Table 2-1. Schedule of Activities

PROCEDURE			Screening[a] [b] (up to 21 days before Day 1)	Treatment Period: Cycle 1-2 Day 1	2	8	9	15	16	22	23	Cycle 3-12 1	8	15	21	Safety FU[c] (30 [+3] days post last dose)	Notes
Concomitant therapies review			Continuous														
LABORATORY ASSESSMENTS																	
Pregnancy test (FCBP only)[d]	Kd Arm	Urine or serum	X	X								X				X	
	KPd and KRd Arms	Serum	X													X	
		Urine or serum cycle 1 (predose)		X		X		X		X							Within 24 hours prior to dose of lenalidomide or pomalidomide for subjects in the KRd or KPd arms, respectively
		Urine or serum cycle 2 to 12 (predose; regular menses)		X								X					
		Urine or serum cycle 2 to 12 (predose; irregular menses)		X				X				X		X			
Hematology			X	X								X				X	Hematology and chemistry samples from screening may be used for C1D1 if taken within 3 days prior to C1D1. Lab results must be evaluated for potential dose modification assessment prior to dosing (see Section 7.4). Chemistry and hematology assessments, other than for C1D1, may be taken within 2 days prior to the scheduled assessment.
Chemistry			X	X								X				X	

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Footnotes defined on last page of this table.

Completion Instructions - Electronic Adverse Event Contingency Report Form (for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

5. **IP Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.
6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. **Case Description**
    Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

odds ratio = 3.47) (Stewart et al, 2015), health-related quality-of-life (Stewart et al, 2016), as well as OS (median OS: 48.3 vs 40.4 months, HR = 0.79 [Siegel et al, 2018]). Safety results from the final analysis were consistent with the known safety profile of carfilzomib, with no new safety signals observed after extended follow-up.

Despite the favorable benefit-risk profile of the KRd regimen, as demonstrated in the ASPIRE study, compliance with the currently available twice-weekly KRd dosing schedule may be less than optimal because of the convenience-related attributes of this regimen.

Pomalidomide and dexamethasone (Pd) has been approved for subjects with RRMM and has proven efficacy in subjects who were refractory to both bortezomib and lenalidomide. Several phase 2 studies have demonstrated improved efficacy and safety of adding carfilzomib to Pd (KPd) in advanced RRMM compared to historical outcomes with Pd. The key benefits of carfilzomib, pomalidomide, dexamethasone as a triplet-therapy for patients with relapsed and refractory multiple myeloma include increases in PFS, OS, and ORR (San Miguel et al, 2013).

The purpose of this study is to:

- Describe the safety profile of 3 different weekly carfilzomib based regimens:
  - carfilzomib plus dexamethasone regimen (Kd 56 mg/m^2 twice weekly in cycles 1-2 followed by Kd 70 mg/m^2 once weekly in cycles 3–12);
  - carfilzomib plus lenalidomide and dexamethasone regimen (KRd 27 mg/m^2 twice weekly in cycles 1-2 followed by KRd 56 mg/m^2 once weekly in cycles 3-12);
  - carfilzomib plus pomalidomide and dexamethasone regimen (KPd 27 mg/m^2 twice weekly in cycles 1-2 followed by KPd 56 mg/m^2 once weekly in cycles 3-12) in subjects with RRMM with 1–3 prior lines of therapy at study entry.
- Describe subjects' adherence these carfilzomib based regimens.

