Title Page

Protocol Title:		Post-marketing Phase 4 Study to Evaluate Safety, Tolerability, and Efficacy of Kyprolis® (Carfilzomib) in Indian Patients With Relapsed or Refractory Multiple Myeloma: A Prospective, Open-label, Non-comparative, Multicenter Study
Short Protocol Title:		Phase 4 Study to Evaluate Safety, Tolerability, and Efficacy of Kyprolis (Carfilzomib) in Relapsed or Refractory Multiple Myeloma
Protocol Number:		20160372
Investigational Product:		Carfilzomib
Trade Name:		Kyprolis
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EudraCT Number:		Not Applicable
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Investigator's Agreement:

I have read the attached protocol entitled Post-marketing Phase 4 Study to Evaluate Safety, Tolerability, and Efficacy of Kyprolis® (Carfilzomib) in Indian Patients With Relapsed or Refractory Multiple Myeloma: A Prospective, Open-label, Non-comparative, Multicenter Study, dated **29 October 2019**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

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)

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1. Protocol Synopsis

Protocol Title: Post-marketing Phase 4 Study to Evaluate Safety, Tolerability, and Efficacy of Kyprolis® (Carfilzomib) in Indian Patients With Relapsed or Refractory Multiple Myeloma: A Prospective, Open-label, Non-comparative, Multicenter Study

Short Protocol Title: Phase 4 Study to Evaluate Safety, Tolerability, and Efficacy of Kyprolis (Carfilzomib) in Relapsed or Refractory Multiple Myeloma

Study Phase: 4

Indication: Relapsed Refractory Multiple Myeloma

Rationale

Kyprolis® (K; carfilzomib) was approved in India on 17 January 2017 as a prescription medication in combination with dexamethasone (Kd) or with lenalidomide (Revlimid®) plus dexamethasone (KRd) for the treatment of patients with relapsed or refractory multiple myeloma (RRMM) following 1 to 3 prior lines of therapy.

This non-comparative, interventional phase 4 study is designed to fulfill the post-marketing requirement to assess safety, tolerability, and efficacy of Kyprolis on Indian subjects with RRMM as per the locally approved label.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
To characterize safety associated with the use of Kyprolis under the locally approved label	The subject incidence, severity, and outcome of treatment-emergent adverse events using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03 including clinically significant laboratory parameter changes over time

Objectives	Endpoints
Secondary	
To characterize efficacy of Kyprolis when administered under the locally approved label	Progression free survival (PFS), overall response rate (ORR), clinical benefit rate (CBR), time to response (TTR), and duration of response (DOR) will be evaluated by the investigator as per local standard procedure using International Myeloma Working Group-Uniform Response Criteria (IMWG-URC). • PFS is defined as the time from first dose of study treatment until the earliest date of disease progression or death due to any cause • ORR is defined as the proportion of subjects with either a best overall response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR)
	• CBR is defined as the proportion of subjects with either a best overall response of sCR, CR, VGPR, PR, and minimal response (MR) • TTR is calculated only for subjects who achieve a best overall response of PR or better and is defined as the time from first dose of study treatment to the earliest date a response of PR or better is first achieved and subsequently confirmed • DOR is defined as the time from initial response (sCR, CR, VGPR, or PR) to date of disease progression

Hypotheses

This phase 4 study is descriptive in nature. There is no hypothesis to be tested. The study will provide descriptive data on the safety profile associated with the use of Kyprolis under the locally approved label as well as its efficacy in terms of PFS, ORR, CBR, TTR, and DOR.

Overall Design

This open-label, multicenter, non-comparative phase 4 study of Kyprolis is part of Amgen's post-marketing requirement to the Indian Regulatory Authority. The study population consists of approximately 100 subjects with RRMM and for whom Kyprolis is indicated in accordance with the approved prescribing information in India.

A subject will be considered on study treatment while receiving Kyprolis. If Kyprolis is discontinued, lenalidomide and/or dexamethasone may be continued outside of the study. No crossover between the treatments will be allowed.

Number of Subjects

Approximately 100 subjects with previously treated RRMM will be enrolled.

Summary of Subject Eligibility Criteria

The key inclusion criteria include:

- documented RRMM after last treatment
- eligible to receive Kyprolis per the locally approved label
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
- adequate organ and bone marrow function within 28 days prior to treatment

The key exclusion criteria include:

- active congestive heart failure, clinically significant echocardiogram (ECHO) abnormalities, screening electrocardiogram (ECG) with corrected QT interval (QTc) of > 470 msec, pericardial disease, or myocardial infarction within 4 months prior to enrollment
- uncontrolled hypertension
- infiltrative pulmonary disease and/or known pulmonary hypertension
- prior treatment with Kyprolis (carfilzomib)

For a full list of eligibility criteria, please refer to Section 6.1 to Section 6.2.

Treatments

Subjects will receive Kyprolis according to the locally approved label either as triplet (KRd) or doublet (Kd) combination, assigned by the investigator based on clinical evaluation and before the decision to include the patient in this study.

For the triplet combination with lenalidomide and dexamethasone, Kyprolis will be administered as an infusion over approximately 10 minutes on days 1, 2, 8, 9, 15, and 16 of repeated 28-day treatment cycles. The recommended starting dose of Kyprolis is 20 mg/m^2 on days 1 and 2, and if tolerated, escalated to a target dose of 27 mg/m^2 starting on day 8 of cycle 1 and thereafter. From cycle 13, the day 8 and day 9 doses of Kyprolis will be omitted. After cycle 18, Kyprolis will be discontinued. Lenalidomide 25 mg is taken orally on days 1 to 21 and dexamethasone 40 mg by mouth or intravenously on days 1, 8, 15, and 22 of the 28-day cycles.

For the doublet combination with dexamethasone, Kyprolis should be administered as a 30-minute infusion on days 1, 2, 8, 9, 15, and 16 of repeated 28-day treatment cycles. The recommended starting dose of Kyprolis is 20 mg/m^2 on days 1 and 2, and if tolerated, escalated to a target dose of 56 mg/m^2 starting on day 8 of cycle 1 and thereafter. Dexamethasone 20 mg is taken by mouth or intravenously on days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day cycle.

Procedures

Informed consent must be obtained before starting any screening procedure. The following procedures will occur per the Schedule of Assessments: demographics, medical/surgical history, physical measurements, vital signs, ECG, ECOG performance status, ECHO/multigated acquisition (MUGA) scan, review of adverse event/serious adverse event, concomitant medications, and review of disease status. Laboratory assessments will include pregnancy testing, coagulation tests, hematology, chemistry tests**, and other analytes specified in Table 12-1**.

For a full list of study procedures, including the timing of each procedure, please refer to Section 9.2 and the Schedule of Activities in Table 2-1.

Statistical Considerations

The primary analysis of safety and efficacy will be performed on the Safety Analysis Set. The Safety Analysis Set will include all subjects who received at least 1 dose of the investigational product. The primary analysis will occur when the last subject enrolled has had the opportunity to receive the study treatment for at least 9 months.

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class, preferred term, and severity grade. The safety laboratory endpoints, vital signs, physical measurements, and ECG measurements will also be analyzed. Descriptive statistics will be produced to describe the exposure to investigational product (Kyprolis) and non-Amgen non-investigational products (dexamethasone and/or lenalidomide).

Secondary efficacy endpoints include PFS, ORR, CBR, TTR, and DOR. Progression free survival will be summarized descriptively using with the Kaplan-Meier (KM) method. The point estimates of ORR and CBR will be summarized along with exact binomial 95% confidence intervals. TTR and DOR are calculated only for the responders, and will be summarized descriptively. KM method will be used to analyze DOR.

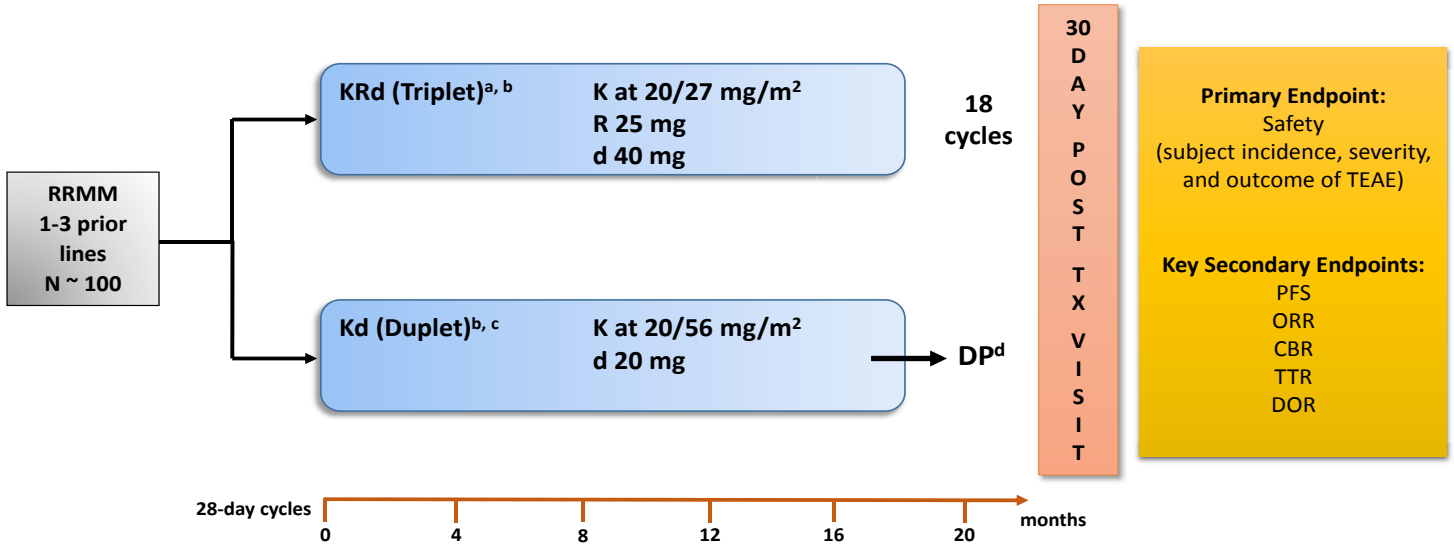
For a full description of statistical analysis methods, please refer to Section 10.

Sponsor Name: Amgen Inc.

2. Study Schema and Schedule of Activities

2.1 Study Schema

Figure 2-1. Study Schema



CBR = clinical benefit rate; D = day; d = dexamethasone; DOR = duration of response; DP = disease progression; K = Kyprolis; ORR = overall response rate; PFS = progression free survival; R = Revlimid (lenalidomide); RRMM = relapsed or refractory multiple myeloma; TEAE = treatment-emergent adverse events; TTR = time to response; TX = treatment.

[a] KRd: K is administered by 10-minute infusion on D 1, 2, 8, 9, 15, 16 of repeated 28-day cycles. From cycle 13, omit the D 8 and D 9 doses of Kyprolis. Discontinue Kyprolis after cycle 18. Revlimid 25 mg is taken orally on days 1-21 and dexamethasone 40 mg by mouth or intravenously on D 1, 8, 15, and 22 of the 28-day cycles.
[b] For patients with mild or moderate hepatic impairment, reduce the dose of Kyprolis by 25% (ie, 15 mg/m^2 day 1 and 2 of cycle 1 for KRd and Kd, 20 mg/m^2 day 8 cycle 1 and thereafter for KRd and 42 mg/m^2 day 8 cycle 1 and thereafter for Kd.
[c] Kd: K is administered by 30 min infusion on D 1, 2, 8, 9, 15, 16 of repeated 28-day cycles until disease progression or unacceptable toxicity occurs. Dexamethasone 20 mg is taken by mouth or intravenously on D 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day cycle.
[d] Treat until disease progression or a maximum of 3 years.

2.2 Schedule of Activities

Table 2-1. Schedule of Activities

Procedure	SCR[a]	Treatment Period Days (All Cycles) 1	2	8	9	15	16	22	End of Study Visit[b]	Notes
General and Safety Assessments										
Informed consent	X									
Inclusion and exclusion criteria	X									
Demographic data	X									
Medical/surgical history	X									Including multiple myeloma history
Physical measurements: height	X									
Physical measurements: weight, BSA	X	X								BSA should be calculated per institutional standard and utilized to calculate required study drug doses. BSA should be recalculated if there is > 20% change in body weight.
Physical examination	X	X							X	C1D1: Screening exam may be used if within 7 days prior to C1D1.
ECG	X								X	
Vital signs: Kd arm (all cycles) and KRd arm (cycles 1-12)	X	X	X	X	X	X	X		X	Checked prior to administration of study drug in all cycles.
Vital signs: KRd arm (cycle 13+)		X	X			X	X		X	Checked prior to administration of study drug in all cycles.
ECOG performance status	X								X	

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Footnotes and abbreviation definitions are after last page of table.

Table 2-1. Schedule of Activities

Procedure	SCR[a]	Treatment Period Days (All Cycles) 1	2	8	9	15	16	22	End of Study Visit[b]	Notes
ECHO/MUGA scan	X								**X**	**Repeated ECHO every 6 months (± 2 weeks) from C1D1 until end of study visit, or if clinically indicated. An ECHO must be performed within 72 hours of the onset of a suspected cardiac failure event.**
Review of AE/SAE	Continually									
Concomitant medications	Continually									Will be collected from 30 days prior to signing of informed consent to 30 days after last dose of study treatment.
Review of disease status	Performed per local standards									Disease status will be evaluated by the investigator using IMWG-URC starting from screening until EOT.
Laboratory Assessments										
Serum or urine pregnancy test (FCBP)[c]	X	X							X	Must be confirmed negative at screening, on day 1 of each cycle prior to dosing, and at end of study visit.
Additional serum or urine pregnancy test (KRd-treated FCBP only)[d]: Cycle 1		X[e]		X		X		X		Weekly pregnancy tests required during cycle 1. See Table 12-2 for additional information on lenalidomide-specific pregnancy testing requirements.
Coagulation tests	X									
Hematology	X	X		(X)		(X)				C1D1: Results from screening may be used if taken within 14 days prior to C1D1. (X): Day 8 and 15 samples only collected during cycle 1.
Chemistry	X	X		(X)		(X)				
NTproBNP	**X**									

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Footnotes and abbreviation definitions are after last page of table.

