Statistical Analysis Plan

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
Short Protocol Title:	Phase 1b Study Evaluating OPomD in Relapsed or Refractory Multiple Myeloma (INTREPID-1)
Protocol Number:	20160104
NCT Number:	NCT02939183
Authors:	[redacted]
Sponsor:	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320 Phone: +1-805-447-1000
SAP Date:	**Document Version** — **Date** **Original (v1.0)** — **07 September 2017** **Amendment 1 (v2.0)** — **19 August 2019**

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	07 September 2017	Original Version
Amendment 1 (v2.0)	19 August 2019	**Rationale:** The purpose of this SAP amendment is for: The protocol amendment of country-specific supplemental protocol for United States. This is an open label roll-over study of Oprozomib parent trials, which evaluates Oprozomib extended release (ER) tablet in multiple myeloma or Waldenstrom macrogolobulinemia patients. **Changes:** **1.Introduction:** Deleted: Protocol date -16 February 2017 Added: Protocol date - 13 December 2018 The global protocol and its country-specific US supplement for study 20160104, Oprozomib dated 13 December 2018 **2.1. Objective and Endpoints** **Primary Objective** Added: Roll-over subjects only: Evaluate the safety profile for all subjects on continued oprozomib treatment **Primary Endpoint** Added: Roll-over subjects only: Incidence of treatment-emergent adverse events and treatment-emergent serious adverse events for all subjects on continued oprozomib treatment

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Amendment 1 (v2.0) (Continued)		**2.2. Hypotheses and/or Estimations** Added: For United States: for subjects previously treated on a separate Amgen protocol with oprozomib, the clinical hypothesis is that continued treatment with oprozomib will be well tolerated and sustain the response and/or clinical benefit achieved in previous oprozomib studies. **3.1. Study design** Added: For United States: this multicenter, open-label study will permit subjects who have completed the planned duration of treatment on a separate Amgen oprozomib study to continue treatment. Subjects who participated in study 20160104 are not eligible to roll-over into this part of the study after their study completion. Subjects who have completed the planned duration of oprozomib treatment on a separate Amgen protocol, are currently receiving oprozomib as a monotherapy or a combination of oprozomib with dexamethasone and have a stable disease or better at the time of screening are eligible to participate in this study. **3.2. Sample Size** Added: In Part 1, at least 3 DLT-evaluable subjects will be enrolled for each of the oprozomib formulations. For United States: for the roll-over portion of the study, the sample size for this study cannot be determined prospectively, as it is contingent on the number of subjects completing previous studies or having clinical benefit but not otherwise being able to continue the previous oprozomib study.

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Amendment 1 (v2.0) (Continued)		**5.Definitions** Added: Study Treatment: Any combination of oprozomib, pomalidomide and dexamethasone, or monotherapy of oprozomib. Progression Free Survival: Progression free survival data will be censored as described below: 1.Patients who are alive and do not have documented disease progression at the time of analysis will be censored at the date of the last disease assessment. 2.Patients who are alive and do not have disease assessment at the time of analysis will be censored at the first study dose date. 3.Patients who are alive without documented disease progression, and have withdrawn consent at the time of analysis will be censored at the date of the last disease assessment before withdrawal of consent. 4.Patients who have started an anti-cancer therapy other than the study treatment prior to documentation of disease progression will be censored at the date of the last disease assessment prior to start of new therapy. Duration of Grade II GI Toxicity: The intermittent adverse events will be excluded from the analysis of duration of Grade II GI toxicity, and not to be counted as one ongoing adverse event**.**

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Amendment 1 (v2.0) (Continued)		Duration of Grade III or above GI Toxicity: Duration of Grade III or above GI toxicity is defined as the number of days between the start date through to the subsequent end date of the Grade III or above GI toxicity, or where applicable date of censoring [end date of the Grade III or above GI toxicity or date of censoring – start date of the Grade III or above GI toxicity +1]. Subjects whose Grade III or above GI toxicity do not end while on study will be censored at the date when they are last on study. Subjects who do not experience Grade III or above GI toxicity will be excluded from the analysis of duration of Grade III or above GI toxicity. The intermittent adverse events will be excluded from the analysis of duration of Grade III or above GI toxicity, and not to be counted as one ongoing adverse event. Non-roll over subjects: Subjects that were enrolled into this study and do not participate in the open-label roll-over part of the study will be referred to as “non-roll over subjects”. Roll-over subjects: Subjects that were previously treated on a separate Amgen protocol and participate in the open-label roll-over part of the study will be referred to as “roll-over subjects”. Treatment Emergent Adverse Events (TEAE): Treatment-emergent adverse events are events categorized as Adverse Events (AEs) starting on or after first dose of investigational product as determined by the flag indicating if the adverse event started prior to 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 Study date, whichever is earlier.

