessment only if SPEP or UPEP results are zero or undetectable.
14 Quantitative Immunoglobulin (Total IgG, IgA and IgM) is obtained at screening and will be repeated if clinically indicated (i.e, frequent infection despite multiple myeloma disease control).
15 A bone marrow sample will be collected from all subjects during screening for fluorescent in situ hybridization (FISH), to quantify percent myeloma involvement. Part of the bone marrow sample will also be used for the [redacted]. An additional bone marrow sample will only be required to confirm a complete response (CR). Samples can be collected during screening up to pre-dose of cycle 1 day 1.
[redacted]
17 For subjects with a history of extramedullary disease, plasmacytoma evaluation is to be repeated during treatment only to confirm a response of PR or better, to confirm PD, or if clinically indicated. The same technique used during screening must be employed for each measurement (may include ultrasound, CT scan, MRI, PET or other standard of care method). Assessment by physical examination at screening is acceptable.
18 Bone lesion assessment to be repeated Q8W if clinically indicated (i.e, new symptoms of bone pain arise). Consider obtaining an MRI for subjects with bone pain if the skeletal survey is normal.

19 End of Study: visit should be performed approximately 30 (+7) days after the last dose of study drug.

10.2 General Study Procedures

A signed and dated IRB-approved informed consent must be obtained before any study-specific procedures are performed. Procedures that are part of routine care are not considered study-specific procedures and may be used at screening to determine eligibility. All subjects will be screened for eligibility before enrollment. Only eligible subjects will be enrolled into the study.

10.2.1 Informed Consent

A signed informed consent must be obtained from each subject prior to any study mandated procedures.

10.2.2 Medical History

The investigator or designee will collect a complete medical and surgical history prior to enrollment. Medical history will include information on the subject's concurrent medical health conditions, relevant past medical conditions, and surgical history.

Relevant medical history, including antecedent hematologic or oncologic disease, other diseases/symptoms such as fatigue, bleeding and infection (resolved and ongoing) will be collected. The current toxicity grade will be collected for each condition that has not resolved.

10.2.3 Prior Therapy

The investigator or designee will collect relevant prior therapy which includes previous chemotherapy or radiotherapy and anticancer therapies (eg, stem cell transplant).

10.2.4 Physical Examinations

A complete physical examination will be performed by the investigator or designee according to local practices at screening and time points specified in the Schedule of Assessments (Table 6). The physical exam will include a neurological assessment.

10.2.5 Peripheral Neuropathy Assessment

The peripheral neuropathy assessment should be done at screening and time points specified in the Schedule of Assessments (Table 6). All assessments must be reported on the corresponding eCRF page (see Appendix G for peripheral neuropathy assessment tool).

10.2.6 Height Measurements

Height (cm) will be measured without shoes at screening.

10.2.7 Weight Measurements

Weight (kg) without shoes will be obtained at screening and time points specified in the Schedule of Assessments (Table 6).

10.2.8 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure (BP), respiratory rate, heart rate and temperature. Subject must be in rested and calm state for at least 5 minutes before BP assessments are conducted. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign eCRF. Record all measurements on the vital signs eCRF.

The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs/temperature eCRF. Vital signs will be recorded by the investigator or designated site physician at screening and time points specified in the Schedule of Assessments (see Table 6).

Abnormal measurements may be repeated at the discretion of the investigator and must be reported on the corresponding eCRF page. When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn.

10.2.9 Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group Performance Status (Appendix E) assessments will occur at time points specified in the Schedule of Assessments (see Table 6).

10.2.10 Electrocardiogram

Subject must be in a supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position as possible.

ECGs should be performed in accordance with the Schedule of Assessments (see Table 6), in triplicate, in a standardized method, prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

Electrocardiograms will be performed as follows:

- Triplicate ECGs will be performed at screening approximately 30 seconds apart and run consecutively, the interval between tracings should not be greater than 60 seconds
- All other ECGs will be performed in triplicate (approximately 30 seconds apart and run consecutively, the interval between tracings should not be greater than 60 seconds)
- After cycle 2, ECGs are only required if oprozomib dose is less than 270 mg and it is clinically indicated. If interval prolongation $>$ 480 msec occurs (and is a 30 msec increase above baseline), subject's serum potassium, magnesium, calcium and phosphorus should be measured immediately and replaced if needed
- All subjects receiving 270 mg or higher of oprozomib (IR tablet only) in combination with pomalidomide and dexamethasone will require triplicate ECGs 1 and 2 hours after oprozomib dose on C1D8 and C2D1.

When ECGs, vital signs, blood for laboratory tests and PK are to be collected at the same time points, the ECGs and vital signs will be collected prior to blood collections.

The principal investigator or designated site physician will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

Findings will be recorded on the ECG eCRF.

10.2.11 Echocardiogram (ECHO) / Multigated Acquisition (MUGA) Scan

ECHO or MUGA will be performed to assess cardiac ejection fraction and cardiac valve abnormalities and will occur at screening only. The test can be repeated if clinically indicated by the investigator.

10.2.12 Tumor Assessments

10.2.12.1 Serum Protein Electrophoresis (SPEP) and 24-hour Urine Protein Electrophoresis (UPEP)

Serum protein electrophoresis (SPEP) and 24-hour urine protein electrophoresis (UPEP) are required for all subjects at screening. Thereafter, SPEP and UPEP with 24-hour urine collection are to be done at each time point for all subjects as indicated in the Schedule of Assessments.