Table 2-1. Schedule of Activities

Procedure	SCR[a]	Treatment Period Days (All Cycles) 1	2	8	9	15	16	22	End of Study Visit[b]	Notes
Hepatitis B Virus (HBV)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**Local serology testing for HBsAg, anti-HBs, and anti-HBc. Testing is required:** • **For subjects with a prior history of HBV infection at screening and HBV DNA testing every 12 weeks ± 2 weeks through end of study visit.** • **For all other subjects at screening unless obtained within 6 months of screening and there was no change in the subject's risk factors within these 6 months.** • **For subjects positive at screening, who become positive for serology during treatment, or who are at risk of becoming positive, HBV DNA testing will be performed every 12 weeks ± 2 weeks (and as clinically indicated) through end of study visit.** **A specialist should be consulted for all subjects who test positive for HBV serology. Subjects who have received Hepatitis B vaccination with only anti-HBs positivity and no clinical signs of hepatitis do not require HBV DNA monitoring.** **See Section 9.2.3.4.2**

AE = adverse events; **BNP = b-type natriuretic peptide**; BSA = body surface area; CXDX = cycle X day X; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; FCBP = female of child bearing potential; **anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus**; IMWG-URC = International Myeloma Working Group-Uniform Response Criteria; MUGA = multigated acquisition scan; **NTproBNP = N-terminal pro b-type natriuretic peptide**; SAE = serious adverse event; SCR = screening.
[a] Screening: up to 28 days before enrollment

[b] End of study visit is 30 days (+ 3) after last dose of Kyprolis
[c] Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.
[d] The subject may not receive lenalidomide until the investigator has verified that the results of these pregnancy tests are negative.
[e] KRd-treated FCBP must have 2 negative pregnancy tests (combined sensitivity of at least 50 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. 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 discontinuation from the study.

3. Introduction

3.1 Study Rationale

Kyprolis® (K; carfilzomib) was approved in India on 17 January 2017 as a prescription medication in combination with dexamethasone (Kd) or with lenalidomide (Revlimid®) plus dexamethasone (KRd) for the treatment of patients with relapsed or refractory multiple myeloma (RRMM) following 1 to 3 prior lines of therapy and as single agent for the treatment of patients with RRMM who have received 1 or more lines of therapy.

This non-comparative, interventional phase 4 study is designed to fulfil the post-marketing requirement to assess safety, tolerability, and efficacy of Kyprolis on Indian subjects with RRMM as per the locally approved label.

3.2 Background

3.2.1 Disease

Multiple myeloma, a clonal neoplastic proliferation of plasma cells, is the second most common hematologic malignancy and is responsible for approximately 80 000 annual deaths worldwide (1% of cancer deaths) (Ferlay et al, 2015). In 2012, the estimated incidence of multiple myeloma in India was 6955, which represents 0.7% of all cancers. The 5 year prevalence of multiple myeloma was estimated at 11 886 persons; (WHO Fact Sheet). Multiple myeloma is a disease of older adults, with a median age at diagnosis of 70 years (Howlader et al, 2013).

While treatment for multiple myeloma will typically induce remission, multiple myeloma eventually relapses in most patients. Remissions are increasingly transient with successive lines of therapy, with disease eventually becoming refractory (nonresponsive to the most recent therapy or progression within 60 days of discontinuation from the most recent therapy), and most patients ultimately die of myeloma-related complications (Richardson et al, 2007; Kumar et al, 2004).

The primary goal of treatment for relapsed and refractory multiple myeloma is to achieve the longest progression-free survival (PFS) and subsequently overall survival (OS). In this setting, the depth of response is an important prognostic factor and associated with OS (Chanan-Khan and Giralt, 2010; Richardson et al, 2007). Additional goals are to control disease activity to prevent or delay progression and its associated complications (such as bone fractures, renal insufficiency, and infections), to maintain an acceptable health-related quality of life (HRQoL), and to provide relief of pain and other

disease-related symptoms. These goals must be achieved by using regimens with an acceptable tolerability.

3.2.2 Amgen Investigational Product Background: Kyprolis

3.2.2.1 Kyprolis Background (Non-clinical)

Kyprolis is a tetrapeptide epoxyketone based inhibitor of the 20S proteasome. Kyprolis, showed less off target activity when measured against a broad panel of proteases including metallo-, aspartyl-, and serine proteases compared to bortezomib; bortezomib showed off target inhibitory activity in the nanomolar range against several serine proteases (Arastu-Kapur et al, 2009). This selectivity may be responsible for the reductions in myelosuppression and neuropathy observed in studies comparing Kyprolis with bortezomib.

Incubation of hematologic tumor cell lines with Kyprolis for as little as 1 hour led to rapid inhibition of proteasome activity followed by accumulation of polyubiquitinated proteins and induction of apoptotic cell death (Suzuki et al, 2011; Kuhn et al, 2007).

Kyprolis has also been administered to rats and monkeys for 6 and 9 months, respectively (twice weekly for 3 weeks on a 28-day cycle). Kyprolis was well tolerated at doses resulting in more than 80% proteasome inhibition, with no behavioral or histological evidence of peripheral neuropathy (PN) and no neutropenia (Carfilzomib Investigator's Brochure).

3.2.2.2 Kyprolis Background (Clinical)

Kyprolis entered clinical studies in September 2005. On 20 July 2012, Kyprolis (Carfilzomib for Injection) was approved under the United States Food and Drug Administration's (US FDA) accelerated approval program for the treatment of patients with multiple myeloma who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent (IMiD). This initial approval was based upon overall response rate (ORR) in a heavily pretreated population studied in the phase 2 PX-171-003-A1 study. Subsequent full approval in the US and globally were based on 2 large open-label phase 3 trials: PX 171-009 ASPIRE and 2011-003 ENDEAVOR. Following these approvals, Kyprolis is indicated for use in combination with either lenalidomide (Revlimid) and dexamethasone (20/27 mg/m^2 K) or dexamethasone alone (20/56 mg/m^2 K) for the treatment of RRMM following 1 to 3 prior lines of therapy. In various countries, Kyprolis is also approved as a single agent (20/27 mg/m^2 or 20/56 mg/m^2) for subjects with RRMM who have received at least 1 prior treatment

regimen. The exact indication wording varies by region. Additional data on clinical background is summarized in the Investigator's Brochure.

As of 19 January 2017, an estimated 3504 subjects (2911 subject-years) have been exposed to Kyprolis in clinical trials conducted by Amgen since the beginning of the development program. An estimated 51 275 patients (19 760 patient-years) have been cumulatively exposed to the product in the marketed setting.

A detailed description of the chemistry, pharmacology, efficacy, and safety of Kyprolis is provided in the Investigator's Brochure.

3.2.3 Non-Amgen Investigational Product Background: Lenalidomide and Dexamethasone

3.2.3.1 Lenalidomide

Lenalidomide, a thalidomide analogue is commercially available in 5, 10, 15, or 25 mg capsules for oral administration and will not be supplied by Amgen. Details regarding the description, supply, and storage instructions for lenalidomide are found in the Prescribing Information. Sites are advised to refer to the prescribing information for information that is specific to the brand or formulation of the drug product in use.

3.2.3.2 Dexamethasone

Dexamethasone is commercially available and will not be supplied by Amgen. Details regarding the description, supply, and storage instructions for dexamethasone are found in the prescribing information. Sites are advised to refer to the prescribing information for information that is specific to the brand or formulation of the drug product in use.

Refer to the regional manufacturer package insert for additional information.

4. Objectives, Endpoints and Hypotheses

4.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To characterize safety associated with the use of Kyprolis under the locally approved label	The subject incidence, severity, and outcome of treatment-emergent adverse events using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03 including clinically significant laboratory parameter changes over time
Secondary	
To characterize efficacy of Kyprolis when administered under the locally approved label	Progression free survival (PFS), overall response rate (ORR), clinical benefit rate (CBR), time to response (TTR), and duration of response (DOR) will be evaluated by the investigator as per local standard procedure using International Myeloma Working Group-Uniform Response Criteria (IMWG-URC). • PFS is defined as the time from first dose of study treatment until the earliest date of disease progression or death due to any cause • ORR is defined as the proportion of subjects with either a best overall response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) • CBR is defined as the proportion of subjects with either a best overall response of sCR, CR, VGPR, PR, and minimal response (MR) • TTR is calculated only for subjects who achieve a best overall response of PR or better and is defined as the time from first dose of study treatment to the earliest date a response of PR or better is first achieved and subsequently confirmed • DOR is defined as the time from initial response (sCR, CR, VGPR, or PR) to date of disease progression

4.2 Hypotheses

This phase 4 study is descriptive in nature. There is no hypothesis to be tested. The study will provide descriptive data on the safety profile associated with the use of

Kyprolis under the locally approved label as well as its efficacy in terms of PFS, ORR, CBR, TTR, and DOR.

5. Study Design

5.1 Overall Design

This open-label, multicenter, non-comparative phase 4 study of Kyprolis is part of Amgen's post-marketing requirement to the Indian Regulatory Authority. The study population consists of approximately 100 subjects with RRMM and for whom Kyprolis is indicated in accordance with the approved prescribing information in India. The sample size of 100 is as directed by the regulatory authority.

The assignment of subjects to protocol treatment will be decided by the investigator based on clinical evaluation and before the decision to include the subject in this study.

A subject will be considered on study treatment while receiving Kyprolis. If Kyprolis is discontinued, lenalidomide and/or dexamethasone may be continued outside of the study. No crossover between the treatments will be allowed.

Safety assessments include the collection of adverse events and serious adverse events until the last follow-up visit. In addition, laboratory tests will be performed according to the assessment schedule outlined in Table 2-1.

All subjects will be evaluated by the investigator for multiple myeloma disease response based on local standard procedures.

Following disease progression or discontinuation of study treatment, all subjects will have 1 final assessment that occurs 30 days (+ 3 days) after the last dose of Kyprolis.

The overall study design is described by a study schema in Section 2.1. The endpoints are defined in Section 4.1.

5.2 Number of Subjects

Approximately 100 subjects with previously treated RRMM will be enrolled.

Subjects in this clinical investigation shall be referred to as "subjects". For the sample size justification, see Section 10.1.

5.2.1 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study will not be replaced.

5.2.2 Number of Sites

Approximately 15 investigative sites in India will be included in the study. Sites that do not enroll subjects within 5 months of site initiation may be closed.

5.3 End of Study

5.3.1 End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early. Primary completion is planned to occur when the last subject has had the opportunity to receive the study treatment for at least 9 months.

The primary completion date is the date when data for the primary endpoint are last collected for the purposes of conducting the primary analysis.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit). This study will conclude when all subjects discontinue study treatment or have received study treatment for a maximum of 3 years, whichever occurs first.

5.3.2 Study Duration for Subjects

Total study duration for an individual subject may vary by the assigned study treatment. For subjects receiving KRd the total study duration is estimated to be approximately 20 months. For subjects receiving Kd, the total study duration is estimated to be approximately 23 months.

5.4 Justification for Investigational Product Dose

The study is being conducted as a post authorization safety study as mandated by the Indian Regulatory Authority. The doses chosen are the approved doses in the local Kyprolis Prescribing Information.

6. Study Population

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, enrolled into study, reason for ineligibility, or refusal to participate).

Eligibility criteria will be evaluated during screening.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Appendix 3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, will not be provided.

6.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

101 Documented RRMM after last treatment. Refractory is defined as meeting 1 or more of the following:

- Nonresponsive to most recent therapy (stable disease [SD] or progressive disease [PD]) while on treatment, or
- Disease progression within 60 days of discontinuation from the most recent therapy

102 Eligible to receive Kyprolis per the locally approved label

103 Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2

104 Adequate hepatic function within 28 days prior to enrollment:

- bilirubin < 1.5 times the upper limit of normal (ULN)
- aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5 times the ULN

105 Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L within 28 days prior to enrollment. (Screening ANC should be independent of granulocyte- and granulocyte macrophage-colony stimulating factor support for at least 1 week and of pegylated granulocyte stimulating factor for ≥ 2 weeks).

106 Hemoglobin ≥ 80 g/L within 28 days prior to enrollment. Subjects should not have received red blood cell (RBC) transfusions for at least 7 days prior to obtaining the screening hemoglobin.

107 Platelet count ≥ 75 x 10^9/L (≥ 50 x 10^9/L if myeloma involvement in the bone marrow is ≥ 50%) within 28 days prior to enrollment. Subjects should not have received platelet transfusions for at least 7 days prior to obtaining the screening platelet count.

108 Adequate renal function within 28 days prior to enrollment (either measured or calculated using a standard formula such as the Cockcroft and Gault):

- Calculated or measured creatinine clearance (CrCl) of ≥ 50 mL/min for subjects receiving KRd
- Calculated or measured CrCl of ≥ 15 mL/min for subjects receiving Kd

109 Left ventricular ejection fraction ≥ 40% as assessed by transthoracic echocardiogram (TTE) or multigated acquisition scan (MUGA)

110 Females of childbearing potential (FCBP) must have a negative serum pregnancy test within the 10 to 14 days prior to enrollment and a negative urine pregnancy test within the 24 hours prior to day 1 of each cycle prior to dosing.

111 Subject or legally acceptable representative has provided informed consent/assent prior to initiation of any study specific activities/procedures

6.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply.