2.2 Schedule of Activities

Table 2-1. Schedule of Activities

PROCEDURE		Screening[a b] (up to 21 days before Day 1)	Treatment Period: Cycle 1-2 Day 1	2	8	9	15	16	22	23	Cycle 3-12 1	8	15	21	Safety FU[c] (30 [+3] days post last dose)	Notes
GENERAL AND SAFETY ASSESSMENTS																
Informed consent		X														
Inclusion and exclusion criteria		X														
Demographics		X														
Physical examination		X													X	
Physical measurements	Height, BMI	X														BSA should be calculated per Mosteller formula and utilized to calculate required study drug doses. BSA should be recalculated if weight changes by 20% or more (gain or loss)
	Weight	X	X								X					
	BSA	X	(X)													
Medical history		X														
Cardiac history		X														See Section 9.2.1.3
Substance use		X														
ECG		X														
Vital signs		X	X	X	X	X	X	X			X	X	X		X	Checked prior to administration of study drug(s) in all cycles.
ECOG performance status		X													X	
Echocardiogram		X														At screening and as clinically indicated (per Section 12.9)
Adverse events/serious adverse events		Continuous														Adverse events are to be captured during screening, starting with the signing of the informed consent. Recommended dyspnea evaluation per investigator's judgment per Section 12.9

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Footnotes defined on last page of this table.

5. Study Design

5.1 Overall Design

This is a phase 2, multicenter, open-label study in subjects with RRMM in US community oncology centers. Subjects with 1-3 prior lines of therapy at study entry are eligible to be screened for participation. Subjects refractory to their last line of treatment are eligible to participate as long as their last line of treatment did not include a PI. The study will consist of a screening period of up to 28 days for bone marrow aspirate, bone lesion assessment, and plasmacytoma assessment and up to 21 days for all other assessments, up to 12 cycles of treatment, and a 30-day safety follow-up period following the last dose of study drug.

During the treatment period, subjects in the Kd arm will be treated with Kd 20/56 mg/m^2 twice weekly for up to two 28-day cycles followed by Kd 70 mg/m^2 once weekly for another ten 28-day cycles; subjects in the KRd arm will be treated with KRd 20/27 mg/m^2 twice weekly for up to two 28-day cycles followed by Kd 56 mg/m^2 once weekly for another ten 28-day cycles; subjects in the KPd arm will be treated with KPd 20/27 mg/m^2 twice weekly for up to two 28-day cycles followed by KPd 56 mg/m^2 once weekly for another ten 28-day cycles. After discontinuation of study drugs, subjects will be followed for 30 days for safety.

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

A total of approximately 75 subjects will be enrolled in the study with approximately 25 subjects in each arm.

Subjects in this clinical investigation shall be referred to as “subjects”. A sample size of approximately 75 subjects will provide for descriptive statistics to be generated for patient safety and treatment adherence. 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 40 investigative sites in the United States 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.

The primary completion date is the date when the last subject has completed the assessments for the safety follow-up visit.

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), following any additional parts in the study (eg, long-term follow-up), as applicable.

5.3.2 Study Duration for Subjects

The study will consist of a screening period (up to 28 days for bone marrow aspirate, bone lesion assessment, and plasmacytoma assessment and up to 21 days for all other assessments), approximately 12-month treatment period, and a 30 (+3)-day safety follow-up. Therefore, the total study duration for an individual subject is estimated to be approximately 14 months.

5.4 Justification for Investigational Product Dose

The dose and dosing frequency of carfilzomib regimens used in this study were selected based on data from phase 1/2 and phase 3 studies.

5.4.1 Justification for Investigational Product Dose for Kd Arm

The safety and efficacy of 20/56 mg/m^2 twice weekly carfilzomib combined with dexamethasone has been defined in a randomized phase 3 trial (ENDEAVOR; Dimopoulos et al, 2016). ENDEAVOR compared carfilzomib administered at 56 mg/m^2 over a 30-min infusion twice per week with dexamethasone against Vd in subjects with RRMM who had received between 1 and 3 previous treatments, a similar subject population to what is being proposed in this phase 2 trial. The carfilzomib arm proved superior at the first interim analysis for efficacy reducing the risk of progression or death by 47% (median PFS [Kd vs Vd]: 18.7 months vs 9.4 months), and at the second interim

106 Subjects must have at least partial response (PR) to at least 1 line of prior therapy.

107 Subjects must have received at least 1 but not more than 3 prior lines of therapy for MM (induction therapy followed by stem cell transplant and consolidation/maintenance therapy will be considered as 1 line of therapy; see Section 12.11).