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Amendment 1 (v2.0) (Continued)		**6.1. Safety Analysis Set** Added: The safety population is defined as all subjects, excluding roll-over subjects, who receive any amount of oprozomib, pomalidomide and/or dexamethasone. **6.2. Safety Analysis Set for roll-over subjects (For United States site only)** Added: The safety population for roll-over subjects is defined as all roll-over subjects who receive any amount of oprozomib and/or dexamethasone. **6.3. Efficacy Analysis Set** Added: The efficacy population is defined as subjects, excluding roll-over subjects, who are included in the safety evaluable population, and have a baseline disease assessment and at least 1 post-baseline disease assessment **6.4. Pharmacokinetic Analyses Set** Added: PK population is defined as subjects for whom at least 1 PK parameter can be adequately estimated, excluding roll-over subjects **7.1. Interim Analysis and Early Stopping Guidelines** Added sub-heading: Non-roll over subjects The database will not be cleaned and an as-is snapshot of the database will be used in the analyses.

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Amendment 1 (v2.0) (Continued)		**7.2. Primary Analysis** Added: Sub-heading: Non-roll over subjects Roll-over subjects: the main objective of the primary analysis of roll-over subjects is to evaluate the safety profile for all subjects on continued oprozomib treatment. Safety profile will be presented through descriptive statistics of safety data (treatment-emergent serious adverse events, treatment-emergent adverse events). All available data up to and including the data cutoff date will be cleaned and a locked database will be used in the analysis. **7.3. Final Analysis** Added: At that time the database will be cleaned, processed and a locked database will be used in the analysis. **9.2. Subject Accountability** Added: Key study dates for the first subject enrolled, last subject enrolled, and last subject's end of study will be presented for non-roll over subjects and roll-over subjects. 9.4.2. Medical History Added: The number (%) of subjects who experienced a prior disease or disorder will be summarized by system organ class and preferred term for non-roll over subjects and roll-over subjects.

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Amendment 1 (v2.0) (Continued)		9.4.3. Baseline Characteristics Added: The following baseline characteristics will be summarized for non-roll over subjects: • ECOG performance Status • Disease stage • Myeloma light chain o Kappa light chain o Lambda light chain • Myeloma immunoglobulin o Immunoglobulin A o Immunoglobulin D o Immunoglobulin E o Immunoglobulin G o Immunoglobulin M • Pathology (FISH) o t(11;14) o del(13q;14) o t(4;14) o t(14;16) o Chromosome 1 abnormalities (ie, 1q21 amplification, 1p deletion) o Chromosome 13 abnormalities (ie, chromosome 13 deletion) o Hyperdiploid o Non-hyperdiploid • Prior lines of therapy • Prior radiotherapy • Exposure and refractory status to o Bortezomib o Carfilzomib o Lenadolimide o Pomalidomide o Anti-CD38 antibody (including Daratumumab) • Prior transplant

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Amendment 1 (v2.0) (Continued)		**9.6.2. Adverse Events and Disease-related Events** Added: Roll-over subjects: Subject incidence treatment-emergent adverse events and treatment-emergent serious adverse events will be tabulated by system organ class, preferred term, grade and preferred term in descending order of frequency. **9.6.3. Laboratory Test Results:** Added: Sub-heading: Non-roll over subjects Table heading: Table 9.6.3.1 List of analytes for non-roll over subjects Roll-over subjects: Summary of clinical chemistry, hematology, urinalysis, and coagulation will be listed for each subject. Subjects laboratory parameters toxicities will be classified using CTCAE grade and their percentages will be tabulated. Summary CTCAE grade 3 and higher toxicities will be provided. Below is list of all lab tests performed for roll-over subjects: Table 9.6.3.2 List of Analytes for roll-over subjects (attached above table from amended protocol) **9.7.1. Analysis of pharmacokinetic or pharmacokinetic/[redacted] endpoints** Added sub-heading: Non-roll over subjects