201 Waldenström macroglobulinemia

202 Plasma cell leukemia (> 2.0 x 10^9/L circulating plasma cells by standard differentials)

203 POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)

204 Myelodysplastic syndrome

205 Primary amyloidosis (subjects with multiple myeloma with asymptomatic deposition of amyloid plaques found on biopsy would be eligible if all other criteria are met)

206 History of other malignancy within the past 5 years, with the following exception[s]:

- 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

207 Known immediate or delayed hypersensitivity reaction to Captisol (a cyclodextrin derivative used to solubilize Kyprolis)

208 Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to antiviral drugs

209 Intolerance to hydration

210 Active congestive heart failure (New York Heart Association [NYHA] Class III to IV), symptomatic ischemia, uncontrolled arrhythmias, clinically significant echocardiogram (ECHO) abnormalities, screening ECG with corrected QT interval (QTc) of > 470 msec, pericardial disease, or myocardial infarction within 4 months prior to enrollment

211 Infiltrative pulmonary disease and/or known pulmonary hypertension

212 Active infection within 14 days prior to enrollment requiring systemic antibiotics, antiviral (except antiviral therapy directed at hepatitis B) or antifungal agents. Such infections must be fully resolved prior to initiating study treatment

213 Pleural effusions requiring thoracentesis within 14 days prior to enrollment.

214 Ascites requiring paracentesis within 14 days prior to enrollment.

215 Uncontrolled hypertension, defined as an average systolic blood pressure > 159 mmHg or diastolic > 99 mm/Hg despite optimal treatment (measured following European Society of Hypertension/European Society of Cardiology [ESH/ESC] 2013 guidelines [Appendix 8])

233 Active hepatitis B virus (HBV) infection. Subjects with positive hepatitis B surface antigen (HBsAg) or core antibody (anti-HBc) that achieve sustained virologic response with antiviral therapy directed at hepatitis B are allowed. Subjects with known history or resolved infection (negative for HBsAg but positive for antibodies to surface antigen, and/or core antigen) must be screened with HBV DNA levels. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (hepatitis B surface antibody [anti-HBs] positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA.

216 Known human immunodeficiency virus (HIV) infection, hepatitis C infection (subjects with hepatitis C that achieve a sustained virologic response following antiviral therapy are allowed)

217 Ongoing graft-versus-host disease

218 Subjects with grade 3 or worse neuropathy within 14 days prior to enrollment.

219 Antitumor therapy (eg, chemotherapy, immunotherapy, antibody therapy) or investigational agent within 28 days before enrollment or not recovered from any acute toxicity

220 Subjects on immunosuppressive therapy for graft versus host disease, even if it has resolved

221 Glucocorticoid therapy within 14 days before first dose that exceeds a cumulative dose of 160 mg or dexamethasone or equivalent dose of other corticosteroids

222 Focal radiation therapy within 7 days before enrollment. Radiation therapy to an extended field involving significant volume of bone marrow within 28 days prior to enrollment (ie, prior radiation must have been to less than 30% of the bone marrow)

223 Autologous stem cell transplant less than 100 days prior to enrollment

224 Prior treatment with Kyprolis (carfilzomib)

225 Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study. Other investigational procedures while participating in this study are excluded.

226 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment, during any breaks (interruptions) in the treatment, and for an additional 30 days before the last dose of Kyprolis. Females of childbearing potential should only be included in the study after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test.

227 Female subjects of childbearing potential unwilling to use 1 highly effective method of contraception during treatment, during any breaks (interruptions) in the treatment, and for an additional 30 days after the last dose of Kyprolis. Refer to Appendix 5 for additional contraceptive information.

NOTE: Female subjects of childbearing potential being treated with lenalidomide must agree to use 2 methods of contraception for at least 28 days before starting treatment, during treatment, during any breaks (interruptions) in the treatment, and for an additional 30 days after the last dose of treatment. See Table 12-2 for lenalidomide-specific contraceptive guidance.

228 Male subjects with a female partner of childbearing potential who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use contraception during treatment and for an additional 90 days after the last dose of Kyprolis. Refer to Appendix 5 for additional contraceptive information.

NOTE: Male subjects being treated with lenalidomide must agree to use a male condom with spermicide even if they have undergone a successful vasectomy. See Table 12-2 for lenalidomide-specific contraceptive guidance.

229 Male subjects with a pregnant partner who are unwilling to practice abstinence or use a condom during treatment and for an additional 90 days after the last dose of Kyprolis.

230 Male subjects unwilling to abstain from donating sperm during treatment and for an additional 90 days after the last dose of Kyprolis.

231 Subject likely to not be available to complete all protocol required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge.

232 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

6.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of written approval for study protocol issued by Health Authority and a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Appendix 3).

The subject or the subject's legally acceptable representative must personally sign and date the IRB/IEC and Amgen-approved informed consent before commencement of study-specific procedures.

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

Each subject who enters into the screening period for the study (up to 28 days before enrollment) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by Interactive Voice/Web Response System (IxRS). 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 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.

6.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time.

7. Treatments

Study treatment is defined as any investigational product(s) or non-investigational product(s) intended to be administered to a study subject according to the study protocol. An individual subject will receive study treatment for a maximum of 18 months (if receiving the triplet combination [KRd], consistent with the approved use in this combination) or up to a maximum of 3 years if the subject has not yet experienced disease progression (if receiving the doublet combination [Kd]).

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

7.1 Treatment Procedures

7.1.1 Investigational Products

Subjects will receive Kyprolis according to the locally approved label either as triplet (KRd) or doublet (Kd) combination, assigned by the investigator based on clinical evaluation and before the decision to include the patient in this study.

Kyprolis will be provided by Amgen.

The IPIM, a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of Kyprolis.

Table 7-1. Study Treatments

Study Treatment Name	**Amgen Investigational Product:**[a] Kyprolis
Dosage Formulation	Supplied as a sterile, lyophilized, white to off-white powder, ready for reconstitution. It is supplied for single use in 50 mL Type 1 glass vials containing 60 mg of Kyprolis drug product with an elastomeric stopper and flip-off lid. Upon reconstitution with preservative-free sterile water for injection (sWFI), the reconstituted solution contains 2 mg/mL Kyprolis, sulfobutylether beta-cyclodextrim sodium (SBECD), and citrate buffer. Kyprolis is supplied in labelled cartons containing 4 single use vials per carton.
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	10 minute infusion: 20/27 mg/m^2 30 minute infusion: 20/56 mg/m^2
Route of Administration	IV infusion
Accountability	The planned dose (mg/m^2), **actual** dose (mg) **administered**, start date/time, stop date/time, reason for change in planned dose, reason for dose change/withheld, reason for dose delay, and package lot number of Kyprolis is to be recorded on each subject's eCRF(s).
Dosing Instructions	Triplet: See Section 7.1.2.1 Doublet: See Section 7.1.2.2

[a] Kyprolis will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

7.1.2 General Dosing Instructions

Each subject's first dose of Kyprolis will be calculated based upon baseline body surface area (BSA) per institutional standards. In subjects with BSA of greater than 2.2 m^2, the dose should be capped based on a BSA of 2.2 m^2. The dose for each subject should not be revised unless the subject experiences a > 20% change in body weight in which case the BSA and dose should be recalculated. **The recalculated BSA becomes the**

new baseline. The dose can also be modified in response to toxicity following the dose modification guideline table in local Kyprolis Prescribing Information.

Lenalidomide and dexamethasone (if administered orally [PO]) may be self-administered at home by the subject and should be taken at approximately the same time each day. Missed doses of dexamethasone and lenalidomide will not be made up. Subjects will maintain a diary of outpatient dexamethasone and lenalidomide administration.

For triple combination therapy dosing instructions, see Section 7.1.2.1. For doublet combination therapy dosing instructions, see Section 7.1.2.2.

7.1.2.1 Kyprolis in Combination With Lenalidomide and Dexamethasone (KRd)

For the triplet combination with lenalidomide and dexamethasone, Kyprolis will be administered as an infusion over approximately 10 minutes on days 1, 2, 8, 9, 15, and 16 of repeated 28-day treatment cycles. The recommended starting dose of Kyprolis is 20 mg/m^2 on days 1 and 2 **of cycle 1**, and if tolerated, escalated to a target dose of 27 mg/m^2 starting on day 8 of cycle 1 and thereafter. From cycle 13, the day 8 and day 9 doses of Kyprolis will be omitted. After cycle 18, Kyprolis will be discontinued (Table 7-2). Lenalidomide 25 mg is taken orally on days 1 to 21 and dexamethasone 40 mg by mouth or intravenously on days 1, 8, 15, and 22 of the 28-day cycles.

For patients with mild or moderate hepatic impairment, reduce the dose of Kyprolis by 25% (ie, 15 mg/m^2 day 1 and 2 of cycle 1 and 20 mg/m^2 day 8 cycle 1 and thereafter. **If hepatic function returns to normal, the dose may be re-escalated to the intended dose after the first cycle (ie, 27 mg/m^2 in KRd).**

Table 7-2. Kyprolis (10-minute Infusion) Dosing in Combination With Lenalidomide and Dexamethasone (Triplet Combination)

	Cycle 1										
Week	1			2			3			4	
Day	1	2	3-7	8	9	10-14	15	16	17-21	22	23-28
Kyprolis (mg/m^2)[a, b]	20	20	-	27	27	-	27	27	-	-	-
Dexamethasone (mg)[c]	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide[c]	25 mg daily on days 1-21									-	-
	Cycles 2 to 12										
Week	1			2			3			4	
Day	1	2	3-7	8	9	10-14	15	16	17-21	22	23-28
Kyprolis (mg/m^2)[a, b]	27	27	-	27	27	-	27	27	-	-	-
Dexamethasone (mg)[c]	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide[c]	25 mg daily on days 1-21									-	-
	Cycles 13 and later[d]										
Week	1			2			3			4	
Day	1	2	3-7	8	9	10-14	15	16	17-21	22	23-28
Kyprolis (mg/m^2)[a, b]	27	27	-	-	-	-	27	27	-	-	-
Dexamethasone (mg)[c]	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide[c]	25 mg daily on days 1-21									-	-

[a] Refer to the local Kyprolis Prescribing Information for dose modifications. For patients with mild or moderate hepatic impairment, reduce the dose of Kyprolis by 25% (ie, 15 mg/m^2 day 1 and 2 of cycle 1 and 20 mg/m^2 day 8 cycle 1 and thereafter.
[b] See Section 7.1.2.3 for information regarding IV prehydration before Kyprolis infusion.
[c] Refer to the local lenalidomide and dexamethasone Prescribing Information for concomitant medications, such as the use of anticoagulant and antacid prophylaxis that may be required with those agents.
[d] Kyprolis is administered through cycle 18; lenalidomide and dexamethasone may be continued outside of the study.

7.1.2.2 Kyprolis in Combination With Dexamethasone (Kd)

For the doublet combination with dexamethasone, Kyprolis should be administered as a 30-minute infusion on days 1, 2, 8, 9, 15, and 16 of repeated 28-day treatment cycles. The recommended starting dose of Kyprolis is 20 mg/m^2 on days 1 and 2, and if tolerated, escalated to a target dose of 56 mg/m^2 starting on day 8 of cycle 1 and thereafter (Table 7-3). Dexamethasone 20 mg is taken by mouth or intravenously on days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day cycle.

For patients with mild or moderate hepatic impairment, reduce the dose of Kyprolis by 25% (ie, 15 mg/m^2 day 1 and 2 of cycle 1 and 42 mg/m^2 day 8 cycle 1 and thereafter. **If hepatic function returns to normal, the dose may be re-escalated to the intended dose after the first cycle (ie, 56 mg/m^2 in Kd).**

Table 7-3. Kyprolis (30-minute Infusion) Dosing in Combination With Dexamethasone (Double Combination)

	Cycle 1											
Week	1			2			3			4		
Day	1	2	3-7	8	9	10-14	15	16	17-21	22	23	24-28
Kyprolis (mg/m^2)[a, b]	20	20	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)[c]	20	20	-	20	20	-	20	20	-	20	20	-
	Cycles 2 and later[d]											
Week	1			2			3			4		
Day	1	2	3-7	8	9	10-14	15	16	17-21	22	23	24-28
Kyprolis (mg/m^2)[a, b]	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)[c]	20	20	-	20	20	-	20	20	-	20	20	-

IV = intravenous
[a] Refer to the local Kyprolis Prescribing Information for dose modifications. For patients with mild or moderate hepatic impairment, reduce the dose of Kyprolis by 25% (ie, 15 mg/m^2 day 1 and 2 of cycle 1 and 42 mg/m^2 day 8 cycle 1 and thereafter.
[b] See Section 7.1.2.3 for information regarding IV prehydration before Kyprolis infusion.
[c] Refer to dexamethasone Prescribing Information for other concomitant medications
[d] Treatment may be continued until disease progression or unacceptable toxicity occurs (or for a maximum of 3 years).

7.1.2.3 Intravenous Prehydration

Subjects may receive intravenous (IV) pre-hydration (normal saline or other appropriate IV fluid) prior to each carfilzomib infusion during cycle 1. Investigators must consider IV pre-hydration in subjects at high-risk for tumor lysis or renal toxicity. All subjects must be monitored for fluid overload and hydration should be tailor to individual needs. It is recommended to use no more than 750 mL IV fluids as a combination of pre- and post-hydration. Thereafter, carfilzomib pre- and/or post-hydration may only be administered if the subject's condition and/or risk factors require it. The total volume of pre- and/or post-hydration and the indication will be recorded on the Concomitant Medications eCRF.

7.1.3 Non-investigational Products

Dexamethasone and lenalidomide, both non-Amgen non-investigational products, will also be used in this study. See Full Prescribing Information for dosage, reconstitution and preparation for administration. Lenalidomide and dexamethasone will not be provided by Amgen.

The planned dose (mg), **actual** dose (mg) **administered**, start date/time, stop date/time, reason for change in planned dose, reason for dose change/withheld, reason for dose

delay, and package lot number of lenalidomide and/or dexamethasone is to be recorded on each subject's eCRF(s).

7.1.4 Medical Devices

There are no investigational medical devices being used in this study.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not provided or reimbursed by Amgen. The investigator will be responsible for obtaining supplies of these devices.

7.1.5 Other Protocol-required Therapies

All other protocol-required therapies listed below are commercially available and will not be provided by Amgen. The investigator will be responsible for obtaining supplies of these protocol-required therapies.

7.1.5.1 Antiviral Prophylaxis

An antiviral is required concomitant medication for the duration of treatment with Kyprolis. Acyclovir (eg, 400 mg PO 3 times a day, or 800 mg PO 2 times a day or per institutional standards), famcyclovir (eg, 125 mg PO given 3 days, twice a day or per institutional standards), or valacyclovir (eg, 500 mg PO, twice a day or per institutional standards), dose adjustments for renal function where appropriate, initiated within 1 week of the first dose should continue for the duration of treatment with Kyprolis.

7.1.5.2 Proton-pump Inhibitor

Proton-pump inhibitor (omeprazole or equivalent) is required while on dexamethasone.