109 Measured creatinine clearance (radionucleotide or 24-hour urine) or calculated creatinine clearance per the Chronic Kidney Disease Epidemiology Collaboration formula, of ≥ 30mL/min/1.73 m^2 within 21 days of enrollment (see Section 12.13).

Kd Arm

110 Prior therapy with a PI is allowed as long as the subject was not removed due to toxicity (except for neuropathy, see criterion 213), and if received carfilzomib must have achieved at least a PR and have at least a 6-month carfilzomib treatment-free interval from last dose received until enrollment.

KRd Arm

111 Prior therapy with a PI or lenalidomide is allowed as long as the subject had at least a PR to most recent therapy with PI or lenalidomide, was not removed due to toxicity (except for neuropathy, see criterion 213), and if received carfilzomib must have at least a 6-month carfilzomib treatment-free interval from last dose received until enrollment.

KPd Arm

112 Prior therapy with a PI is allowed as long as the subject had at least a PR to most recent therapy with PI, was not removed due to toxicity (except for neuropathy, see criterion 213), and if received carfilzomib must have at least a 6-month carfilzomib treatment-free interval from last dose received until enrollment.

6.2 Exclusion Criteria

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

Disease-related

201 Waldenström macroglobulinemia.

202 Multiple myeloma of IgM subtype.

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

204 History of plasma cell leukemia.

206 Subjects with nephrotic range proteinuria (≥ 3 g albumin for 24 hours urine OR ≥ 2 g albumin/1 g of creatinine on a random urine specimen).

207 Myelodysplastic syndrome.

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

At the time of implementation of protocol amendment 3, subjects previously enrolled may have completed more than 2 but less than 6 cycles of twice weekly carfilzomib dosing on the Kd arm as per protocol amendment 2. These subjects should complete the dosing regimen as per protocol amendment 2, (ie, 6 cycles of twice weekly dosing for carfilzomib [Kd 56 mg/m^2] transitioning to once weekly dosing for carfilzomib [Kd 70 mg/m^2], starting with cycle 7). For these subjects, the schedule of activities outlined per Table 2-1 for cycles 1 and 2 will continue for cycles 1 through 6. At the start of cycle 7, these subjects will then follow the schedule of activities as outlined per Table 2-1 cycles 3 through 12. In addition, the starting nominal dose of carfilzomib on day 1 cycle 7 (which is the initiation of the once weekly carfilzomib dosing for these subjects) should be reduced by the same number of dose levels and same percentage dose reduction as it was reduced to during cycle 6 (which is the twice weekly carfilzomib dosing). Dexamethasone will be administered at a dose of 20 mg once daily on days 1, 2, 8, 9, 15, 16, 22, and 23 cycles 1 through 6 and at a dose of 40 mg once daily on days 1, 8, 15 for the Kd arm for cycles 7 through 12 for these subjects.

All doses should be administered on the scheduled day ± 2 days, and the day 8 and 15 doses should have at least a 5-day treatment-free interval. The starting dose should be modified for chronic mild hepatic insufficiency per Section 7.1.1.2.1.

Table 7-1. Carfilzomib Dosage

Cycle 1	Cycle 2	Cycles 3-12
Kd Arm		
D1, 2: 20 mg/m^2 D8, 9, 15, 16: 56 mg/m^2	D 1, 2, 8, 9, 15, 16: 56 mg/m^2	D1, 8, 15: 70 mg/m^2
KRd Arm		
D1, 2: 20 mg/m^2 D8, 9, 15, 16: 27 mg/m^2	D 1, 2, 8, 9, 15, 16: 27 mg/m^2	D1, 8, 15: 56 mg/m^2
KPd Arm		
D1, 2: 20 mg/m^2 D8, 9, 15, 16: 27 mg/m^2	D 1, 2, 8, 9, 15, 16: 27 mg/m^2	D1, 8, 15: 56 mg/m^2