10.2.12.2 Immunofixation

Immunofixation is done at screening and is required at next assessment only if SPEP or UPEP results are zero or undetectable.

10.2.12.3 Bone marrow

Bone marrow sample will be collected from all subjects during screening to quantify percent myeloma involvement and for fluorescent in situ hybridization (FISH); FISH will be performed locally. An additional bone marrow sample will only be required to confirm a complete response (CR).

10.2.12.4 Serum Free Light Chain

Serum free light chain (sFLC) assay and ratio will be performed at each time point as specified in the Schedule of Assessments (Table 6).

10.2.12.5 Quantitative Immunoglobulin

Quantitative immunoglobulin (Ig) will be performed at screening. Quantitative immunoglobulin will be repeated only if clinically indicated, ie, frequent infection despite multiple myeloma disease control or when deemed clinically indicated by the investigator.

10.2.12.6 Beta-2 Microglobulin

Beta-2 microglobulin will be performed only at baseline as part of risk stratification.

10.2.13 Imaging Assessments

10.2.13.1 Bone Lesion Assessment

A skeletal survey, low-dose CT scan or bone marrow MRI should be performed during screening. The same methodology will be repeated as clinically required as described in the Schedule of Assessments (Table 6). Skeletal survey is defined by X-rays of lateral view of the skull, anteroposterior and lateral views of the spine and anteroposterior views of the pelvis, ribs, femora, and humeri. Subjects with bone pain that have a normal skeletal survey should have a MRI.

10.2.13.2 Plasmacytoma Assessment

A plasmacytoma survey will be performed at the time points as specified in the Schedule of Assessments (Table 6). For subjects without a history of extramedullary disease, assessment by physical examination at screening is acceptable. Plasmacytoma evaluation is to be repeated during treatment only to confirm a response of PR or better, to confirm PD, or if clinically indicated. If clinically indicated due to history of extramedullary disease, the same technique (may include ultrasound, x-ray, CT scan, MRI, PET, or other standard-of-care method) must be employed for each measurement.

10.2.14 Pharmacokinetic Blood Sampling

Blood samples for quantitative determination of plasma concentrations of oprozomib and its [redacted], will be collected at time points specified in the Schedule of Assessments (Table 6). The time points are:

C1D1: pre-dose, 1-3 hours post-dose and 4-6 hours post-dose

C1D8: pre-dose, 0.5 hours post-dose, 1 hour post-dose, 2 hours post-dose, 4 hours post-dose, 6 hours post-dose, 8 hours post-dose (for the GR formulation only)

C1D9: pre-dose (for the GR formulation only)

C1D22: pre-dose, 0.5 hours post-dose, 1 hour post-dose, 2 hours post-dose, 4 hours post-dose, 6 hours post-dose

C1D23: pre-dose (for the GR formulation only)

C3D1: pre-dose, 1-3 hours post-dose, 4-6 hours post-dose

C5D1: pre-dose, 1-3 hours post-dose, 4-6 hours post-dose.

On PK collection days, the time of meal intake will be recorded on the eCRF. PK samples should be collected at the exact nominal time point as noted. The permitted time windows for PK post-dose collection on C1D8 and C1D22 are: ± 5 minutes for the 0.5 and 1 hour time points, ± 10 minutes for the 2 hour time point and ± 20 minutes thereafter. The C1D8 8 hour post-dose and the C1D9 and C1D23 pre-dose PK collections will occur only for the GR formulation. Sample collection, processing, storage, and shipping instructions are provided in a separate laboratory manual.

10.2.15 Blood Samples

Approximate blood volumes expected to be collected during study participation are presented in Table 7.

Table 7. Approximate Blood Collection Volumes

Test	Volume (mL) per Collection	Approximate Number of Collection	Approximate Total Volume (mL)
Laboratory safety (chemistry, hematology, coagulation)	15 mL	19	285mL
Serology	5 mL	13	65 mL
Quantitative Immunoglobulin	10 mL	1	10 mL
Serum pregnancy test (females of child bearing potential only)	3 mL	16	48 mL
Blood samples for oprozomib PK	3 mL	4	72 mL
[redacted]			
Total blood volume assumes 10 cycles for study participation plus screening and EOS (if applicable)			~520 mL

10.2.16 Clinical Laboratory Assessments

Blood samples for clinical chemistry, hematology, and urine samples for urinalysis, will be collected at screening, and at time points specified in the Schedule of Assessments (Table 6). All tests (except for PK and [redacted]) are to be performed at a local laboratory and test results are to be recorded in the eCRF. Blood samples will be obtained by venipuncture before study drug administration. All laboratory tests must be reviewed by the investigator or qualified designee. Additional safety laboratory assessments may be performed if clinically indicated at the discretion of the investigator. The following tests listed in Table 8 will be conducted on samples collected by standard laboratory procedures.