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
AE	adverse event
AUC	area under the concentration-time curve
AUCinf	AUC from time 0 to the time extrapolated to infinity
AUClast	area under the curve until the last measurable concentration
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DLRM	dose level review meeting
DLRT	dose level review team
DLT	dose limiting toxicity
ECG	electrocardiogram
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
GI	gastrointestinal
GR	gastro-retentive
IR	immediate release
IMWG	International Myeloma Working Group
Mg	milligram
mL	milliliter
MTD	maximum tolerated dose
RRMM	refractory multiple myeloma
Od	oprozomib in combination dexamethasone
OPomd	oprozomib in combination with pomalidomide and dexamethasone
ORR	overall response rate
[redacted]	
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response

Abbreviation or Term	Definition/Explanation
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
t1/2	terminal elimination half-life
Tmax	time when maximum plasma concentration is reached
VGPR	very good partial response

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within **the global protocol and its country-specific US supplement** for study 20160104, Oprozomib dated **13 December 2018**. The scope of this plan includes the primary analysis and the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
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 • **Roll-over subjects only:** **Evaluate the safety profile for all subjects on continued oprozomib treatment**	• 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 • **Roll-over subjects only:** **Incidence of treatment-emergent adverse events and treatment-emergent serious adverse events for all subjects on continued oprozomib treatment**
Secondary	
• 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	• 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)

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Objectives	Endpoints
[redacted]	

2.2 Hypotheses and/or Estimations

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.

For United States: for subjects previously treated on a separate Amgen protocol with oprozomib, the clinical hypothesis is that continued treatment with oprozomib will be well tolerated and sustain the response and/or clinical benefit achieved in previous oprozomib studies.

3. Study Overview

3.1 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 ≥ 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 Dose Level Review 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. 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 United States: this multicenter, open-label study will permit subjects who have completed the planned duration of treatment on a separate Amgen oprozomib study to continue treatment. Subjects who participated in study 20160104 are not eligible to roll-over into this part of the study after their study completion. Subjects who have completed the planned duration of oprozomib treatment on a separate Amgen protocol, are currently receiving oprozomib as a monotherapy or a combination of oprozomib with dexamethasone, and have a stable disease or better at the time of screening are eligible to participate in this study.

For additional details please refer to Section 3.1 and the Study Schema.

3.2 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.

For United States: for the roll-over portion of the study, the sample size for this study cannot be determined prospectively, as it is contingent on the number of subjects completing previous studies, or having clinical benefit but not otherwise being able to continue the previous oprozomib study.

4. Covariates and Subgroups

4.1 Planned Covariates

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.

4.2 Subgroups

[redacted]

5. Definitions

Age at Enrollment

Subject age at enrollment will be determined using the age in years reported in the clinical database.

Baseline

For any variable, unless otherwise specified the baseline is the last assessment taken prior to the first administration of study treatment. For parameters/assessments not scheduled to be performed (or scheduled but not performed) on the same day as the

first administration of study treatment, the baseline value is the value from the screening period measured closest to the day of first administration of study treatment.

Baseline and Post-Baseline ECG Values in Triplicate

The baseline ECG is defined as the mean of all pre-dose assessments; the mean of values in a triplicate should be calculated before taking the mean of the triplicate averages.

For all post-baseline ECG, the mean value for measurements taken at the same assessment will be calculated and used in the analysis.

For pre and post dose ECG measurements, unscheduled ECG measurements taken up to 5 minutes after the last assessments of a triplicate will be included in the average for a timepoint. Where an ECG is missing within a triplicate, all available data will be averaged for that timepoint.

Bazett-corrected QT Interval (QTcB)

The Bazett correction will be calculated from the investigator reported QT (msec) and RR interval (msec), as follows: $QTcB=QT/(RR/1000)^{1/2}$

Change From Baseline

Change from Baseline is the arithmetic difference between post-dose assessments and Baseline value.

Change (absolute) from Baseline=(Post-baseline Value – Baseline Value)

Change (percent) from Baseline=[(Post-baseline Value – Baseline Value)/Baseline Value]x100

Dose Limiting Toxicities (DLT) Window

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. 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.

DLT Evaluable

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 must 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.