D = day

Subjects receiving carfilzomib at doses less than the protocol planned dose (56 mg/m^2 or 27 mg/m^2 based on treatment arm) during cycle 2 may have been reduced by 1 or more dose levels and/or by 25% for hepatic function abnormalities. Subjects should have the starting nominal dose of carfilzomib (70 mg/m^2 or 56 mg/m^2 based on treatment arm) on day 1 cycle 3 reduced by the same number of dose levels and the same

7.1.2.2.2 Dosage, Administration, and Schedule

Lenalidomide will be taken once-daily orally at a dose of 25 mg on days 1-21 of each 28-day cycle. Lenalidomide should be taken at home by the subject at about the same time each day. Lenalidomide capsules should be swallowed whole with water. The capsules should not be opened, broken, or chewed. If a planned dose is missed, it should be taken as soon as possible within the same calendar day and with a return to the regular schedule the following day. If a planned dose is missed for more than a calendar day, subjects should not make up doses, but should resume the dosing regimen on schedule with the next cycle. Dose modifications are permitted in response to toxicity following the dose modification guideline tables.

The planned dose, quantity administered, start date, start time, and reason for dose change are to be recorded on each subject's eCRF.

7.1.2.3 Pomalidomide

7.1.2.3.1 Prescribing Requirements

Pomalidomide, a non-Amgen non-investigational product, will also be used in this study for the KPd treatment arm. Pomalidomide should be administered in accordance with the POMALYST REMS® program of Celgene Corporation (http://www.pomalystrems.com/.) All physicians who prescribe pomalidomide for research subjects assigned to the KPd arm of this study, and all research subjects enrolled on this study who are assigned to the KPd arm, must be registered in and comply with all requirements of the POMALYST REMS® program.

Females of childbearing potential (FCBP) must agree to monitoring for pregnancy. In addition, males and FCBP are subject to certain restrictions as detailed in Section 12.5 while receiving pomalidomide.

7.1.2.3.2 Dosage, Administration, and Schedule

Pomalidomide will be taken once-daily orally at a dose of 4 mg on days 1-21 of each 28-day cycle. Pomalidomide should be taken at home by the subject at about the same time each day. Pomalidomide capsules should be swallowed whole with water. The capsules should not be opened, broken, or chewed. If a planned dose is missed, it should be taken as soon as possible within the same calendar day and with a return to the regular schedule the following day. If a planned dose is missed for more than a calendar day, subjects should not make up doses, but should resume the dosing regimen on schedule with the next cycle. Dose modifications are permitted in response to toxicity following the dose modification guideline tables.

9.1 General Study Periods

9.1.1 Screening and Enrollment

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent form, 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 for bone marrow aspirate, bone lesion assessment, and plasmacytoma assessment and up to 21 days for all other assessments.

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, see Section 6.4, 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 rescreening 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 (for bone marrow aspirate, bone lesion assessment, and plasmacytoma assessment) or a new 21-day (for all other assessments) screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 28 days (for bone marrow aspirate, bone lesion assessment, and plasmacytoma assessment) or more than 21 days (for all other assessments) 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). The date of the first dose of carfilzomib is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. All doses should be administered on the scheduled day $\pm$ 2 days, and the day 8 and 15 doses should have at least a 5-day treatment-free interval (see Section 7.1.1.2 for additional details). Administration of protocol-required therapies is to be administered last during each visit that it is required.

9.2.1.4 Physical Examination

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event). A complete physical examination includes examination of cardiovascular and respiratory systems, abdominal examination, and general neurologic examination. Clinically significant abnormal physical examination findings identified prior to the signing of the ICF should be reported as part of medical history, not as adverse events.

9.2.1.5 Physical Measurements

9.2.1.5.1 Height and Weight

Height in centimeters is to be measured without shoes. Weight in kilograms is to be measured without shoes.

9.2.1.5.2 Body Mass Index

Body Mass Index (BMI) is to be calculated using the following formula:

$BMI\ (kg/m^2) = weight\ (kg)/(height\ [cm]/100)^2$

9.2.1.5.3 Body Surface Area

Body Surface Area (BSA) is to be calculated using the Mosteller formula:

$BSA\ (m^2) = ([Height(cm) \times Weight(kg)] / 3600)^{½}$

9.2.1.6 Substance Abuse History

Obtain a detailed history of prior and/or concurrent use of tobacco (smoking and tobacco).