Table 8. List of Analytes

Chemistry	Hematology	Urinalysis	Coagulation
Albumin	ANC	Blood	PT
ALP	Hematocrit	Protein	PTT
ALT	Hemoglobin	Ketones	INR
Amylase	Platelets	Bilirubin	
AST	RBCs	Glucose	Other Labs:
Bicarbonate	WBCs	Leucocytes esterase (WBC)	Pregnancy
BUN or Urea	Differential:	Microscopic exam (only needed for positive dipstick and should include the following):	Hep B surface antigen
Calcium	▪ Neutrophils	Epithelial, Bacteria, Casts, Crystal, RBCs, WBCs	Hep B antibody
Chloride	▪ Lymphocytes		Hep C antibody
Creatinine	▪ Monocytes		HCV PCR (if applicable)
Direct bilirubin	▪ Eosinophils		HBV PCR (if applicable)
Glucose	▪ Basophils		PK
LDH			[redacted]
Lipase			SPEP
Magnesium			UPEP
Phosphorus			sFLC
Potassium			Quantitative immunoglobulin
Sodium			Beta-2 microglobulin
Total bilirubin			Immunofixation
Total protein			
Uric acid			

Additional procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the investigator's discretion.

10.2.17 Screening

After obtaining informed consent, all screening procedures and tests establishing eligibility will be performed within a period of 28 days before dosing and 14 days for laboratory assessments. If acceptable screening laboratory assessments are within 48 hours of study day 1, the pre-dose laboratory assessments do not need to be obtained. The following procedures are to be completed during the screening period at time points designated in the Schedule of Assessments (Table 6).

10.2.18 Screening Procedures to Determine Eligibility

- Confirmation that the Informed Consent Form has been signed and dated
- Review of inclusion and exclusion criteria to determine eligibility
- Demographic data including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.

- Review of medical and surgical history including:
  - concomitant medication
  - documentation of diagnosis including history of current and prior cancers
  - prior anticancer treatments
- Clinical evaluation which includes the following:
  - physical examination with neurological assessment, ECOG performance status, height and weight
  - assessment according to CTCAE version 4.03 for prior and continuing diagnosis, disease complications and toxicities
- Peripheral neuropathy assessment
- Vital signs (blood pressure, respiratory rate, heart rate, temperature)
- 12-lead ECG in triplicate
  - collected in the supine position after subject has rested for 5 minutes
  - record QRS, QT, QTc, RR and PR intervals
- ECHO or MUGA
- Safety laboratory assessments (locally tested) within 14 days of study day 1
  - Chemistry
  - Hematology
  - Coagulation
  - Urinalysis
- Serum pregnancy test (only for females of childbearing-potential)
- Determination of HIV status (via medical history)
- Hepatitis serology
  - HBsAg and total HBc
    - If results are HBc positive and HBsAg positive, no additional testing is necessary
    - If results are HBc positive and HBsAg negative, additional testing for hepatitis B virus DNA by PCR is necessary
  - HepCAb
    - If results are HepCAb positive, additional testing for hepatitis C virus RNA by PCR is necessary.
- Disease assessments
  - Serum protein electrophoresis (SPEP)
  - 24-hour urine protein electrophoresis (UPEP)
  - Immunofixation
  - Serum free light chain (sFLC)
  - Quantitative immunoglobulin
  - Beta-2 microglobulin
  - Bone marrow aspirate

- [redacted]
- Imaging assessments
  - Plasmacytoma
  - Bone lesions
- Adverse event assessment is preformed throughout the study at every visit
  - Serious adverse events are collected from the time the subject signs the informed consent form
  - Adverse events are collected from the time the subject is dosed on day 1

Subjects can be rescreened at the discretion of the investigator after consultation with Amgen. The investigator must provide appropriate rationale prior to repeating any screening procedures or tests during the screening period. A new consent must be signed unless it has been > 28 days since the last consent was signed.

10.2.19 Treatment

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments (Table 6). Study treatment is to be administered after all protocol-specific pre-dose assessments have been performed during each visit that it is required. A +/-1 day window is allowed for C1D8, C1D15, C1D22, C2D15, C3D15 and C4D15, however study treatment dosing must occur on two sequential days. Starting with C2, there is a +/-2 day window for D1 of every cycle. Subjects may continue on treatment until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

- Clinical evaluation which includes physical examination with neurological assessment and ECOG performance status
- Peripheral neuropathy assessment
- Adverse event assessment
- Documentation of concomitant medications
- Vital signs (blood pressure, respiratory rate, heart rate, temperature)
- 12-lead ECG in triplicate (only performed if clinically indicated after cycle 2)
  - collected in the supine position after subject has rested for 5 minutes
  - record QRS, QT, QTc, RR and PR intervals
- Pregnancy test – serum or urine (only for females of childbearing-potential)
- Safety laboratory assessments (locally tested)
  - Chemistry
  - Hematology

  - Coagulation
  - Urinalysis
- Blood collection
  - Oprozomib PK
  - [redacted]
- Disease assessments
  - SPEP
  - 24-hour urine protein electrophoresis (UPEP)
  - Immunofixation if required
  - sFLC
  - Quantitative immunoglobulin if clinically indicated
- Imaging assessments
  - Plasmacytoma (only to confirm a response of PR or better, to confirm PD, or if clinically indicated)
  - Bone lesions (every 8 weeks if clinically indicated)
- Dexamethasone dosing (taken with food or after meals, may be taken with oprozomib)
- Oprozomib dosing: IR formulation recommended to be taken after a low fat meal. The GR formulation must be taken immediately after a main meal that contains the highest calorie and fat content.
- Pomalidomide dosing (may be taken with or without food) for all subjects except for subjects during cycle 1 in Part 1

10.2.20 Safety Follow-up/End of Study Visit

The end of study visit is a safety follow-up visit that is to be performed approximately 30 (+7) days after the last dose of study treatment. All efforts should be made to conduct this visit. If it is not possible to conduct the end of study visit, documentation of efforts to complete the visit should be provided in the source documents and noted as not done in the eCRFs.