Duration of Response (DOR)

Duration of response is defined as the number of days between the date of the first tumor assessment indicating an objective response through to the subsequent date of progression or death due to any cause, or where applicable date of censoring [date of first progressive disease assessment or death or date of censoring – date of the first objective response result +1]. Subjects who respond and have not progressed while on study will be censored at the date of assessment of the last evaluable tumor assessment. Subjects who do not achieve an objective response will be excluded from the analysis of duration of response. Objective response is defined as any of the following: stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) (all according to Revised International Myeloma Working Group Uniform Response Criteria [IMWG-URC]).

Enrollment Date

Enrollment Date is defined as the date when the dosing of investigational product (oprozomib) is started.

Fridericia-corrected QT Interval (QTcF)

The Fridericia correction will be calculated from the investigator reported QT (msec) and RR interval (msec), as follows: $QTcF=QT/(RR/1000)^{1/3}$

Use above definition for derivation only if QTcF is not collected in the CRF.

Investigational Product

The term ‘investigational product’ is used in reference to oprozomib.

Study Treatment

Any combination of oprozomib, pomalidomide and dexamethasone**, or monotherapy of oprozomib**.

Last Investigational Product Dose Date

The last IP dose date for each subject is defined as the latest date IP is administered.

Maximum Tolerated Dose (MTD)

MTD for each formulation is defined 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%

Study Day 1

It is defined as the first day that protocol specified study treatment is administered to the subject.

Study Day

Post study day: study day= (date - date of Study Day 1) + 1

Pre study day: study day= (date – date of Study Day 1)

Time to Response (TTR)

Time to response defined as the interval from the first administration of study treatment to the first documentation of confirmed response. Response is defined as any of the following: stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) (all according to Revised International Myeloma Working Group Uniform Response Criteria [IMWG-URC].

Time to response is calculated as the number of days:

(date of first response – date of study day 1 +1).

Time to response will be calculated only for subjects with response.

Treatment-Emergent Adverse Event (TEAE)

Treatment-emergent adverse events are events categorized as Adverse Events (AEs) **starting on or after first dose of investigational product as determined by the flag indicating if the adverse event started prior to 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 Study date, whichever is earlier**.

Treatment-Related AE

A treatment-related AE is any treatment-emergent AE that per investigator review has a reasonable possibility of being caused by study treatment.

Disease-Related Events

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

C_{max}

Maximum observed serum concentration.

t_{max}

Time to C_{max}

AUC_{last}

Area under the concentration-time curve from time 0 (time of investigational product administration) to the time of the last quantifiable concentration.

Progression free survival

The number of months from subject's first study dose date to the earlier of disease progression or death due to any cause.

Progression free survival data will be censored as described below:

- **Patients who are alive and do not have documented disease progression at the time of analysis will be censored at the date of the last disease assessment.**
- **Patients who are alive and do not have disease assessment at the time of analysis will be censored at the first study dose date.**
- **Patients who are alive without documented disease progression, and have withdrawn consent at the time of analysis will be censored at the date of the last disease assessment before withdrawal of consent.**
- **Patients who have started an anti-cancer therapy other than the study treatment prior to documentation of disease progression will be censored at the date of the last disease assessment prior to start of new therapy.**

Best Overall Response (BOR)

The best response that a subject achieved during study where the responses are ranked from best to worst as follows: stringent complete response [sCR], complete response [CR], very good partial response [VGPR], and partial response [PR], minimal response [MR], stable disease [SD] and progressive disease [PD] (all according to Revised International Myeloma Working Group Uniform Response Criteria [IMWG-URC])

Overall Response Rate (ORR)

Proportion of subjects with BOR of sCR, CR, VGPR or PR.