7.1.5.3 Prophylaxis for Hepatitis B Virus

Hepatitis B virus reactivation prophylaxis should be considered for patients at risk (ie, patients tested positive on serology or had a prior history of HBV infection), as per institutional guidelines.

7.1.5.4 Supportive Therapies

Refer to the local Kyprolis **Prescribing Information** for Warnings and Precautions, as well as recommended supportive therapies and medications.

7.1.6 Other Treatment Procedures

Not applicable.

7.1.7 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), device(s) or combination product(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

- Kyprolis

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

7.1.8 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

Concurrent therapy with a marketed or investigational anticancer therapeutic or radiation to large bone marrow reserves for either palliative or therapeutic intent is excluded.

Corticosteroids given short-term **(up to 2 weeks)** for nonmalignant conditions (eg, asthma, inflammatory bowel disease) **are permitted provided that the cumulative dose is less than 40 mg per week** dexamethasone **or equivalent dose (see Appendix 12 for corticosteroid dose equivalents)**. **Medical monitor should be contacted if short**-term **corticosteroid use is required** > **2 weeks or at cumulative dose** of **more than 40 mg dexamethasone equivalent or 20 mg for subjects** > **75 years of age.** Investigational agents are not to be used during the study.

7.2 Method of Treatment Assignment

The assignment of subjects to protocol treatment will be decided by the investigator based on clinical evaluation before the decision to include the subject in this study. Subjects who meet eligibility criteria will be included in the study.

The treatment assignment date is to be documented in the subject's medical record and on the enrollment eCRF.

7.3 Blinding

This is an open-label study; blinding procedures are not applicable.

7.4 Dose Modification

Kyprolis may be discontinued, temporarily delayed, or dosage reduced, in the event of a treatment-related toxicity that, in the opinion of the investigator, warrants the discontinuation, temporary delay or dose reduction, as indicated in the Kyprolis Prescribing Information (refer to **Posology and method of administration and Special warnings and precautions for use sections**). See the lenalidomide and dexamethasone Prescribing Information respectively for dosing recommendations.

If day 1 of a cycle is delayed, day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. However, if a within-cycle dose is delayed, then the dates of the subsequent within-cycle doses should not be adjusted.

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

7.4.1.1 Amgen Investigational Product: Kyprolis

The reason for dose change of Kyprolis is to be recorded on each subject's eCRF(s). A subject is considered to be on protocol treatment while receiving Kyprolis. See Table 5 of the Kyprolis Prescribing Information for guidance on dose modifications for toxicity during Kyprolis treatment.

7.4.1.2 Non-Amgen Non-investigational Product: Lenalidomide and Dexamethasone

The reason for dose change of lenalidomide and dexamethasone is to be recorded on each subject's eCRF(s).

7.5 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product are provided in the IPIM.

7.6 Treatment Compliance

Administration of IV medicinal products will occur at the study site.

Oral medication may be dispensed for self-administration at home. Subjects are to document all administered doses and missed doses in a medication diary for all study-required medication taken at home. Subjects are to be instructed to return the medication diary at each visit. Non-compliance is to be documented in the medical file and will be reflected in the eCRF. Non-compliant subjects are to be re-educated on the importance of adhering to the study drug administration schedule and reminded that repeated cycles of non-compliance could be a reason for discontinuation of study treatment.

7.7 Treatment of Overdose

Refer to the local Kyprolis label for signs and symptoms of overdose (Section 4.9).

In the event of an overdose, the patient should be monitored, specifically for the side effects and/or adverse drug reactions in the product label.

7.8 Prior and Concomitant Treatment

7.8.1 Prior Treatment

Prior therapies that were being taken/used from 30 days prior to enrollment through signing the informed consent will be collected. All prior medications that continue after the informed consent are to be recorded as concomitant medication.

For prior therapies being taken for multiple myeloma (eg, chemotherapy), collect therapy name, dose, outcome, start date and stop date. For all other prior therapies, collect therapy name, indication, dose, unit, frequency, route, start date and stop date and enter in the subject's eCRF.

Prior lines of multiple myeloma treatment are defined as a planned course of therapy. Therefore, during initial treatment, the induction ± autologous stem cell transplant ± consolidation and maintenance would be considered 1 line of therapy (see Appendix 9 for additional guidance on lines of therapy).

7.8.2 Concomitant Treatment

A concomitant medication is defined as any prescription or over-the-counter preparation including vitamins and supplements. Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 7.1.8.

All administered concomitant medicines and therapies are to be collected from informed consent through 30 days following the last dose of Kyprolis.

For concomitant therapies being taken, collect therapy name, indication, dose, unit, frequency, route, start date, stop date, and enter in the subject's eCRF.

Concomitant medications used prophylactically should be described as such in the designated eCRF. Blood and blood products are not considered concomitant medications and must be recorded on the appropriate eCRF.

8. Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time

and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 8.1, 8.2.1, and 8.2.2.

8.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product including completion of an end of study visit 30 days after the last dose of investigational product.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Appendix 3.

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

- Decision by Sponsor
- Lost to follow-up
- Death
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Adverse event
- Subject request
- Disease progression
- Pregnancy **and lactation**

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

8.2 Discontinuation From the Study

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. The investigator is to discuss with the

subject appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Appendix 6 for further details). Refer to the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.2.1 Reasons for Removal From Washout, Run-in or Invasive Procedures

Not applicable.

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Discontinuation of Kyprolis
- Decision by sponsor
- Withdrawal of consent from study
- Death
- Lost to follow-up

8.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 2-1).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

9.1 General Study Periods

9.1.1 Screening, Enrollment and/or Randomization

Informed consent must be obtained before starting any screening procedure. After the subject has signed the ICF, the site will register the subject in the IxRS and screen the subject in order to assess eligibility for participation. The screening window is up to 28 days.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening 1 time.

Rescreen subjects must first be registered as screen failures in IxRS and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 28 day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 30 days after the original signing of the ICF, all screening procedures, including informed consent, must be repeated.

9.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 2-1). On-study visits may be completed within 2 days. The date of the first dose of investigational product is defined as cycle 1 day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Administration of protocol-required therapies is to be administered last during each visit that it is required.

9.1.3 End of Study

Upon permanent discontinuation from the study treatment for any reason, the end of study visit will be performed approximately 30 (+ 3) days after the last dose of investigational product.

9.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

9.2.1 General Assessments

9.2.1.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed. Any procedures done as part of routine standard of care prior to signing the ICF may be used as long as they fall within the windows specified in the Schedule of Activities (Table 2-1).

9.2.1.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.

9.2.1.3 Medical History

The investigator or designee will collect a complete medical and surgical history that started within 30 days prior to informed consent. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history eCRF.

In addition to the medical history above, multiple myeloma history must date back to the original diagnosis. For subjects who are being referred to the research site, critical referral information will constitute multiple myeloma information from source notes.

9.2.1.4 Physical Examination

Physical examination will be performed as per standard of care. A complete physical examination is to include examination of cardiovascular and respiratory systems, abdominal examination, and general neurologic examination.

Clinically significant abnormal physical examination findings identified prior to the signing of informed consent should be reported as part of medical history, not as adverse events. Physical examination findings should be recorded on the appropriate eCRF (eg, medical history, event).

9.2.1.5 Physical Measurements

Weight (in kilograms) and height (in centimeters) will be measured (height will be measured only at the screening physical examination). Body surface area will be determined per institutional guidelines/standards.

9.2.1.6 Performance Status

The subject's performance status will be assessed using the ECOG performance scale (see Appendix 10) at intervals identified in the Schedule of Assessments (Table 2-1).

9.2.2 Efficacy Assessments

Disease status will be evaluated by the investigator using IMWG-URC (see Appendix 11) starting from screening until EOT and documented at intervals specified in the Schedule of Activities (Table 2-1). Patients with confirmed sCR, CR, VGPR, or PR will be considered to have achieved an overall response.

9.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities (Table 2-1).

9.2.3.1 Adverse Events

9.2.3.1.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

9.2.3.1.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the CTCAE and is described in Appendix 4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product(s) through the end of study visit are reported using the Event eCRF.

9.2.3.1.1.2 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 dose of investigational product are reported using the Event eCRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

9.2.3.1.1.3 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. Per local requirements in some countries, 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 and handled accordingly based on relationship to investigational product.

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 4.

9.2.3.1.1.4 Reporting a Safety Endpoint as a Study Endpoint

Not applicable.

9.2.3.1.1.5 Serious Adverse Events That Are Not to be Reported by the Sponsor to Regulatory Agencies in an Expedited Manner

Not applicable.

9.2.3.1.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

9.2.3.1.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event eCRF.

9.2.3.1.4 Regulatory Reporting Requirements for Serious Adverse Events

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

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.3.1.5 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and, if indicated, female partners of male subjects will be collected after the start of study treatment and until 30 days following the last dose of investigational product.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Appendix 5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Appendix 5.

9.2.3.2 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Vital sign measurements are performed prior to administration of study drug(s) in all cycles.

Subjects must be in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. The position selected for a subject should be the same that is used throughout the study and documented in the medical record and on the vital sign eCRF. Take at least 2 blood pressure measurements spaced 1 to 2 minutes apart and additional measurements if the first 2 are quite different (Appendix 8). Record the average blood pressure on the vital sign eCRF.

The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs eCRF.

9.2.3.3 Electrocardiograms (ECGs)

Subject must be in 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 most recumbent position as possible. The ECG must include the following measurements: heart rate, QRS, QT, QTc, and PR intervals.

The primary investigator 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.

Electrocardiograms will be required in all subjects at screening and may be repeated more often, if clinically indicated.

9.2.3.4 Other Safety

9.2.3.4.1 Echocardiogram

All subjects will have a baseline transthoracic ECHO (TTE) or MUGA during screening, including assessments of systolic and diastolic left ventricular function and right ventricular function. Echocardiograms are to be repeated every 6 months (± 2 weeks), at the end of study, and/or if clinically indicated. An ECHO

must be performed within 72 hours of the onset of a suspected cardiac failure event.

9.2.3.4.2 Hepatitis B

All hepatitis testing will be performed locally. All subjects will be tested at screening for HBsAg, anti-HBs, and anti-HBc, unless performed within 6 months of screening and there was no change in the subject's risk factors within these 6 months.

Subjects with no history of HBV infection that are negative for hepatitis serologies at screening should be followed as clinically indicated.

Subjects with positive testing or who have a prior history of HBV infection should have consultation with a specialist in HBV and have HBV DNA testing and monitoring of HBV DNA every 12 weeks ± 2 weeks through end of study visit. Subjects that have received hepatitis B vaccination with only anti-HBs positivity and no clinical signs of hepatitis do not require HBV DNA monitoring.

Any subject who becomes HBV DNA positive or develops reactivation of HBV will have study treatment interrupted and received appropriate anti-viral treatment as per a specialist in hepatitis B. Resumption of clinical study treatment may be considered in subjects whose HBV reactivation is controlled and where the benefits of clinical study treatment outweigh the risks. After cessation of study treatment for any reason, any ongoing monitoring and anti-viral treatment should be under the guidance of a specialist in HBV.

9.2.4 Clinical Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event eCRF. The investigator must determine 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 abnormality) are to be recorded as the adverse event.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities.

9.2.4.1 Pregnancy Testing

A high sensitive (urine or serum) pregnancy test should be completed at screening (within 10 to 14 days of initiation of investigational product) and a urine pregnancy test within 24 hours prior to initiation of investigational product for females of childbearing potential.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Worksheet, see Figure 12-2). Refer to Appendix 5 for contraceptive requirements and Table 12-2 for lenalidomide-specific contraception requirements.

Additional pregnancy testing should be performed within 24 hours prior to day 1 of each subsequent cycle and 30 days after the last dose of protocol-required therapies.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

10. Statistical Considerations

10.1 Sample Size Determination

Approximately 100 subjects with previously treated RRMM will be enrolled as directed by the Indian Regulatory Authority.

A total of 100 subjects is large enough, with 95% confidence, to rule out an adverse event incidence rate greater than 3.6% if none is observed.

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

The primary analysis of safety and efficacy will be performed on the Safety Analysis Set. The Safety Analysis Set will include all subjects who received at least 1 dose of the investigational product.

10.2.2 Covariates

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

10.2.3 Subgroups

The baseline covariates will be explored if appropriate to examine safety and efficacy in subgroups.

10.2.4 Handling of Missing and Incomplete Data

Subjects may have missing data points for a variety of reasons. The procedures outlined below describing what will be done when data are missing may be refined during the review of the data.

Incomplete adverse event start dates, concomitant medications start or stop dates, and death date will be imputed and the detailed rules will be specified in statistical analysis plan (SAP). No imputation will be done for the primary analysis of the primary and key secondary endpoints.

Details of missing data analysis and imputation rules will be described in SAP.

10.3 Statistical Analyses

The SAP will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 5.3.1.

10.3.1 Planned Analyses

10.3.1.1 Primary Analysis

The primary analysis will occur when the last subject enrolled has had the opportunity to receive the study treatment for at least 9 months.

10.3.1.2 Final Analysis

The final analysis will occur when last subject completes the last assessment in the study (last subject last visit) or a study duration up to 3 years, whichever occurs earlier.

10.3.2 Methods of Analyses

10.3.2.1 General Considerations

In general, summaries of all data will be presented mainly by overall safety analysis set and also by different regimens, including Kd and KRd.

Summary statistics will be provided for selected endpoints. For continuous variables, the number of subjects with non-missing data (n), mean, standard deviation, median, minimum, and maximum will be presented. For categorical data, the frequency and percent distribution will be presented. Time to event endpoints will be summarized with Kaplan-Meier (KM) curves, KM proportions at select time points, KM quartiles (when estimable), the number of subjects with events, the number of subjects censored, and the pattern of censoring. Point estimates for efficacy endpoints will be accompanied by 2-sided 95% confidence intervals including estimates of KM quartiles

(Klein and Moeschberger, 1997), KM proportions (Kalbfleisch and Prentice, 1980), and binomial proportions (Clopper and Pearson, 1934).