The following procedures will be completed at the EOS as designated in the Schedule of Assessments (Table 6):

- Clinical evaluation which includes physical examination with neurological assessment and ECOG performance status
- Peripheral neuropathy assessment
- Adverse event assessment
- Documentation of concomitant medications
- Vital signs (blood pressure, respiratory rate, heart rate, temperature)

- 12-lead ECG in triplicate
  - collected in the supine position after subject has rested for 5 minutes
  - record QRS, QT, QTc, RR and PR intervals
- Pregnancy test – serum or urine (only for females of childbearing-potential)
- Safety laboratory assessments (locally tested)
  - Chemistry
  - Hematology
  - Coagulation
  - Urinalysis
- Tumor assessments
  - Serum protein electrophoresis (SPEP)
  - 24-hour urine protein electrophoresis (UPEP)
  - Immunofixation if required
  - Serum free light chain (sFLC)
  - Quantitative immunoglobulin if clinically indicated
- [redacted]

[redacted]

[redacted]

10.5 Sample Storage and Destruction

Any blood or tumor samples collected according to the Schedule of Assessments (Table 6) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the multiple myeloma, the dose response and/or prediction of response to oprozomib and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of [redacted] studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood or tumor samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 14.3 for subject confidentiality.

11. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

11.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects can decline to continue receiving investigational product and/or other protocol required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 6) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Table 6) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

11.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product and/or other protocol required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with Amgen investigational product and/or other protocol required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 15.1.

11.3 Reasons for Removal From Treatment or Study

11.3.1 Reasons for Removal From Treatment

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- subject request
- safety concern (eg, due to an adverse event)
- non-compliance (eg, procedural or dosing)
- requirement for alternative therapy
- pregnancy
- decision by Amgen (other than subject request, safety concern, or lost to follow-up)
- decision by investigator (other than subject request, safety concern, or lost to follow-up)
- death
- lost to follow-up
- confirmed disease progression per IMWG (Appendix D)

11.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by Amgen
- withdrawal of consent from study
- death
- lost to follow-up

12. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

12.1 Definition of Safety Events

12.1.1 Disease-Related Events

Disease-Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease.

Disease-Related Events that do not qualify as Adverse Events or Serious Adverse Events:

- An event which is part of the normal course of multiple myeloma (eg, disease progression in oncology or hospitalization due to disease progression)
- Death due to the disease under study (multiple myeloma)

Disease-Related Events that would qualify as an Adverse Event or Serious Adverse Event:

- An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition, or if the investigator believes there is a causal relationship between the study treatment and disease worsening, this must be reported as an Adverse Event or Serious Adverse Event (and not as a Disease-Related Event)

12.1.2 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record. The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease has increased in severity, frequency, and/or duration more than would be expected and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study, or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 11.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

For situations when an adverse event or serious adverse event is due to multiple myeloma, report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, metastatic pancreatic cancer).

Note: The term "disease progression" should not be used to describe the disease-related event or adverse event.

12.1.3 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria (unless it meets the definition of a Disease-Related Event as defined in Section 12.1.1):

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- results in a congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug induced liver injury (DILI) (see Appendix A for DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

12.2 Safety Event Reporting Procedures

12.2.1 Disease Related Events

The investigator is responsible for ensuring that all Disease-Related Events observed by the investigator or reported by the subject that occur after the first dose of study treatment through the end of study visit are reported using the Event CRF.

- Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, multiple myeloma).
- The investigator is required to report a fatal Disease-Related Event on the Event CRF as a Disease-Related Event.
- For multiple myeloma related events, report all known signs and symptoms.

Note: The term "disease progression" should not be used to describe the disease-related event.

12.2.2 Adverse Events

12.2.2.1 Reporting Procedures for Adverse Events That Do Not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the first dose of study treatment through the end of study visit are reported using the Event CRF.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity (and/or toxicity per protocol),
- Assessment of relatedness to investigational product(s) or other protocol-required therapies, and
- Action taken.

The adverse event grading scale used will be the CTCAE, Version 4.03, described in Appendix A. The investigator must assess whether the adverse event is possibly related to the investigational product and/or other protocol-required therapies. This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product and/or other protocol-required therapies?

The investigator must assess whether the adverse event is possibly related to any study mandated activity. This relationship is indicated by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may have been caused by a study activity?”

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject’s baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae, not the laboratory abnormalities, are to be recorded as the adverse event.

The investigator is expected to follow reported adverse events until stabilization or reversibility.

Note: The term “disease progression” should not be used to describe the adverse event

12.2.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last day of the dosing interval of investigational product/end of study visit are recorded in the subject’s medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator’s knowledge of the event via the Event CRF.

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the investigator’s knowledge of the event. See Appendix B for a sample of the eSAE Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the eSAE Contingency Report Form, the data must be entered into the EDC system when the system is again available.

The investigator must assess whether the serious adverse event is possibly related to the investigational product and/or other protocol-required therapies. This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product and/or other protocol-required therapies?

The investigator must assess whether the adverse event is possibly related to any study mandated activity. This relationship is indicated by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may have been caused by a study-related activity?”

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

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

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and good clinical practice.