Duration of Grade II GI Toxicity

Duration of Grade II GI toxicity is defined as the number of days between the start date through to the subsequent end date of the Grade II GI toxicity, or where applicable date of censoring [end date of the Grade II GI toxicity or date of censoring – start date of the Grade II GI toxicity +1]. Subjects whose Grade II GI toxicity do not end while on study will be censored at the date when they are last on study. Subjects who do not experience Grade II GI toxicity will be excluded from the analysis of duration of Grade II GI toxicity. **The intermittent adverse events will be excluded from the analysis of duration of Grade II GI toxicity, and not to be counted as one ongoing adverse event.**

Duration of Grade III or above GI Toxicity

Duration of Grade III or above GI toxicity is defined as the number of days between the start date through to the subsequent end date of the Grade III or above GI toxicity, or where applicable date of censoring [end date of the Grade III or above GI toxicity or date of censoring – start date of the Grade III or above GI toxicity +1]. Subjects whose Grade III or above GI toxicity do not end while on study will be censored at the date when they are last on study. Subjects who do not experience Grade III or above GI toxicity will be excluded from the analysis of duration of Grade III or above GI toxicity. The intermittent adverse events will be excluded from the analysis of duration of Grade III or above GI toxicity, and not to be counted as one ongoing adverse event.

Non-roll over subjects

Subjects that were enrolled into this study and do not participate in the open-label roll-over part of the study will be referred to as "non-roll over subjects".

Roll-over subjects

Subjects that were previously treated on a separate Amgen protocol and participate in the open-label roll-over part of the study will be referred to as "roll-over subjects".

6. Analysis Sets

6.1 Safety Analysis Set

The safety population for roll-over subjects is defined as all roll-over subjects who receive any amount of oprozomib and/or dexamethasone.

6.2 Efficacy Analysis Set

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

6.3 Pharmacokinetic Analyses Set

PK population is defined as subjects for whom at least 1 PK parameter can be adequately estimated**, excluding roll-over subjects**.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

Non-roll over subjects:

No formal interim analysis will be conducted. Safety data will be reviewed on an ongoing basis. Amgen, in consultation with the site investigator, will review in Dose Level Review Meetings (DLRMs) all available cumulative data by cohort prior to making dose escalation decisions. **The database will not be cleaned and an as-is snapshot of the database will be used in the analyses.** Adverse events and DLTs observed in all subjects will be evaluated continually and fully integrated into all DLRMs and considered in all enrollment and dosing decisions.

7.2 Primary Analysis

Non-roll over subjects:

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. 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.

Roll-over subjects: the main objective of the primary analysis of roll-over subjects is to evaluate the safety profile for all subjects on continued oprozomib treatment. Safety profile will be presented through descriptive statistics of safety data (treatment-emergent serious adverse events, treatment-emergent adverse events).

The primary analysis will be based on subject data collected up to two months from the date of last subject enrollment. **All available data up to and including the data cutoff date will be cleaned and a locked database will be used in the analysis**.

7.3 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 days safety follow-up, whichever occurs first. **At that time the database will be cleaned, processed and a locked database will be used in the analysis**.

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database.

8.3 Handling of Missing and Incomplete Data

The following imputation for missing or incomplete data will be performed if required:

Incomplete adverse event and concomitant medication dates missing data will be imputed as described in Appendix A. If imputed dates are used, then they will be identified as such in the final study report.

Laboratory measurements that are below the quantification limits will be considered equal to the lower limit of quantification for all analyses unless explicitly noted otherwise.

Non-pharmacokinetic measurements (eg, [redacted] data) that are below the lower limit of quantification will be considered equal to half of the lower limit of quantification for all analyses unless specified otherwise.

PK concentrations that are below the quantification limits will be set to zero when engaging non-compartmental model to compute PK parameters.

8.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by assessing the incidence of important protocol deviations in each cohort. The clinical study team will identify and document the criteria for important protocol deviations.

8.5 Outliers

Pharmacokinetic (PK) concentration data will be evaluated for outliers by visual inspection, and decisions to re-assay individual samples will be made in accordance with standard pharmacokinetic evaluation practice.

8.6 Distributional Characteristics

Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed. If required, data transformations or alternative non-parametric methods of analyses will be utilized.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

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

Data analysis will occur at the following time points:

- The primary analysis will occur when target enrollment is complete and each subject either completes 2 months on study or withdraws from the study.
- A final analysis is planned when the last subject is assessed or receives an intervention for evaluation in the study.

9.2 Subject Accountability

A summary of subject disposition with discontinuation reasons, and oprozomib completion and discontinuation will be provided. Key study dates for the first subject enrolled, last subject enrolled, and last subject's end of study will be presented **for non-roll over subjects and roll-over subjects**.