10.3.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Not Applicable
Secondary	Secondary efficacy endpoints include PFS, ORR, CBR, TTR, and DOR. PFS is defined as the time from first dose of the study treatment until the earliest date of disease progression or death due to any cause, whichever is the earliest. Subjects alive who did not have progression will be censored at last date of tumor assessment. If the last disease assessment date is after the date that triggers the analysis, the subject will be censored at the analysis trigger date. PFS will be summarized descriptively using with the KM method. ORR is defined as the proportion of subjects with either best overall response of sCR, CR, VGPR, or PR. CBR is defined as the proportion of subjects with either best overall response of sCR, CR, VGPR, PR, or MR. The point estimates of ORR and CBR will be summarized along with exact binomial 95% confidence intervals. TTR and DOR are calculated only for the responders. TTR is defined as the time from first dose of study treatment to the earliest date a response of PR or better is first achieved and subsequently confirmed. DOR is defined as the time from initial response (sCR, CR, VGPR, or PR) to the date of disease progression. A subject who did not have progression of disease, or death will be censored at last tumor assessment date. If the last disease assessment date is after the date that triggers the analysis, the subject will be censored at the analysis trigger date. TTR will be summarized descriptively. KM method will be used to analyze DOR.
Exploratory	Not applicable

10.3.2.3 Safety Analyses

10.3.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	The subject incidence, severity, and outcome of treatment emergent adverse events using NCI CTCAE v. 4.03 including clinical significant laboratory parameter changes over time. Each reported adverse event term will be mapped to a Preferred Term and a System Organ Class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are defined as adverse events that start on or after the first day of study treatment and within 30 days of the last day of study treatment. Treatment-emergent adverse events will be summarized based on the number (%) of subjects experiencing events by MedDRA SOC and preferred term. The denominator for the percentage will be based on the number of subjects in the Safety population. A subject reporting the same treatment-emergent adverse event more than once will be counted only once when calculating 1) within a given SOC, and 2) within a given SOC and preferred term combination. For such cases, the maximum NCI; US - CTCAE 4.03 toxicity grade and strongest causal relationship to study treatment for the event will be used in the incidence calculations. Treatment-emergent adverse events will also be summarized by severity, seriousness, and by relationship to study treatment.

10.3.2.3.2 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class, preferred term, and severity grade. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol required therapies, and significant treatment-emergent adverse events will also be provided.

10.3.2.3.3 Laboratory Test Results

The analyses of safety laboratory endpoints will include summary statistics over time by treatment group. Changes will be calculated relative to the baseline visit. Shifts in grades of safety laboratory values between the baseline and the worst on-study value will be tabulated by treatment group.

10.3.2.3.4 Vital Signs

The analyses of vital signs will include summary statistics at selected time points by treatment group. Changes will be calculated relative to the baseline visit. Shifts in vital sign values between the baseline and the worst on-study value will be tabulated by treatment group.

10.3.2.3.5 Physical Measurements

The analyses of physical measurements will include summary statistics at scheduled time points by treatment group. Changes will be calculated relative to the baseline visit.

10.3.2.3.6 Electrocardiogram

The 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 QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials.

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters.

10.3.2.3.7 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to Kyprolis. The number of cycles will be summarized with an additional breakdown of the number of cycles completed, discontinued, and re-started. In addition, the duration of therapy, the cumulative dose, and the percent of intended dose will be summarized by cycle and overall. The number and percent of subjects with dose modifications (eg, dose changes and dose interruptions) and reason for modification will be summarized.

Descriptive statistics will be produced to describe the exposure to non-Amgen non-investigational products (dexamethasone and/or lenalidomide). The cumulative dose, number of cycles, duration of usage, number and percentage of subjects with dose modifications, reasons for modification will be summarized using descriptive statistics.

10.3.2.3.8 Exposure to Other Protocol-required Therapy

Descriptive statistics of average daily dose and duration of usage will be produced to describe the exposure to other protocol-required therapies by treatment group.

10.3.2.3.9 Exposure to Concomitant Medication

Number and proportion of subjects receiving concomitant medications will be summarized by preferred term or category as coded by the World Health Organization Drug (WHODRUG) dictionary.

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WHO Fact Sheet: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx

12. Appendices

Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ANC	absolute neutrophil count
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BSA	body surface area
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CR	complete response
CrCl	creatinine clearance
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eCRF	electronic case report form
ESC	European Society of Cardiology
ESH	European Society of Hypertension
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early
End of Study (end of trial)	defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
eSAE	electronic serious adverse event
FCBP	females of childbearing potential
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
anti-HBc	**Hepatitis B core antibody**
anti-HBs	**Hepatitis B surface antibody**
HBsAg	**Hepatitis B surface antigen**
HBV	**hepatitis B virus**

Abbreviation or Term	Definition/Explanation
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HRT	hormonal replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IMiD	immunomodulatory agent
IMWG-URC	International Myeloma Working Group-Uniform Response Criteria
IPIM	Investigational Product Instruction Manual
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
IV	intravenous
IxRS	Interactive Voice/Web Response System
Kd	Kyprolis in combination with dexamethasone
KM	Kaplan-Meier
KRd	Kyprolis in combination with lenalidomide plus dexamethasone
MedDRA	Medical Dictionary for Regulatory Activities
MR	minimal response
MUGA	multigated acquisition scan
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PN	peripheral neuropathy
PO	orally
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes
POR	proof of receipts
PR	partial response
QTc	corrected QT interval
RBC	red blood cell
RRMM	relapsed or refractory multiple myeloma

Abbreviation or Term	Definition/Explanation
SAg	surface antigen
SAP	statistical analysis plan
SBECD	sulfobutylether beta-cyclodextrim sodium
sCR	stringent complete response
SD	stable disease
SFLC	serum free light chains
SOC	system organ class
SPEP	serum protein electrophoresis
SPD	maximal perpendicular diameter
SUSAR	suspected unexpected serious adverse reaction
sWFI	sterile water for injection
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
TTE	transthoracic echocardiogram
TTR	time to response
ULN	upper limit of normal
UPEP	urine protein electrophoresis
US FDA	United States Food and Drug Administration's
VGPR	very good partial response
WHODRUG	World Health Organization Drug

Appendix 2. Clinical Laboratory Tests

All laboratory tests detailed in Table 12-1 will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 6.1 to 6.2.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Evaluation of lab results for dose determination as required per Schedule of Assessments must be documented prior to dosing in each cycle. Any local lab values that lead to dose modification decisions must be recorded in the electronic case report form (eCRF). Any local lab results that fulfill ≥ grade 3 values per CTCAE must be recorded in the eCRF. For cycle 1 day 1, hematology and serum chemistry panel from screening may be used if within 14 days of day 1. For subsequent visits in cycle 1, hematology and chemistry may be completed up to 72 hours prior to scheduled dose weekly for cycle 1. Starting in cycle 2, only day 1 is required.

Table 12-1. Analyte Listing

Chemistry	Coagulation	Hematology	Other Labs
Amylase (screening only) Lipase (screening only) Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Calcium corrected (if albumin < 4) Magnesium Phosphorus Glucose BUN or Urea Creatinine Creatinine clearance (CrCl) Uric acid Total bilirubin Direct bilirubin ALP LDH AST (SGOT) ALT (SGPT)	PT PTT/INR (aPTT or PTT)	Circulating plasma cells (screening only) RBC count Hemoglobin Hematocrit Platelet count WBC count with differential: • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	Serum or highly sensitive urine pregnancy **NTproBNP[a]** **BNP[a]** **CK2[b]** **CPKMB[b]** **Troponin I[b]** **Troponin T[b]** **Hepatitis B serologies (HBsAg, anti-HBs, and anti-HBc)[c]** **HBV DNA[d]**

ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; **BNP = b-type natriuretic peptide**; BUN = blood urea nitrogen; **CK2 = creatine kinase 2; CPKMB = creatine kinase-muscle/brain; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus**; INR = international normalized ratio; LDH = lactate dehydrogenase; **NTproBPN = N-terminal pro b-type natriuretic peptide**; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell count.

[a] NTproBNP is only required at screening and BNP can be recorded if NTproBNP is not available.

[b] As clinically indicated.

[c] Testing is required for all subjects at screening unless obtained within 6 months of screening and there was no change in the subject's risk factors within these 6 months.

[d] If prior history of HBV infection obtain HBV DNA at screening and every 12 weeks through safety follow-up. Subjects that have received hepatitis B vaccination with only anti-HBs positivity and no clinical signs of hepatitis do not require HBV DNA monitoring.

Appendix 3. Study Governance Considerations

Data Monitoring Committee(s)

Not applicable.

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of written approval for study protocol issued by Health Authority and a copy of the written approval of the protocol and ICF issued by the IRB/IEC must be received from the investigator, by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. 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 must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- 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 must be sent to Amgen

- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the US Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Informed Consent Process

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

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

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 unless it is a local requirement. The investigator shall then inform the primary care physician. 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 ICF is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 8.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

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 ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

Data Protection/Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the electronic case report form (eCRF) demographics page, in addition to the unique subject identification number, include the age at 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 age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed ICFs) are to be kept in confidence by the investigator, except as described below.

In compliance with 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 such individuals to have access to his/her study-related records, including personal information.

Publication Policy

To coordinate dissemination of data from this study, the investigator will obtain input and assistance from Amgen staff as appropriate.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors (ICMJE 2013) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states:

Authorship credit is to 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; 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 need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must 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 must qualify for authorship, and all those who qualify are to be listed.

Each author must 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 review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter 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

Data Quality Assurance

All subject data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

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.

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.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research & Development 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.

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

eCRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

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

Source Documents

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 eCRFs will be included on the Amgen Delegation of Authority Form.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Source documents are original documents, data, and records from which the subject's eCRF 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. Source documents may also include data captured in the Interactive Voice/Web Response System (IxRS) system (if used, such as subject ID and randomization number) and eCRF entries if the eCRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The

investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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 ICFs, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy 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), and/or medical device(s) or combination product(s) documentation, as applicable

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

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

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(s) 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 the product(s) is/are available commercially.

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.

Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, echocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • 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. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording
• When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant adverse event/serious adverse event information in the Event electronic case report form (eCRF). – Additionally, the investigator is required to report a fatal disease-related event on the Event eCRF. • 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 (or toxicity defined below); – Assessment of relatedness to investigational product, and – Action taken. • If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Event eCRF. • It is not acceptable for the investigator to send photocopies of the subject's medical records to Amgen in lieu of completion of the Event eCRF page. • If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity
The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on: The Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 which is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Assessment of Causality
• The investigator is obligated to assess the relationship between investigational product, protocol-required therapies, and each occurrence of each adverse event/serious adverse event. • Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality. • There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data. • The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. • The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed Event eCRF. • The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the EDC system via the Safety Report Form. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an electronic Serious Adverse Event (eSAE) Contingency Report Form (see Figure 12-1) within 24 hours of the investigator's knowledge of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on the eSAE Contingency Report Form (see Figure 12-1).

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Report Form

AMGEN Study # 20160372 Carfilzomib (Kyprolis) for Injection 60mg/vial	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

<<For completion by COM prior to providing to sites: + 91 22 6786 9146 / 6786 9138

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? <Device> 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 #
<<IP/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____

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AMGEN Study # 20160372 Carfilzomib (Kyprolis) for Injection 60mg/vial	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

								☐ Unavailable / Unknown

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:

Test / Unit / Date (Day Month Year)											

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 # 20160372 Carfilzomib (Kyprolis) for Injection 60mg/vial	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for male and female of childbearing potential are outlined in Section 6.2. For subjects receiving Kyprolis in combination with lenalidomide plus dexamethasone (KRd) triplet therapy, see Table 12-2 for lenalidomide-specific contraceptive guidelines.

Male and female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant or father a child during treatment, during treatment interruptions, and for:

- female subjects: 30 days after the last dose of Kyprolis
- male subjects: 90 days after the last dose of Kyprolis

Kyprolis could decrease the effectiveness of oral contraceptives. The investigator should notify subjects of this risk when choosing the methods of birth control.

Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use highly effective methods of contraception and for an increased length of time. In addition, male subjects may also be required to use contraception. The investigator must discuss these contraceptive changes with the subject. For subjects receiving KRd triplet therapy, see Table 12-2 for lenalidomide-specific contraceptive guidelines.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.

- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

Note: Failure rate of < 1% per year when used consistently and correctly.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system (IUS)
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Contraception Methods for Male Subjects

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with protocol-required therapies; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- Use a condom during treatment and for an additional 90 days after the last dose of protocol-required therapies

The female partner should consider using an acceptable method of effective contraception such as: hormonal, IUD, IUS, female barrier method (diaphragm, cap,

sponge [a female condom is not an option because there is a risk of tearing when both partners use a condom]).

Note: If the male's sole female partner is of non-childbearing potential or has had a bilateral tubal ligation/occlusion, he is not required to use additional forms of contraception during the study.

Unacceptable Methods of Birth Control for Male and Female Subjects

Birth control methods that are considered unacceptable in clinical trials include:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 30 days after last dose of protocol-required therapies.
- Information will be recorded on the Pregnancy Notification Worksheet (see Figure 12-2). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 30 days after last dose of the study drug. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.

- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 8.1 for details).

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

- In the event a male subject fathers a child during treatment, and for an additional 90 days after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see Figure 12-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws.)
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 30 days after last dose of protocol-required therapies.
- Information will be recorded on the Lactation Notification Worksheet (Figure 12-2) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.

- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion (See Section 6.2).
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 30 days after last dose of protocol-required therapies after discontinuing protocol-required therapies.

Table 12-2. Lenalidomide: Contraceptive Guidelines and Collection of Pregnancy and Lactation Information

Risks Associated with Pregnancy (For the region specific use of lenalidomide, please refer to the regional label)
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryo fetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.
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 a female of childbearing potential, lenalidomide is contraindicated unless all of the following are met (ie, all females of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy): • She understands the potential teratogenic risk to the unborn child • She understands the need for effective contraception, without interruption, 4 weeks 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

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Table 12-2. Lenalidomide: Contraceptive Guidelines and Collection of Pregnancy and Lactation Information

Counseling (Continued)

- She understands the need to commence the study treatment as soon as study drug 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 lenalidomide

The investigator must ensure that for females of childbearing potential:

- Complies 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, lenalidomide is contraindicated unless all of 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 lenalidomide study therapy):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide
- Traces of lenalidomide have been found in semen. Male subjects taking lenalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):
  - Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female 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 pregnant female or a female of childbearing potential.