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

12.2.2.3 Reporting Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

12.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is taking oprozomib, report the pregnancy to Amgen Global Patient Safety as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies for female subjects that occur through 30 **(+ 7)** days after the last dose of oprozomib. Investigators should report pregnancies of female partners of male subjects that occur through 90 days after the last dose of oprozomib.

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a female subject breastfeeds while taking oprozomib, report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should report lactation cases that occur through 30 **(+ 7)** days after the last dose of oprozomib.

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

13. STATISTICAL CONSIDERATIONS

13.1 Study Endpoints, Analysis Sets, and Covariates

13.1.1 Study Endpoints

Primary Endpoints

- MTD for each formulation as the dose that has the highest posterior probability of having a DLT rate within the target toxicity interval (15% to 25%), while the posterior probability of excessive/unacceptable toxicity (> 25% to 100%) is < 40%
- Incidence of treatment-related, treatment-emergent adverse events and changes in laboratory test results

Secondary Endpoints

- PK parameters for oprozomib, including, but not limited to maximum observed concentration (C_{max}), time to C_{max} (t_{max}), and the area under the concentration-time curve from time 0 to the time of last quantifiable concentration (AUC_{last})
- Overall response and best overall response according to the IMWG uniform response criteria, progression free survival (PFS), and duration of response (DOR)

[redacted]

13.1.2 Analysis Sets

The safety population is defined as all subjects who receive any amount of oprozomib, pomalidomide and/or dexamethasone.

The efficacy population is defined as subjects who are included in the safety evaluable population, and have a baseline disease assessment and at least 1 post-baseline disease assessment.

PK population is defined as subjects for whom at least 1 PK parameter can be adequately estimated.

13.1.3 Covariates and Subgroups

No covariate or subgroup is pre-specified for the analysis of the primary, secondary, and safety endpoints.

The relationship of covariates to efficacy endpoints will be explored if appropriate.

[redacted].

13.2 Sample Size Considerations

Approximately 64 DLT-evaluable subjects will be enrolled in the phase 1b study. Initially, during Part 1, at least 3 DLT-evaluable subjects will be enrolled for each oprozomib formulation administered at 150 mg 2/7 in combination with dexamethasone only. In Part 2 and thereafter, a Bayesian design will be applied to evaluate up to 2 oprozomib formulations administered at different increasing dose levels in combination with pomalidomide and dexamethasone. The maximum sample size for testing the IR formulation is set to 36 DLT-evaluable subjects. Assuming 11 cohorts will be evaluated for the GR formulation, the anticipated sample size for the GR formulation dose escalation cohorts is 22 DLT-evaluable subjects. In the event that additional subjects are deemed necessary by DLRT, extra subjects may be enrolled.

13.3 Planned Analysis

13.3.1 Dose Level Review Team (DLRT)

Dose Level Review Meetings (DLRMs) will be held by the DLRT to review data, evaluate safety, and make decisions on dose escalation/change. The DLRT will be composed of the investigators or designees, and the following Amgen representatives: medical monitor, global safety officer or designee, clinical study manager, biostatistician and additional members may be added as needed (eg, clinical pharmacologist). The following members are responsible for DLRT decisions: investigators, Amgen medical monitor, and global safety officer or designee. A quorum must be in attendance for the

DLRM. The quorum is defined as > 50% of the participating investigators or their qualified designee (ie, sub-investigator or research nurse or study coordinator possessing written documentation [eg e-mail] of the investigator`s vote). All Amgen representatives or designees must be present. The DLRM will be rescheduled if a quorum is not reached.

All available study data, including data collected after the initial DLT window, demographics, investigational product administration, medical history, concomitant medications, adverse events, ECGs, vital signs, laboratory data and PK/[redacted] information will be reviewed. Data will not need to be source data verified and queries will not need to be resolved prior to the DLRM.

Modeling of available potential safety risk data to predict safety risk for dose escalation decisions may also be considered.

13.3.2 Primary Analysis

The main objectives of the primary analysis are to determine the MTD for each formulation of oprozomib in combination with pomalidomide and dexamethasone and further evaluate the safety, tolerability and efficacy of the OPomd combination in subjects with relapsed or refractory multiple myeloma. The primary analysis will be based on subject data collected up to two months from the date of last subject enrollment. In addition, this analysis will be used to possibly recommend the most appropriate oprozomib dose and formulation to be tested in future clinical trials in an OPomd combination. The selection of the oprozomib recommended dose and formulation will be based on all data from the escalation cohorts.

Safety and tolerability will be assessed through summaries of study drug administration, DLTs, adverse events, changes in selected laboratory analytes, vital signs, and physical findings by dose level. Means and standard deviations will be used to summarize the total dose for each component of study drug received. All summaries will be presented by the assigned dose level and for all subjects.

All adverse event data will be listed by study site, dose level, subject identification number, and study day. All adverse events will be summarized by preferred term, appropriate thesaurus levels, and CTCAE (Version 4.03) toxicity grade. In addition, all serious adverse events, including deaths, will be listed separately and summarized.

Efficacy analyses of ORR and BOR will be performed using both the efficacy and safety population as defined previously.

13.3.3 Final Analysis

The objective of the final analysis is to provide an update on safety and tolerability, and efficacy results. The statistical methods used in the final analysis will be the same as those employed in the primary analysis. The final analysis will be based on subject data collected through study discontinuation or at the end of the study which includes the 30 day safety follow-up, whichever occurs first.