A subject listing and summary noting inclusion in each analysis subset will be provided for all subjects enrolled. A subject listing noting duration of oprozomib administration, reason for discontinuation of treatment, and reason for discontinuing the study will be provided. A list of subjects screened but not enrolled (screen failures) will be provided.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

9.4 Demographic and Baseline Characteristics

9.4.1 Demographics

Demographic (ie, age, age groups [18-64, 65-74, 75-84 and > = 85], sex, race, ethnicity) and baseline characteristics will be summarized by dose cohort and overall using

descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple race as well as by the combination of race.

9.4.2 Medical History

The number (%) of subjects who experienced a prior disease or disorder will be summarized by system organ class and preferred term for non-roll over subjects and roll-over subjects.

9.4.3 Baseline Characteristics

The following baseline characteristics will be summarized for non-roll over subjects:

- **ECOG performance Status**
- **Disease stage**
- **Myeloma light chain**
  - **Kappa light chain**
  - **Lambda light chain**
- **Myeloma immunoglobulin**
  - **Immunoglobulin A**
  - **Immunoglobulin D**
  - **Immunoglobulin E**
  - **Immunoglobulin G**
  - **Immunoglobulin M**
- **Pathology (FISH)**
  - **t(11;14)**
  - **del(13q;14)**
  - **t(4;14)**
  - **t(14;16)**
  - **Chromosome 1 abnormalities (ie, 1q21 amplification, 1p deletion)**
  - **Chromosome 13 abnormalities (ie, chromosome 13 deletion)**
  - **Hyperdiploid**
  - **Non-hyperdiploid**
- **Prior lines of therapy**
- **Prior radiotherapy**
- **Exposure and refractory status to**
  - **Bortezomib**
  - **Carfilzomib**
  - **Lenadolimide**
  - **Pomalidomide**
  - **Anti-CD38 antibody (including Daratumumab)**
- **Prior transplant**

9.5 Efficacy Analyses

All efficacy assessments will follow IMWG uniform response criteria and be performed every 4 weeks (± 1 week). See Section 9.5.2 for details.

9.5.1 Analyses of Primary Efficacy Endpoint(s)

NA

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

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]

9.6 Safety Analyses

9.6.1 Analyses of Primary 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).

9.6.2 Adverse Events and Disease-related Events

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.

The Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term.

The subject incidence of adverse events will be summarized for all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, and fatal adverse events and adverse events of interest when defined.

Subject incidence of all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, and fatal adverse events will be tabulated by system organ class and preferred term in alphabetical order.

Subject incidence of events of interest (standardized MedDRA queries and/or Amgen customized queries) will also be summarized according to their categories and preferred term.

In addition, summaries of treatment-emergent and serious adverse events by preferred term in any treatment arm will be provided in descending order of frequency.

Summaries of treatment-emergent and serious adverse events will be tabulated by system organ class, preferred term, and grade.

Subject incidence of disease-related events will be summarized for all treatment-emergent disease-related events and fatal disease-related events.

Roll-over subjects: Subject incidence treatment-emergent adverse events and treatment-emergent serious adverse events will be tabulated by system organ class, preferred term, grade and preferred term in descending order of frequency.

9.6.3 Laboratory Test Results

Non-roll over subjects:

Clinical chemistry, hematology, and urinalysis data will be listed and reviewed for each subject. Values outside the normal laboratory reference ranges will be flagged as high or low on the listings.

The number and percentage of subjects experiencing treatment emergent laboratory toxicities with worst post dose CTCAE grades of ≥1, ≥2, ≥3 and 4 will be presented. The direction of the laboratory worsening will be denoted. The summary will be presented for all laboratory parameters for which at least one subject experienced a treatment emergent toxicity with a worst grade ≥ 3.

Additionally, the number and percentage of subjects experiencing 1, 2, 3 and 4 worsening CTCAE grade shifts from baseline will be presented. The direction of the laboratory worsening will again be denoted.

Shifts tables indicating the change between the baseline and the maximum post dose CTCAE grades for an increased value, and the maximum post dose grade for a decreased value will be provided for selected laboratory parameters of interest.

A listing of CTCAE grade 3 or higher laboratory toxicities will be provided. This listing will include all laboratory data for the subject and laboratory parameter of interest in order to provide proper context. A flag will indicate the grade 3 or higher toxicity.

Summaries of the absolute value and/or changes from baseline at each scheduled assessment will be provided for selected laboratory parameters of interest.