Contraception

FCBP enrolled in this protocol must agree to use 2 reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact 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. 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:

- IUD
- Hormonal (birth control pills, injections, implants)
- Tubal ligation
- Partner's vasectomy

Table 12-2. Lenalidomide: Contraceptive Guidelines and Collection of Pregnancy and Lactation Information

Contraception (Continued)
Additional effective methods:
• Male condom **or female condom, with or without spermicide** • Diaphragm **with spermicide** • Cervical Cap **with spermicide** 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 Lenalidomide
Female Subjects • FCBP must have 2 negative pregnancy tests (combined sensitivity of at least 50 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the Investigator has verified that the results of these pregnancy tests are negative. • Will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure. • Must agree to abstain from donating blood during study participation and for at least 28 days after discontinuation from the study. Male Subjects • Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy. • Will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure. • Must agree to abstain from donating blood, semen, or sperm during study participation and for at least 28 days after discontinuation from the study.

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Table 12-2. Lenalidomide: Contraceptive Guidelines and Collection of Pregnancy and Lactation Information

During Study Participation and for 28 Days Following Discontinuation From the Study

Female Subjects

- FCBP 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 discontinuation from the study. 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 discontinuation from the study.
- In addition to the required pregnancy testing, the Investigator must confirm with FCBP that she is continuing to use 2 reliable methods of birth control at each visit.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days and at the time that lenalidomide treatment is discontinued. During counseling, subjects must be reminded to not share study drug and to not donate blood.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after discontinuation from the study.
- If pregnancy or a positive pregnancy test does occur in a study subject, study drug must be immediately discontinued.

Male Subjects

- Counseling about the requirement for latex condom use during sexual contact with females of childbearing potential and the potential risks of fetal exposure must be conducted at a minimum of every 28 days and at the time that lenalidomide treatment is discontinued. During counseling, subjects must be reminded to not share study drug and to not donate blood, sperm, or semen.
- 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 study doctor at the end of treatment.
- Female subjects should not donate blood during therapy and for at least 28 days following discontinuation of study drug.
- Male subjects should not donate blood, semen or sperm during therapy or for at least 90 days following discontinuation of study drug.
- Only enough study drug for 1 cycle of therapy may be dispensed with each cycle of therapy.

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Figure 12-2. Pregnancy and Lactation Notification Worksheet

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

FAX# +91 22 6786 9146 / 6786 9138

1. Case Administrative Information

Protocol/Study Number: 20160372

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# enter fax number

1. Case Administrative Information

Protocol/Study Number: 20160372

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
Kyprolis (carfilzomib)				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No
If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____
Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No
If No, provide stop date: mm_____/dd_____/yyyy_____
Infant date of birth: mm_____/dd_____/yyyy_____
Infant gender: ☐ Female ☐ Male
Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

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

Form Completed by:
Print Name: _____ **Title:** _____
Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2.

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Appendix 6. Sample Storage and Destruction

Not applicable.

Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments

Please refer to Sections **7.1.2.1, 7.1.2.2, and** 7.4.1.1 for details regarding dose modification and toxicity.

Appendix 8. 2013 ESH/ESC Office Blood Pressure Measurement

Table 5 Office blood pressure measurement

When measuring BP in the office, care should be taken:
• To allow the patients to sit for 3–5 minutes before beginning BP measurements.
• To take at least two BP measurements, in the sitting position, spaced 1–2 min apart, and additional measurements if the first two are quite different. Consider the average BP if deemed appropriate.
• To take repeated measurements of BP to improve accuracy in patients with arrhythmias, such as atrial fibrillation.
• To use a standard bladder (12–13 cm wide and 35 cm long), but have a larger and a smaller bladder available for large (arm circumference >32 cm) and thin arms, respectively.
• To have the cuff at the heart level, whatever the position of the patient.
• When adopting the auscultatory method, use phase I and V (disappearance) Korotkoff sounds to identify systolic and diastolic BP, respectively.
• To measure BP in both arms at first visit to detect possible differences. In this instance, take the arm with the higher value as the reference.
• To measure at the first visit, BP 1 and 3 min after assumption of the standing position in elderly subjects, diabetic patients, and in other conditions in which orthostatic hypotension may be frequent or suspected.
• To measure, in case of conventional BP measurement, heart rate by pulse palpation (at least 30 s) after the second measurement in the sitting position.

BP = blood pressure.

Appendix 9. Guidelines for Documenting Prior Treatment

Subjects must have documented relapse after at least 1, but no more than 3 prior treatment regimens or lines of therapy for multiple myeloma. When documenting prior treatments for multiple myeloma, the following guidelines should be used:

- A new line of therapy is considered to start when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of lack of adequate response, progressive disease (PD) (even if the level of progression has not yet met International Myeloma Working Group-Uniform Response Criteria [IMWG-URC] for PD), relapse, or toxicity.
- An increase in dose of therapy, with the intention of recapturing response in a patient who has evidence of progression on that therapy, is considered a new therapy.
- A new line of therapy is also considered to start when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.
- Examples of 1 line of therapy include:
  - Induction therapy and stem cell transplant followed by planned maintenance therapy (provided there is no intervening PD)
  - Induction therapy followed by maintenance therapy (provided there is no intervening PD)
- Documentation of at least partial response (PR) to at least 1 prior therapy

Appendix 10. ECOG Performance Scale

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

ECOG = Eastern Cooperative Oncology Group.
Source: Oken et al, 1982.
Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair

Appendix 11. International Uniform Response Criteria for Multiple Myeloma

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

Response Subcategory	Multiple Myeloma Response Criteria
sCR	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow and • Normal SFLC ratio and • Absence of clonal plasma cells in bone marrow by immunohistochemistry or 2- to 4-color FC
CR	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow • In patients with measurable disease only by SFLC, normal SFLC ratio
VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-component with urine M-component < 100 mg per 24 hours • In patients with measurable disease only by SFLC, a decrease ≥ 90% in the difference between involved and uninvolved FLC levels
PR	• ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours (if both are measurable at baseline) • In patients with measurable disease only by SFLC, a decrease ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • If the serum and urine M-protein are not measurable, and SFLC assay is also not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥ 30%. • In addition to the above criteria, if present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.
MR	• ≥ 25% but ≤ 49% reduction of serum M-protein and reduction in 24-hour urinary M-protein by 50% to 89%. In addition to the above listed criteria, if present a baseline a ≥ 50% reduction in the size (SPD) of soft tissue plasmacytoma is required
Stable Disease	• Not meeting criteria for CR, VGPR, PR, or PD

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Footnotes defined on the next page of the table.

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

Response Subcategory	Multiple Myeloma Response Criteria
PD	• Increase of 25% from lowest response value in one or more of the following: – Serum M-component (absolute increase must be ≥ 0.5 g/dL) and/or – Urine M-component (absolute increase must be ≥ 200 mg per 24 hours) and/or – Only in patients without measurable serum and urine M protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) – Only in patients without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute percentage must be ≥ 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.75 mmol/L) attributed solely to the plasma cell proliferative disorder

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CR = complete response; FC = flow cytometry; FLC = free light chain; IMWG-URC = International Myeloma Working Group-Uniform Response Criteria MR = minimal response; PD = progressive disease; PR = partial response; sCR = stringent complete response; SFLC = serum free light chain; SPD = maximal perpendicular diameter; VGPR = very good partial response.

All response categories (complete response [CR], stringent complete response [sCR], very good partial response [VGPR], partial response [PR]) require 2 consecutive assessments made at any time before the initiation 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.

For sCR: presence/absence of clonal cells is based upon the kappa lambda. "Measurable" disease is defined by at least 1 of serum protein electrophoresis (SPEP) ≥ 0.5 g/dL, urine protein electrophoresis (UPEP) ≥ 200 mg per 24 hours, or in subjects without detectable serum or urine M-protein, serum free light chain (SFLC) > 100 mg/L (involved light chain) and an abnormal kappa lambda ratio.

Determination of progressive disease (PD) 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 nadir M-component is ≥ 5 g/dL.

Plasmacytomas: A definite increase in the size is defined as a ≥ 50% increase from nadir as measured serially by the sum of the products of the maximal perpendicular diameter (SPD) of the measurable lesion or a ≥ 50% increase in the longest diameter of a previous lesion with ≥ 1 cm short axis. 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. The requirement for bi-directional measurements applies only to plasmacytomas.

Sources: Kumar et al, 2016; Rajkumar et al, 2011; Durie et al, 2006.

Appendix 12. Corticosteroid Dose Equivalents

Equivalent Dose (mg)	Steroid
1.5	dexamethasone (long-acting)
8	methylprednisolone (intermediate-acting)
10	prednisone (intermediate-acting)
10	prednisolone (intermediate-acting)
40	hydrocortisone (short-acting)

Superseding Amendment 1

Protocol Title: Post-marketing Phase 4 Study to Evaluate Safety, Tolerability, and Efficacy of Kyprolis® (Carfilzomib) in Indian Patients With Relapsed or Refractory Multiple Myeloma: A Prospective, Open-label, Non-comparative, Multicenter Study

Amgen Protocol Number (carfilzomib) 20160372

Amendment Date:	08 October 2019
Superseding Amendment Date:	29 October 2019

Superseding Amendment 1 Rationale: Superseding amendment 1 has been issued to correct a shift in eligibility criteria numbering introduced in Amendment 1. The correction is required to avoid extensive reprogramming in IVRS and RAVE systems. Exclusion criterion 216, per protocol amendment 1, has been corrected to exclusion criterion 233 and all other exclusion criteria have reverted back to the original criteria numbers as was presented in the original protocol.

Amendment 1 Rationale:

The protocol is amended to:

- Hepatitis B testing (hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody) has been expanded to include all subjects that do not already have a prior medical history of hepatitis B or who have not had testing within the previous 12 weeks. Guidance has been provided regarding HBV DNA testing and monitoring for subjects with positive hepatitis B serology or a prior history of HBV. In addition, guidance has been provided on the prophylaxis of HBV reactivation in patients at risk.
- Implement ECHO assessments every 6 months, EOS, and/or if clinically indicated. An ECHO must be performed within 72 hours of the onset of a suspected cardiac failure.
- Removed Self-Evident Corrections as they are no longer completed by DM per change in Amgen processes.
- Removed Adjusted calcium from lab analyte chart (redundant with Calcium corrected [if albumin < 4]). Added NTproBNP, BNP, CK2, CKMB, Troponin I, and Troponin T to lab analyte chart
- Added clarification around dose adjustments required for change of body weight > 20%.
- Added clarification around concomitant short- and long-term corticosteroid use.
- Added clarification around Intravenous Pre-hydration use.

Description of Changes:

Section: Global

Change: Minor corrections (eg, correcting typographical and formatting errors) have been introduced throughout the protocol.

Section: Global

Change: Version date has been updated from 09 June 2017 to **29 October 2019**

Section: Title Page

Add: **Amendment 1 08 October 2019**

Add: Superseding Amendment 1 29 October 2019

Section: Synopsis, Procedures

Replace: Informed consent must be obtained before starting any screening procedure. The following procedures will occur per the Schedule of Assessments: demographics, medical/surgical history, physical measurements, vital signs, ECG, ECOG performance status, ECHO/multigated acquisition (MUGA) scan, review of adverse event/serious adverse event, concomitant medications, and review of disease status. Laboratory assessments will include pregnancy testing, coagulation tests, and hematology and chemistry tests.

With: Informed consent must be obtained before starting any screening procedure. The following procedures will occur per the Schedule of Assessments: demographics, medical/surgical history, physical measurements, vital signs, ECG, ECOG performance status, ECHO/multigated acquisition (MUGA) scan, review of adverse event/serious adverse event, concomitant medications, and review of disease status. Laboratory assessments will include pregnancy testing, coagulation tests, hematology, chemistry tests, **and other analytes specified in Table 12-1.**

Section: 2.2 Schedule of Activities, Table 2-1. Schedule of Activities

Replace:

Procedure	SCR[a]	Treatment Period Days (All Cycles) 1	2	8	9	15	16	22	End of Study Visit[b]	Notes
General and Safety Assessments										
Informed consent	X									
Inclusion and exclusion criteria	X									
Demographic data	X									
Medical/surgical history	X									Including multiple myeloma history
Physical measurements: height	X									
Physical measurements: weight, BSA	X	X								BSA should be calculated per institutional standard and utilized to calculate required study drug doses. BSA should be recalculated if there is 20% change in body weight.
Physical examination	X	X							X	C1D1: Screening exam may be used if within 7 days prior to C1D1.
ECG	X								X	
Vital signs: Kd arm (all cycles) and KRd arm (cycles 1-12)	X	X	X	X	X	X	X		X	Checked prior to administration of study drug in all cycles.
Vital signs: KRd arm (cycle 13+)		X	X			X	X		X	Checked prior to administration of study drug in all cycles.
ECOG performance status	X								X	
ECHO/MUGA scan	X									

Footnotes and abbreviation definitions are after last page of table.

Procedure	SCR[a]	Treatment Period Days (All Cycles) 1	2	8	9	15	16	22	End of Study Visit[b]	Notes
Review of AE/SAE	Continually									
Concomitant medications	Continually									Will be collected from 30 days prior to signing of informed consent to 30 days after last dose of study treatment.
Review of disease status	Performed per local standards									Disease status will be evaluated by the investigator using IMWG-URC starting from screening until EOT.
Laboratory Assessments										
Serum or urine pregnancy test (FCBP)[c]	X	X							X	Must be confirmed negative at screening, on day 1 of each cycle prior to dosing, and at end of study visit.
Additional serum or urine pregnancy test (KRd-treated FCBP only)[d]: Cycle 1		X[e]		X		X		X		Weekly pregnancy tests required during cycle 1. See Table 12-2 for additional information on lenalidomide-specific pregnancy testing requirements.
Coagulation tests	X									
Hematology	X	X		(X)		(X)				C1D1: Results from screening may be used if taken within 14 days prior to C1D1. (X): Day 8 and 15 samples only collected during cycle 1.
Chemistry	X	X		(X)		(X)				

AE = adverse events; BSA = body surface area; CXDX = cycle X day X; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; FCBP = female of child bearing potential; IMWG-URC = International Myeloma Working Group-Uniform Response Criteria; MUGA = multigated acquisition scan; SAE = serious adverse event; SCR = screening.