13.4 Planned Methods of Analysis

13.4.1 General Considerations

All analyses for the study are [redacted] and hypothesis generating. Descriptive statistics will be used to summarize most analysis results.

13.4.2 Primary Endpoints

13.4.2.1 Maximum Tolerated Dose

Refer to Section 9.2.1.2 for a description of the dose escalation method.

The number of DLTs and adverse events at each dose level will be summarized separately for each oprozomib formulation in combination with dexamethasone and in combination with pomalidomide and dexamethasone.

13.4.2.2 Safety Endpoint(s)

Subject incidence of all treatment emergent adverse events of interest will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product, other protocol-required therapies or from study, and adverse events of interest will also be provided. Relevant laboratory and vital sign (temperature, heart rate, respiratory rate, and blood pressure) data will be displayed by visit and time (when available), with CTCAE (Version 4.03) Grade 3 and 4 values identified where appropriate. Additionally, all laboratory data will be summarized by CTCAE Grade.

ECG analyses include summary changes from baseline for ECG intervals, summaries of the proportion of subjects with on-study corrected QT interval (QTc) values that reach certain values (eg, $>$ 450 msec), and summaries of the proportion of subjects with categorical changes from baseline (eg, $<$ 30 msec).

13.4.3 Secondary Endpoint(s)

13.4.3.1 Pharmacokinetic Endpoints

The PK endpoints include, but are not limited to C_{max}, t_{max}, and AUC_{last} of oprozomib following dosing on cycle 1 day 8 and cycle 1 day 22.

Blood samples will be collected from all subjects for determination of plasma concentrations of oprozomib at time points specified in the schedule of assessments (Table 6). Individual oprozomib concentration-time data and summary statistics will be tabulated for each dose level. Individual, mean, and standard deviation concentration-time data may be plotted for each dose level.

PK parameters will be calculated using non-compartmental methods. Actual dosing and sampling times will be used for calculation of PK parameters. PK parameter estimates will be summarized descriptively. Other pharmacokinetic parameters such as AUC_{inf}, apparent clearance (CL/F), and terminal half-life ($t_{1/2}$) may be analyzed. Population PK modeling may be performed to better characterize the PK of oprozomib using intense sampling following dosing on cycle 1 day 8 and cycle 1 day 22 and sparse sampling in day 1 of cycles 1, 3 and 5.

13.4.3.2 Efficacy Endpoints

All efficacy assessments will follow IMWG uniform response criteria and be performed every 4 weeks (± 1 week).

Overall response rate (defined as the proportion of best overall response of stringent complete response [sCR], complete response [CR], very good partial response [VGPR], and partial response [PR]), best overall response, PFS (defined as the number of months from subject's first study dose date to the earlier of disease progression or death due to any cause), and DOR will be summarized for all subjects overall, by formulation, by dose cohort level, and by formulation and dose cohort level along with 95% confidence intervals when applicable.

All subjects who receive treatment with any amount of the OPomd and have a baseline disease assessment and at least 1 post-baseline disease assessment will be included in the efficacy analyses. Additional efficacy analyses will be performed based on subjects who receive treatment with any amount of OPomd.

[redacted]

14. REGULATORY OBLIGATIONS

14.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Study Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential subject population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specific screening procedures or oprozomib is administered.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record. The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent form is to be

retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. [Refer to ICH GCP guideline, Section 4.8.9.]

14.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval/renewal must be sent to Amgen.

14.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained:

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the demographics page, in addition to the unique subject identification number, include the age at the time of enrollment.

- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in strict confidence by the investigator, except as described below.

In compliance with governmental/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named such individuals to have access to his/her study related records, including personal information.

14.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- a recognized expert in the therapeutic area
- an investigator who provided significant contributions to either the design or interpretation of the study
- an investigator contributing a high number of eligible subjects

15. ADMINISTRATIVE AND LEGAL OBLIGATIONS

15.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the investigator must be obtained. The IRB/IEC must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IRB/IEC to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product by an extension protocol or as provided for by the local country's regulatory mechanism.

However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s), and by what mechanism, after termination of the study and before it is available commercially.

15.2 Study Documentation and Archive

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed eCRF, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.
- Non-investigational product(s) documentation, as applicable.

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

Retention of study documents will be governed by the Clinical Trial Agreement.

15.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Clinical Monitor is responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Monitor is to have access to subject medical records and other study related records needed to verify the entries on the eCRFs.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Quality, Compliance, and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the eCRFs must be maintained and readily available.
- Updates to eCRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that the investigator inspected or reviewed the data on the eCRF, the data queries, and agrees with the content.

15.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 6), the investigator can search publicly available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

15.5 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

15.6 Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff as appropriate as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, 3 and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

15.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

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17. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The CTCAE V 4.03 is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronicapplications/ctc.htm.