A summary of the change from baseline to the post dose maximum, time to post-dose maximum, change from baseline to the post dose minimum, and the time to the post dose minimum may also be provided for selected parameters of interest.

Below is list of all lab tests performed for non-roll over subjects:

9.6.3.1 List of Analytes for Non-roll Over Subjects

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			Biomarker
Lipase			SPEP
Magnesium			UPEP
Phosphorus			sFLC
Potassium			Quantitative immunoglobulin
Sodium			Beta-2 microglobulin
Total bilirubin			Immunofixation
Total protein			
Uric acid			

Roll-over subjects:

Summary of clinical chemistry, hematology, urinalysis, and coagulation will be listed for each subject. Subjects laboratory parameters toxicities will be classified using CTCAE grade and their percentages will be tabulated. Summary CTCAE grade 3 and higher toxicities will be provided.

Below is list of all lab tests performed for roll-over subjects:

9.6.3.2 List of Analytes for Roll-over Subjects

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		~~Hep B antibody~~
Chloride	Lymphocytes		~~Hep C antibody~~
Creatinine	Monocytes	Epithelial, Bacteria, Casts, Crystal, RBCs, WBCs	~~HCV PCR (if applicable)~~
Direct bilirubin	Eosinophils		~~HBV PCR (if applicable)~~
Glucose	Basophils		~~PK~~
LDH			~~Biomarker~~
Lipase			~~SPEP~~
Magnesium			~~UPEP~~
Phosphorus			~~sFLC~~
Potassium			~~Quantitative immunoglobulin~~
Sodium			~~Beta-2 microglobulin~~
Total bilirubin			~~Immunofixation~~
Total protein			
Uric acid			

9.6.4 Vital Signs

Vital signs data will be listed and reviewed for each subject. Depending on the size and scope of changes, summaries of vital signs data over time and/or changes from baseline over time may be provided.

9.6.5 Physical Measurements

The change in weight from baseline to each scheduled assessment time point will be summarized.

9.6.6 Electrocardiogram

The electrocardiogram (ECG) measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QT interval corrected (QTc) effect. Because these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data, these data would not be expected to be useful for meta-analysis with data from other trials.

9.6.7 Antibody Formation

NA

9.6.8 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group.

9.6.9 Exposure to Other Protocol-required Therapy

Descriptive statistics will be produced to describe the exposure to each of the protocol specified treatment by treatment group.

9.6.10 Exposure to Concomitant Medication

The number and proportion of subjects receiving therapies of interest will be summarized by preferred term or category as coded by the World Health Organization Drug (WHO DRUG) dictionary.

9.7 Other Analyses

[redacted]

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/[redacted] Endpoints

Non-roll over subjects:

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 4 in the protocol). 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 from time 0 to the time extrapolated to infinity (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.

9.7.2 Analyses of Clinical Outcome Assessments

NA

9.7.3 Analyses of Health Economic Endpoints

NA

[redacted]

10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

11. Literature Citations / References

Clopper CJ, Person ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometricka* 1934; 26, 404-13.

Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Statistics in Medicine 2008;27:2420-2439

12. Appendices

Appendix A. Technical Detail and Supplemental Information Regarding Statistical Procedures and Programs

Handling of Missing or Incomplete Dates for Adverse Events and Concomitant Medications

Imputation Rules for Partial or Missing Stop Dates

If the month and year are present, impute the last day of the month. If only the year is present, impute December 31 of that year. If the stop date is entirely missing, assume the event or medication is ongoing. If a partial or complete stop date is present and the 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or conmed stopped and the stop date will be imputed, if partial.

Imputation Rules for Partial or Missing Start Dates

		Stop Date						
		Complete: yyyymmdd		Partial: yyyymm		Partial: yyyy		Missing
Start Date		<1st Dose	≥1st Dose	<1st Dose yyyymm	≥1st Dose yyyymm	<1st Dose yyyy	≥1st Dose yyyy	
Partial: yyyymm	=1st Dose yyyymm	2	1	2	1	N/A	1	1
	≠1st Dose yyyymm		2		2	2	2	2
Partial: yyyy	=1st Dose yyyy	3	1	3	1	N/A	1	1
	≠1st Dose yyyy		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose

2 = Impute the first of the month

3 = Impute January 1 of the year

4 = Impute January 1 of the stop year

Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month.

Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date