[a] Screening: up to 28 days before enrollment

[b] End of study visit is 30 days (+ 3) after last dose of Kyprolis

[c] Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.

[d] The subject may not receive lenalidomide until the investigator has verified that the results of these pregnancy tests are negative.

[e] KRd-treated FCBP must have 2 negative pregnancy tests (combined sensitivity of at least 50 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. 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 discontinuation from the study.

With:

Procedure	SCR[a]	Treatment Period Days (All Cycles) 1	2	8	9	15	16	22	End of Study Visit[b]	Notes
General and Safety Assessments										
Informed consent	X									
Inclusion and exclusion criteria	X									
Demographic data	X									
Medical/surgical history	X									Including multiple myeloma history
Physical measurements: height	X									
Physical measurements: weight, BSA	X	X								BSA should be calculated per institutional standard and utilized to calculate required study drug doses. BSA should be recalculated if there is > 20% change in body weight.
Physical examination	X	X							X	C1D1: Screening exam may be used if within 7 days prior to C1D1.
ECG	X								X	
Vital signs: Kd arm (all cycles) and KRd arm (cycles 1-12)	X	X	X	X	X	X	X		X	Checked prior to administration of study drug in all cycles.
Vital signs: KRd arm (cycle 13+)		X	X			X	X		X	Checked prior to administration of study drug in all cycles.
ECOG performance status	X								X	

Footnotes and abbreviation definitions are after last page of table.

Procedure	SCR[a]	Treatment Period Days (All Cycles) 1	2	8	9	15	16	22	End of Study Visit[b]	Notes
ECHO/MUGA scan	X								**X**	**Repeated ECHO every 6 months (± 2 weeks) from C1D1 until end of study visit, or if clinically indicated. An ECHO must be performed within 72 hours of the onset of a suspected cardiac failure event.**
Review of AE/SAE	Continually									
Concomitant medications	Continually									Will be collected from 30 days prior to signing of informed consent to 30 days after last dose of study treatment.
Review of disease status	Performed per local standards									Disease status will be evaluated by the investigator using IMWG-URC starting from screening until EOT.
Laboratory Assessments										
Serum or urine pregnancy test (FCBP)[c]	X	X							X	Must be confirmed negative at screening, on day 1 of each cycle prior to dosing, and at end of study visit.
Additional serum or urine pregnancy test (KRd-treated FCBP only)[d]: Cycle 1		X[e]		X		X		X		Weekly pregnancy tests required during cycle 1. See Table 12-2 for additional information on lenalidomide-specific pregnancy testing requirements.
Coagulation tests	X									
Hematology	X	X		(X)		(X)				C1D1: Results from screening may be used if taken within 14 days prior to C1D1. (X): Day 8 and 15 samples only collected during cycle 1.
Chemistry	X	X		(X)		(X)				
NTproBNP	**X**									

Footnotes and abbreviation definitions are after last page of table.

Procedure	SCR[a]	Treatment Period Days (All Cycles) 1	2	8	9	15	16	22	End of Study Visit[b]	Notes
Hepatitis B Virus (HBV)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**Local serology testing for HBsAg, anti-HBs, and anti-HBc. Testing is required:** • **For subjects with a prior history of HBV infection at screening and HBV DNA testing every 12 weeks ± 2 weeks through end of study visit.** • **For all other subjects at screening unless obtained within 6 months of screening and there was no change in the subject's risk factors within these 6 months.** • **For subjects positive at screening, who become positive for serology during treatment, or who are at risk of becoming positive, HBV DNA testing will be performed every 12 weeks ± 2 weeks (and as clinically indicated) through end of study visit.** **A specialist should be consulted for all subjects who test positive for HBV serology. Subjects who have received Hepatitis B vaccination with only anti-HBs positivity and no clinical signs of hepatitis do not require HBV DNA monitoring.**

AE = adverse events; **BNP = b-type natriuretic peptide**; BSA = body surface area; CXDX = cycle X day X; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; FCBP = female of child bearing potential; **anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus**; IMWG-URC = International Myeloma Working Group-Uniform Response Criteria; MUGA = multigated acquisition scan; **NTproBNP = N-terminal pro b-type natriuretic peptide**; SAE = serious adverse event; SCR = screening.

[a] Screening: up to 28 days before enrollment

[b] End of study visit is 30 days (+ 3) after last dose of Kyprolis

[c] Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.

[d] The subject may not receive lenalidomide until the investigator has verified that the results of these pregnancy tests are negative.
[e] KRd-treated FCBP must have 2 negative pregnancy tests (combined sensitivity of at least 50 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. 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 discontinuation from the study.

Section: 6.2 Exclusion Criteria

Add:

233 Active hepatitis B virus (HBV) infection. Subjects with positive hepatitis B surface antigen (HBsAg) or core antibody (anti-HBc) that achieve sustained virologic response with antiviral therapy directed at hepatitis B are allowed. Subjects with known history or resolved infection (negative for HBsAg but positive for antibodies to surface antigen, and/or core antigen) must be screened with HBV DNA levels. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (hepatitis B surface antibody [anti-HBs] positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA.

Section: 6.2 Exclusion Criteria

Delete:

216 Known human immunodeficiency virus (HIV) infection, hepatitis C infection (subjects with hepatitis C that achieve a sustained virologic response following antiviral therapy are allowed), ~~or hepatitis B infection (subjects with hepatitis B surface antigen [SAg] or core antibody that achieve sustained virologic response with antiviral therapy directed at hepatitis B are allowed)~~

Section: 7.1.1 Investigational Products, Table 7-1. Study Treatments

Replace:

Study Treatment Name	Amgen Investigational Product:[a] Kyprolis
Dosage Formulation	Supplied as a sterile, lyophilized, white to off-white powder, ready for reconstitution. It is supplied for single use in 50 mL Type 1 glass vials containing 60 mg of Kyprolis drug product with an elastomeric stopper and flip-off lid. Upon reconstitution with preservative-free sterile water for injection (sWFI), the reconstituted solution contains 2 mg/mL Kyprolis, sulfobutylether beta-cyclodextrim sodium (SBECD), and citrate buffer. Kyprolis is supplied in labelled cartons containing 4 single use vials per carton.
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	10 minute infusion: 20/27 mg/m^2 30 minute infusion: 20/56 mg/m^2
Route of Administration	IV infusion
Accountability	The planned dose (mg/m^2), dose (mg), start date/time, stop date/time, reason for change in planned dose, reason for dose change/withheld, reason for dose delay, and package lot number of Kyprolis is to be recorded on each subject's eCRF(s).
Dosing Instructions	Triplet: See Section 7.1.2.1 Doublet: See Section 7.1.2.2

[a] Kyprolis will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

With:

Study Treatment Name	Amgen Investigational Product:[a] Kyprolis
Dosage Formulation	Supplied as a sterile, lyophilized, white to off-white powder, ready for reconstitution. It is supplied for single use in 50 mL Type 1 glass vials containing 60 mg of Kyprolis drug product with an elastomeric stopper and flip-off lid. Upon reconstitution with preservative-free sterile water for injection (sWFI), the reconstituted solution contains 2 mg/mL Kyprolis, sulfobutylether beta-cyclodextrim sodium (SBECD), and citrate buffer. Kyprolis is supplied in labelled cartons containing 4 single use vials per carton.
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	10 minute infusion: 20/27 mg/m^2 30 minute infusion: 20/56 mg/m^2
Route of Administration	IV infusion
Accountability	The planned dose (mg/m^2), **actual** dose (mg) **administered**, start date/time, stop date/time, reason for change in planned dose, reason for dose change/withheld, reason for dose delay, and package lot number of Kyprolis is to be recorded on each subject's eCRF(s).
Dosing Instructions	Triplet: See Section 7.1.2.1 Doublet: See Section 7.1.2.2

[a] Kyprolis will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

Section: 7.1.2 General Dosing Instructions

Replace: Each subject's first dose of Kyprolis will be calculated based upon baseline body surface area (BSA) per institutional standards. In subjects with BSA of greater than 2.2 m^2, the dose should be capped based on a BSA of 2.2 m^2. The dose for each subject should not be revised unless the subject experiences a > 20% change in body weight in which case the BSA and dose should be recalculated. The recalculated BSA becomes the new baseline. The dose can also be modified in response to toxicity following the dose modification guideline table in local Kyprolis Prescribing Information.

With: Each subject's first dose of Kyprolis will be calculated based upon baseline body surface area (BSA) per institutional standards. In subjects with BSA of greater than 2.2 m^2, the dose should be capped based on a BSA of 2.2 m^2. The dose for each subject should not be revised unless the subject experiences a > 20% change in body weight in which case the BSA and dose should be recalculated**. The recalculated BSA becomes the new baseline. The dose can also be modified in response to toxicity following the dose modification guideline table in local Kyprolis Prescribing Information.**

Section: 7.1.2.1 Kyprolis in Combination With Lenalidomide and Dexamethasone (KRd)

Replace: For the triplet combination with lenalidomide and dexamethasone, Kyprolis will be administered as an infusion over approximately 10 minutes on days 1, 2, 8, 9, 15, and 16 of repeated 28-day treatment cycles. The recommended starting dose of Kyprolis is 20 mg/m^2 on days 1 and 2, and if tolerated, escalated to a target dose of 27 mg/m^2 starting on day 8 of cycle 1 and thereafter. From cycle 13, the day 8 and day 9 doses of Kyprolis will be omitted. After cycle 18, Kyprolis will be discontinued (Table 7-2). Lenalidomide 25 mg is taken orally on days 1 to 21 and dexamethasone 40 mg by mouth or intravenously on days 1, 8, 15, and 22 of the 28-day cycles.

For patients with mild or moderate hepatic impairment, reduce the dose of Kyprolis by 25% (ie, 15 mg/m^2 day 1 and 2 of cycle 1 and 20 mg/m^2 day 8 cycle 1 and thereafter.

With: For the triplet combination with lenalidomide and dexamethasone, Kyprolis will be administered as an infusion over approximately 10 minutes on days 1, 2, 8, 9, 15, and 16 of repeated 28-day treatment cycles. The recommended starting dose of Kyprolis is 20 mg/m^2 on days 1 and 2 **of cycle 1**, and if tolerated, escalated to a target dose of 27 mg/m^2 starting on day 8 of cycle 1 and thereafter. From cycle 13, the day 8 and day 9 doses of Kyprolis will be omitted. After cycle 18, Kyprolis will be discontinued (Table 7-2). Lenalidomide 25 mg is taken orally on days 1 to 21 and dexamethasone 40 mg by mouth or intravenously on days 1, 8, 15, and 22 of the 28-day cycles.

For patients with mild or moderate hepatic impairment, reduce the dose of Kyprolis by 25% (ie, 15 mg/m^2 day 1 and 2 of cycle 1 and 20 mg/m^2 day 8 cycle 1 and thereafter**. If hepatic function returns to normal, the dose may be re-escalated to the intended dose after the first cycle (ie, 27 mg/m^2 in KRd).**

Section 7.1.2.1 Kyprolis in Combination With Lenalidomide and Dexamethasone (KRd) (Paragraph 2)

Replace: For patients with mild or moderate hepatic impairment, reduce the dose of Kyprolis by 25% (ie, 15 mg/m^2 day 1 and 2 of cycle 1 and 20 mg/m^2 day 8 cycle 1 and thereafter.

With: For patients with mild or moderate hepatic impairment, reduce the dose of Kyprolis by 25% (ie, 15 mg/m^2 day 1 and 2 of cycle 1 and 20 mg/m^2 day 8 cycle 1 and thereafter**. If hepatic function returns to normal, the dose may be re-escalated to the intended dose after the first cycle (ie, 56 mg/m^2 in Kd).**

Section 7.1.2.3 Intravenous Prehydration

Replace: Adequate hydration is required prior to each Kyprolis infusion in cycle 1, especially in subjects at high risk of tumor lysis syndrome or renal toxicity. Prehydration will consist of 250 to 500 mL normal saline or other appropriate intravenous (IV) fluid. Thereafter, Kyprolis prehydration should continue only if the subject's condition and/or risk factors require it. The total volume and the reason for prehydration after cycle 1 will be recorded. Monitor subjects for evidence of volume overload and adjust hydration to individual subject needs, especially in subjects with or at risk for cardiac failure.

With: **Subjects may receive intravenous (IV) pre-hydration (normal saline or other appropriate IV fluid) prior to each carfilzomib infusion during cycle 1. Investigators must consider IV pre-hydration in subjects at high-risk for tumor lysis or renal toxicity. All subjects must be monitored for fluid overload and hydration should be tailor to individual needs. It is recommended to use no more than 750 mL IV fluids as a combination of pre- and post-hydration. Thereafter, carfilzomib pre- and/or post-hydration may only be administered if the subject's condition and/or risk factors require it. The total volume of pre- and/or post-hydration and the indication will be recorded on the Concomitant Medications eCRF.**

Section: 7.1.3 Non-investigational Products (Paragraph 2)

Replace: The planned dose (mg/m^2), dose (mg), start date/time, stop date/time, reason for change in planned dose, reason for dose change/withheld, reason for dose delay, and package lot number of lenalidomide and/or dexamethasone is to be recorded on each subject's eCRF(s).

With: The planned dose (mg), **actual** dose (mg) **administered**, start date/time, stop date/time, reason for change in planned dose, reason for dose change/withheld, reason for dose delay, and package lot number of lenalidomide and/or dexamethasone is to be recorded on each subject's eCRF(s).

Section: 7.1.5.3 Prophylaxis for Hepatitis B Virus

Add: **7.1.5.3 Prophylaxis for Hepatitis B Virus**

Hepatitis B virus reactivation prophylaxis should be considered for patients at risk (ie, patients tested positive on serology or had a prior history of HBV infection), as per institutional guidelines.

Section: 7.1.5.4 Supportive Therapies

Replace: Refer to the local Kyprolis label for Warnings and Precautions, as well as recommended supportive therapies and medications.

With: Refer to the local Kyprolis **Prescribing Information** for Warnings and Precautions, as well as recommended supportive therapies and medications.