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in Section 9.5 require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate eCRF (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 12.2.2.2

Additional Clinical Assessments and Observations

All subjects in whom investigational product or protocol-required therapies are withheld (either permanently or conditionally) due to potential DILI as specified in Sections 9.5.1 and 9.5.2 or who experience AST or ALT elevations $>$ 3 x ULN are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels. Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL $>$ 2x ULN or INR $>$ 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve
- Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.
- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
  - Obtain complete blood count (CBC) with differential to assess for eosinophilia
  - Obtain serum total immunoglobulin IgG, anti-nuclear antibody (ANA), anti smooth muscle antibody, and liver kidney microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
  - Obtain serum acetaminophen (paracetamol) levels

  - Obtain a more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
    - Prior and/or concurrent use of alcohol, recreational drugs and special diets
    - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
  - Obtain viral serologies
  - Obtain CPK, haptoglobin, LDH, and peripheral blood smear
  - Perform appropriate liver imaging if clinically indicated
- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in corresponding eCRFs.

Appendix B. Sample Serious Adverse Event Contingency Form

AMGEN
Study # 20160104
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

US: +888 814 8653

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?	Previous 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? Oprozomib (No / Yes) <Device> (No / Yes) <Device> (No / Yes) <Device> (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
<<IP/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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AMGEN Study # 20160104 Oprozomib	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

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

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

Date Day Month Year	Test											
	Unit											

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

Date Day Month Year	Additional Tests	Results	Units

AMGEN Study # 20160104 Oprozomib	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

1. Case Administrative Information

Protocol/Study Number: _____

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
				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

AMGEN Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: _____

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
				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 withdrew 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

Appendix D. International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma (IMWG-URC)

Response Subcategory[a]	Multiple Myeloma Response Criteria
sCR[b]	• CR as defined below and • Normal SFLC ratio and • Absence of clonal cells in bone marrow[c] by immunohistochemistry or immunofluorescence[c]
CR[b]	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow[c]
VGPR[b]	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-protein with urine M-protein level< 100 mg/24 hours • If the serum and urine M-protein are not measurable, a decrease of ≥ 90% in the difference between the involved and uninvolved FLC levels required in place of the M-protein criteria. However, documentation of VGPR requires collection and analysis of 24 hour urine sample for UPEP and immunofixation and confirmed to be negative. • If present at Baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.
PR[b]	• ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/ 24 h • If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • If serum and urine M-protein are not measureable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow cell percentage was ≥ 30% • If present at Baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease	• Not meeting criteria for CR, VGPR, PR, or PD

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Footnotes defined on last page of this table

Response Subcategory[a]	Multiple Myeloma Response Criteria
PD[b]	• Any one or more of the following: • Increase of ≥ 25% from lowest response value in: ○ Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL) ○ Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h) ○ Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dL ○ Bone marrow plasma cell percentages (absolute percentage must be ≥ 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas[e, f, g] • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder

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Source: Durie 2006; Rajkumar 2011 (*modified for protocol purposes*).
CR = complete response; sCR = stringent complete response; FLC = serum light chain; MR = minor response; PD = progressive disease; PR = partial response; SFLC = serum free light chain; VGPR = very good partial response.
Note:
[a] Patients 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 MR or better. Conversely, it should be noted that criteria for PD only needs to be met, and confirmed, in one parameter. For patients without measurable protein on UPEP at Baseline, UPEP will need to be repeated to confirm a response.
[b] All response categories (CR, sCR, VGPR, PR) require 2 consecutive assessments made at any time before the institution of any new therapy, as well as no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow, plasmacytoma, and skeletal survey assessments are not required to be confirmed by repeat testing. SD requires a duration of ≥ 6 weeks.
[c] Presence/absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of > 4:1 or < 1:2.
[d] Determination of PD while on study requires 2 consecutive assessments made at any time before classification of PD and/or the institution of new therapy. Serum M-component increases of ≥ 1 g/dL from nadir are sufficient to define progression if starting M-component is ≥ 5 g/dL.
[e] 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 non-measurable.
[f] The requirement for bi-directional measurements applies only to plasmacytomas.
[g] The plasmacytoma specifications for PD are based on interpretation of the IMWG-URC and practical considerations for study execution.

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 E. ECOG Performance Status and NYHA Classification

Eastern Cooperative Oncology Group (ECOG) Performance Status

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

New York Heart Association Functional Classification

1. Class I No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea.
2. Class II Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
3. Class III Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnea.
4. Class IV Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Appendix F. Definition of Relapsed or Refractory Disease and Line of Therapies

Relapsed disease is defined as progression occurs in the absence of therapy.

Refractory disease is defined as disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy.

A line of therapy is defined as one or more cycles of a planned treatment program. This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered one line of therapy. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease (Rajkumar, 2011).

Appendix G. Peripheral Neuropathy Assessment

TNSr Items	0	1	2	3	4
Symptom extension (tingling, numbness, neuropathic pain)[a]	None	Symptoms limited to fingers or toes	Symptoms extend to ankle or wrist	Symptoms extend to knee or elbow	Symptoms above knees or elbows or functionally Disability
Pin sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced up to above elbow/knee
Vibration sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced up to above elbow/knee
Strength[b]	Normal	Mild weakness	Moderate weakness	Severe Weakness	Paralysis
Tendon reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent/others reduced	All reflexes absent

[a] The worse score of the 3 subcomponents (tingling/paresthesia, numbness, and neuropathic pain proximal extension) was used as the subjective symptom extension score.

[b] The muscle with the worse score is used as the strength score (toe, ankle, wrist and finger extensors and flexors, quadriceps, hamstrings, biceps, and triceps). TNSr and pain items were adapted with permission [Lavoie Smith, 2010]

Appendix H. 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 (ie, 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 (ie, 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 (ie, 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 (ie, 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

Males 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 I. Pomalidomide Education and Counselling Guidance Document

Protocol Number: 20160104

Patient Name (Print): _____ DOB: _____/_____/_____ (dd/mm/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 (ie, 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 J. 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.