Section: 7.1.8 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

Replace: Concurrent therapy with a marketed or investigational anticancer therapeutic or radiation to large bone marrow reserves for either palliative or therapeutic intent is excluded. Long-term corticosteroids for nonmalignant conditions (eg, asthma, inflammatory bowel disease) equivalent to a dexamethasone dose > 4.0 mg/day or prednisone > 2 mg/day are not permitted. Higher steroid doses given for short term exacerbations of nonmalignant conditions (eg, asthma flare) are permitted with the approval of the study medical monitor. Investigational agents are not to be used during the study.

With: Concurrent therapy with a marketed or investigational anticancer therapeutic or radiation to large bone marrow reserves for either palliative or therapeutic intent is excluded.

Corticosteroids **given short-term (up to 2 weeks)** for nonmalignant conditions (eg, asthma, inflammatory bowel disease) **are permitted provided that the cumulative dose is less than 40 mg per week dexamethasone or equivalent dose (see Appendix 12 for corticosteroid dose equivalents). Medical monitor should be contacted if short-term corticosteroid use is required > 2 weeks or at cumulative dose of more than 40 mg dexamethasone equivalent or 20 mg for subjects > 75 years of age**. Investigational agents are not to be used during the study.

Section: 7.4 Dose Modification

Replace: Kyprolis may be discontinued, temporarily delayed, or dosage reduced, in the event of a treatment-related toxicity that, in the opinion of the investigator, warrants the discontinuation, temporary delay or dose reduction, as indicated in the Kyprolis Prescribing Information (refer to Warnings and Precautions section). See the lenalidomide and dexamethasone Prescribing Information respectively for dosing recommendations.

With: Kyprolis may be discontinued, temporarily delayed, or dosage reduced, in the event of a treatment-related toxicity that, in the opinion of the investigator, warrants the discontinuation, temporary delay or dose reduction, as indicated in the Kyprolis Prescribing Information (refer to **Posology and method of administration and Special warnings and precautions for use** section**s**). See the lenalidomide and dexamethasone Prescribing Information respectively for dosing recommendations.

Section: 9.2.3.4.1 Echocardiogram

Replace: 9.2.3.4 Other Safety

All subjects will have a baseline transthoracic ECHO (TTE) or MUGA during screening, including assessments of systolic and diastolic left ventricular function and right ventricular function. Echocardiograms are to be repeated if clinically indicated.

With: 9.2.3.4 Other Safety

9.2.3.4.1 Echocardiogram

All subjects will have a baseline transthoracic ECHO (TTE) or MUGA during screening, including assessments of systolic and diastolic left ventricular function and right ventricular function. Echocardiograms are to be repeated **every 6 months (± 2 weeks), at the end of study, and/or** if clinically indicated**. An ECHO must be performed within 72 hours of the onset of a suspected cardiac failure event.**

Section 9.2.3.4.2 Hepatitis B

Add: **9.2.3.4.2 Hepatitis B**

All hepatitis testing will be performed locally. All subjects will be tested at screening for HBsAg, anti-HBs, and anti-HBc, unless performed within 6 months of screening and there was no change in the subject's risk factors within these 6 months.

Subjects with no history of HBV infection that are negative for hepatitis serologies at screening should be followed as clinically indicated.

Subjects with positive testing or who have a prior history of HBV infection should have consultation with a specialist in HBV and have HBV DNA testing and monitoring of HBV DNA every 12 weeks ± 2 weeks through end of study visit. Subjects that have received hepatitis B vaccination with only anti-HBs positivity and no clinical signs of hepatitis do not require HBV DNA monitoring.

Any subject who becomes HBV DNA positive or develops reactivation of HBV will have study treatment interrupted and received appropriate anti-viral treatment as per a specialist in hepatitis B. Resumption of clinical study treatment may be considered in subjects whose HBV reactivation is controlled and where the benefits of clinical study treatment outweigh the risks. After cessation of study treatment for any reason, any ongoing monitoring and anti-viral treatment should be under the guidance of a specialist in HBV.

Section: Appendix 2 Clinical Laboratory Tests, Table 12-1. Analyte Listing

Replace:

Chemistry	Coagulation	Hematology	Other Labs
Amylase (screening only) Lipase (screening only) Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Calcium corrected (if albumin < 4) Adjusted calcium Magnesium Phosphorus Glucose BUN or Urea Creatinine Creatinine clearance (CrCl) Uric acid Total bilirubin Direct bilirubin ALP LDH AST (SGOT) ALT (SGPT)	PT PTT/INR (aPTT or PTT)	Circulating plasma cells (screening only) RBC count Hemoglobin Hematocrit Platelet count WBC count with differential: • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	Serum or highly sensitive urine pregnancy

ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell count.

With:

Chemistry	Coagulation	Hematology	Other Labs
Amylase (screening only) Lipase (screening only) Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Calcium corrected (if albumin < 4) Magnesium Phosphorus Glucose BUN or Urea Creatinine Creatinine clearance (CrCl) Uric acid Total bilirubin Direct bilirubin ALP LDH AST (SGOT) ALT (SGPT)	PT PTT/INR (aPTT or PTT)	Circulating plasma cells (screening only) RBC count Hemoglobin Hematocrit Platelet count WBC count with differential: • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	Serum or highly sensitive urine pregnancy **NTproBNP[a]** **BNP[a]** **CK2[b]** **CPKMB[b]** **Troponin I[b]** **Troponin T[b]** **Hepatitis B serologies (HBsAg, anti-HBs, and anti-HBc)[c]** **HBV DNA[d]**

ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; **BNP = b-type natriuretic peptide**; BUN = blood urea nitrogen; **CK2 = creatine kinase 2; CPKMB = creatine kinase-muscle/brain; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus;** INR = international normalized ratio; LDH = lactate dehydrogenase; **NTproBPN = N-terminal pro b-type natriuretic peptide;** PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell count.

[a] **NTproBNP is only required at screening and BNP can be recorded if NTproBNP is not available.**

[b] **As clinically indicated.**

[c] **Testing is required for all subjects at screening unless obtained within 6 months of screening and there was no change in the subject's risk factors within these 6 months.**

[d] **If prior history of HBV infection obtain HBV DNA at screening and every 12 weeks through safety follow-up. Subjects that have received hepatitis B vaccination with only anti-HBs positivity and no clinical signs of hepatitis do not require HBV DNA monitoring.**

Section: Appendix 3 Study Governance Considerationos, Data Quality Assurance

(Paragraph 10)

Delete~~: Amgen (or designee) will perform Self-Evident Corrections (SECs) to obvious data errors in the clinical trial database. SECs will be documented in the eCRF~~

~~Standard Instructions and the eCRF Specific Instructions, both of these will be available through the electronic data capture (EDC) system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same date with different visit, [eg, C1D9 and C1D15]) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).~~

Section: Appendix 5 Contraceptive Guidance and Collection of Pregnancy and Lactation Information, Table 12-2. Lenalidomide: Contraceptive Guidelines and Collection of Pregnancy and Lactation Information

Replace:

Risks Associated with Pregnancy (For the region specific use of lenalidomide, please refer to the regional label)
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryo fetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.
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 a female of childbearing potential, lenalidomide is contraindicated unless all of the following are met (ie, all females of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy): • She understands the potential teratogenic risk to the unborn child • She understands the need for effective contraception, without interruption, 4 weeks 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 study drug 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 lenalidomide

The investigator must ensure that for females of childbearing potential:

- Complies 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, lenalidomide is contraindicated unless all of 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 lenalidomide study therapy):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide
- Traces of lenalidomide have been found in semen. Male subjects taking lenalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):
  - Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female 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 pregnant female or a female of childbearing potential.

Contraception

FCBP enrolled in this protocol must agree to use 2 reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact 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. 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:

- IUD
- Hormonal (birth control pills, injections, implants)
- Tubal ligation
- Partner's vasectomy

Additional effective methods:

- Male condom
- Diaphragm
- Cervical Cap

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 Lenalidomide

Female Subjects

- FCBP must have 2 negative pregnancy tests (combined sensitivity of at least 50 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the Investigator has verified that the results of these pregnancy tests are negative.
- Will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure.
- Must agree to abstain from donating blood during study participation and for at least 28 days after discontinuation from the study.

Male Subjects

- Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.
- Will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure.
- Must agree to abstain from donating blood, semen, or sperm during study participation and for at least 28 days after discontinuation from the study.

During Study Participation and for 28 Days Following Discontinuation From the Study

Female Subjects

- FCBP 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 discontinuation from the study. 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 discontinuation from the study.
- In addition to the required pregnancy testing, the Investigator must confirm with FCBP that she is continuing to use 2 reliable methods of birth control at each visit.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days and at the time that lenalidomide treatment is discontinued. During counseling, subjects must be reminded to not share study drug and to not donate blood.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after discontinuation from the study.
- If pregnancy or a positive pregnancy test does occur in a study subject, study drug must be immediately discontinued.

Male Subjects

- Counseling about the requirement for latex condom use during sexual contact with females of childbearing potential and the potential risks of fetal exposure must be conducted at a minimum of every 28 days and at the time that lenalidomide treatment is discontinued. During counseling, subjects must be reminded to not share study drug and to not donate blood, sperm, or semen.

- 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 study doctor at the end of treatment.
- Female subjects should not donate blood during therapy and for at least 28 days following discontinuation of study drug.
- Male subjects should not donate blood, semen or sperm during therapy or for at least 90 days following discontinuation of study drug.
- Only enough study drug for 1 cycle of therapy may be dispensed with each cycle of therapy.

With:

Risks Associated with Pregnancy

(For the region specific use of lenalidomide, please refer to the regional label)

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryo fetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

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 a female of childbearing potential, lenalidomide is contraindicated unless all of the following are met (ie, all females of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks 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

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Counseling (Continued)

- She understands the need to commence the study treatment as soon as study drug 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 lenalidomide

The investigator must ensure that for females of childbearing potential:

- Complies 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, lenalidomide is contraindicated unless all of 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 lenalidomide study therapy):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide
- Traces of lenalidomide have been found in semen. Male subjects taking lenalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):
  - Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female 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 pregnant female or a female of childbearing potential.

Contraception

FCBP enrolled in this protocol must agree to use 2 reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact 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. 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:

- IUD
- Hormonal (birth control pills, injections, implants)
- Tubal ligation
- Partner's vasectomy

Contraception (Continued)

Additional effective methods:

- Male condom **or female condom, with or without spermicide**
- Diaphragm **with spermicide**
- Cervical Cap **with spermicide**

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 Lenalidomide

Female Subjects

- FCBP must have 2 negative pregnancy tests (combined sensitivity of at least 50 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the Investigator has verified that the results of these pregnancy tests are negative.
- Will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure.
- Must agree to abstain from donating blood during study participation and for at least 28 days after discontinuation from the study.

Male Subjects

- Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.
- Will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure.
- Must agree to abstain from donating blood, semen, or sperm during study participation and for at least 28 days after discontinuation from the study.

During Study Participation and for 28 Days Following Discontinuation From the Study
Female Subjects • FCBP 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 discontinuation from the study. 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 discontinuation from the study. • In addition to the required pregnancy testing, the Investigator must confirm with FCBP that she is continuing to use 2 reliable methods of birth control at each visit. • Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days and at the time that lenalidomide treatment is discontinued. During counseling, subjects must be reminded to not share study drug and to not donate blood. • Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide treatment must be discontinued during this evaluation. • Females must agree to abstain from breastfeeding during study participation and for at least 28 days after discontinuation from the study. • If pregnancy or a positive pregnancy test does occur in a study subject, study drug must be immediately discontinued. Male Subjects • Counseling about the requirement for latex condom use during sexual contact with females of childbearing potential and the potential risks of fetal exposure must be conducted at a minimum of every 28 days and at the time that lenalidomide treatment is discontinued. During counseling, subjects must be reminded to not share study drug and to not donate blood, sperm, or semen. • 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 study doctor at the end of treatment. • Female subjects should not donate blood during therapy and for at least 28 days following discontinuation of study drug. • Male subjects should not donate blood, semen or sperm during therapy or for at least 90 days following discontinuation of study drug. • Only enough study drug for 1 cycle of therapy may be dispensed with each cycle of therapy.

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Section: Appendix 7: Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments

Replace: Please refer to Section 7.4.1.1 for details regarding dose modification and toxicity.

With: Please refer to Sections **7.1.2.1, 7.1.2.2, and** 7.4.1.1 for details regarding dose modification and toxicity.

Section: Appendix 12. Corticosteroid Dose Equivalents

Add: **Appendix 12. Corticosteroid Dose Equivalents**

Equivalent Dose (mg)	Steroid
1.5	**dexamethasone (long-acting)**
8	**methylprednisolone (intermediate-acting)**
10	**prednisone (intermediate-acting)**
10	**prednisolone (intermediate-acting)**
40	**hydrocortisone (short-acting)**

Amendment 1

Protocol Title: Post-marketing Phase 4 Study to Evaluate Safety, Tolerability, and Efficacy of Kyprolis® (Carfilzomib) in Indian Patients With Relapsed or Refractory Multiple Myeloma: A Prospective, Open-label, Non-comparative, Multicenter Study

Amgen Protocol Number (carfilzomib) 20160372

Amendment Date: 08 October 2019

Rationale:

The protocol is amended to:

- Hepatitis B testing (hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody) has been expanded to include all subjects that do not already have a prior medical history of hepatitis B or who have not had testing within the previous 12 weeks. Guidance has been provided regarding HBV DNA testing and monitoring for subjects with positive hepatitis B serology or a prior history of HBV. In addition, guidance has been provided on the prophylaxis of HBV reactivation in patients at risk.
- Implement ECHO assessments every 6 months, EOS, and/or if clinically indicated. An ECHO must be performed within 72 hours of the onset of a suspected cardiac failure.
- Removed Self-Evident Corrections as they are no longer completed by DM per change in Amgen processes.
- Removed Adjusted calcium from lab analyte chart (redundant with Calcium corrected [if albumin < 4]). Added NTproBNP, BNP, CK2, CKMB, Troponin I, and Troponin T to lab analyte chart
- Added clarification around dose adjustments required for change of body weight > 20%.
- Added clarification around concomitant short- and long-term corticosteroid use.
- Added clarification around Intravenous Pre-hydration use.