Amendment 5

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of Oprozomib in Combination With Pomalidomide and Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma

Amgen Protocol Number Oprozomib 20160104

EudraCT number 2016-002406-40

NCT number: NCT02939183

Amendment Date: 27 January 2021

Rationale:

This protocol is being amended to allow subjects to switch from immediate release (IR) to extended release (gastro-retentive [GR]) formulation of ozoprozomib. Changes made in this amendment include:

- Addition of summary of clinical experience safety data from Phase 1 study to support 150 mg GR formulation dosage;
- Addition of language to allow for subjects to switch from IR to GR formulation;
- Update prescribing information as needed; and
- Administrative, typographical, and formatting changes throughout the protocol.

Amendment 4

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of Oprozomib in Combination With Pomalidomide and Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma

Amgen Protocol Number (Oprozomib) 20160104

EudraCT Number: 2016-002406-40

NCT Number: NCT02939183

Amendment Date: 13 December 2018

Rationale:

The purpose of this protocol amendment is to:

- Offer an option to switch GR formulation to IR for subjects who have clinical benefit due to overall superiority of IR formulation.
- Remove language ”Once the MTDs are determined” since the DLRT will review data to recommend a formulation and a dose regardless of MTD.
- Allow using a local standard for pomalidomide where 1 or 2 mg are not available.
- Allow comcomitant use of drugs that are sensitive CYP3A substrates with narrow therapeutic range based on results of clinical drug-drug interaction study and a product label review of CYP3A4 substrates given comcomitantly with oprozomib indicating no clinically relevant drug-drug interaction of oprozomib on metabolism of CYP3A substrates.

Amendment 3

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of Oprozomib in Combination With Pomalidomide and Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma

Amgen Protocol Number 20160104

IND Number 117851

EudraCT number 2016-002406-40

Amendment Date: 20 June 2018

Rationale:

The protocol is being amended to address comments from the German and Belgium Health Authorities. The changes include:

- Additional cardiac monitoring for subjects receiving 270 mg of oprozomib or higher in combination with dexamethasone and pomalidomide during Cycles 1 and 2.
- Clarification to eligibility language regarding washout period, known hypersensitivities to drugs on study and contraceptive language
- Revised pomalidomide dose modifications to align with regional prescribing information
- Addition of prophylaxis treatment of gastrointestinal toxicities
- Other changes include clarifications and corrections of inconsistencies, administrative and typographical changes

Amendment 2

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of Oprozomib in Combination With Pomalidomide and Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma

Amgen Protocol Number Oprozomib 20160104

Amendment Date: 16 February 2017

Rationale:

The following changes were made to protocol 20160104, dated 14 November 2016:

- The protocol was amended to address Health Canada request (16 February 2017) "The Study Protocol and Informed Consent Forms should have a consistent approach on meal status for administration of GR formulation of oprozomib and include a clarification that a main meal means a meal with the highest calorie and fat content."

Amendment 1.0

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of Oprozomib in Combination With Pomalidomide and Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma

Amgen Protocol Number Oprozomib 20160104

Amendment Date: 14 November 2016

Rationale:

The following changes were made to protocol 20160104, dated 12July 2016:

- The protocol was amended to address the FDA deficiency (18 August 2016) "Thirty-three percent as the upper bound for the target toxicity interval using NCRM is not acceptable. This should be decreased to 25%." The upper bound of the target toxicity interval was therefore decreased from 33% to 25%. This change carried the risk of defining an MTD of lesser therapeutic effect. To mitigate this risk, the dose will be escalated in 25 mg increments (instead of 50 mg increments) during dose escalation. The number of cohorts in Part 2 has been increased. The number of subjects needed has been increased from 38 to 64.
- Corrections to the Guidelines for Oprozomib and Pomalidomide Dose Modifications and Treatments figure; grade 4 neutropenia was incorrect. Aligned the table to be consistent with information in the Investigator Brochure.
- Title page updated with new study manager and study acronym: INTREPID-1.
- The protocol has been updated throughout to include the information on the gastro-retentive (GR) formulation (referred to as the "alternate" formulation in the initial document).
- [redacted]
- Pomalidomide administration instructions have been updated throughout to reflect the changes in the latest Pomalidomide Prescribing Information (Celgene, June 2016).
- Thromboprophylaxis changed from "required" to "recommended" throughout to align with the Pomalidomide Prescribing Information.
- Exclusion criterion 213 was modified to align with the Pomalidomide Prescribing Information.
- Exclusion criterion 223 was modified to include language on sperm donation: "Males must also refrain from donating sperm for at least 90 days after the last dose of oprozomib."
- New exclusion criterion 231: "Prior pomalidomide use is allowed unless subjects required pomalidomide dose reduction or pomalidomide discontinuation due to toxicity.

- Section 6.2.1.3 The following sentence has been deleted: “The investigator must discuss the safety findings with all ongoing subjects before continuing study treatment to ensure that the subjects understand the risks of continuing therapy.” This sentence implied a deviation to the standard process. The informed consent form will be revised if a new identified risk or a change in the nature of an existing risk was identified through safety governance.
- Template required language was added to the adverse event section.
- Administration, typographical and formatting changes were made throughout the protocol.