9.2.1.7 Performance Status

The subject's performance status will be assessed using the ECOG PS (Section 12.10).

9.2.2 Efficacy Assessments

Investigators are required to follow International Myeloma Working Group (IMWG) criteria for assessment of response and disease progression (see Section 12.8).

Disease assessments are required during screening to confirm eligibility and for determination of disease response (per the Schedule of Activities, Table 2-1). Per IMWG, determination of disease response requires: serum free light chain (SFLC), serum and urine protein electrophoresis (SPEP, UPEP, respectively), serum and urine immunofixation (SIFE, UIFE, respectively), bone marrow aspirate (for CR confirmation; Section 9.2.2.1), corrected calcium, and plasmacytoma evaluation, if present at screening (Section 9.2.2.3).

Investigators are responsible for the determination of response and disease progression. Disease assessments based on local laboratory data will start on day 1 of cycle 1 and are performed every 28 (± 7) days regardless of cycle duration, including dose delays until confirmed PD or cycle 12. The cycle 12 disease assessment is conducted 28 (± 7) days post cycle 12, day 1.

Subjects who discontinue treatment prior to confirmed PD should continue to complete disease assessments until up to 12 months from enrollment, death, loss to follow-up, withdrawal of consent or PD, whichever occurs first.

9.2.2.1 Bone Marrow Sample Evaluation Including FISH Assessment

A baseline bone marrow sample evaluation with fluorescence in-situ hybridization (FISH, aspirate slides and/or biopsy) will be performed prior to first dose and will be used to confirm the diagnosis and quantify the percent (%) of myeloma cell involvement. Biopsy or aspirate slides obtained as standard of care may be used as baseline if performed within 28 days of cycle 1 day 1.

Additional bone marrow biopsy or aspirate should be obtained as clinically indicated to confirm a response of CR or stringent CR.

9.2.2.2 Bone Lesion Assessment (Skeletal Survey, Computed Tomography, or Positron Emission Tomography/Computed Tomography)

Skeletal survey will include lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. Low-dose whole body computed tomography (CT) or fluorodeoxyglucose-positron emission tomography/computed tomography (PET/CT) may be used in place of skeletal survey. Bone lesion assessment will be conducted at screening and for confirmation of PD, if PD is based on bone lesions (see IMWG criteria in Section 12.8). Bone lesion assessments obtained as part of standard of care may be used as baseline if performed within 28 days of cycle 1 day 1. The same method of assessment used at baseline will be used throughout the study. These imaging studies will be read locally.

9.2.2.3 Extramedullary Plasmacytoma

Extramedullary plasmacytoma evaluation will be conducted at screening only if a lesion is clinically suspected. The evaluation may be performed within 28 days of cycle 1 day 1 if performed as a part of standard of care. If an extramedullary plasmacytoma is detected, evaluation will be repeated to confirm a response of MR or better or to confirm PD (see IMWG criteria in Section 12.8). Assessment of sites of extramedullary disease measurable by physical examination may be performed once per cycle. If assessment

can only be performed radiologically, then evaluation of extramedullary plasmacytomas should be done to confirm a response or as clinically indicated. The same technique (which may include clinical evaluation by palpation, ultrasound, CT scan, magnetic resonance imaging [MRI], or PET/CT) should be employed for each measurement of plasmacytoma dimensions as clinically appropriate (Section 12.8). Bidimensional lesion measurements should be performed (see Section 9.2.2.3.1).

9.2.2.3.1 Sum of Perpendicular Dimensions

Response and progression of soft tissue plasmacytomas or progression of bone lesions should be determined by the change in the sum of perpendicular dimensions (SPD) measured radiographically or by physical examination, as clinically indicated.

The SPD is defined as the sum of the longest dimension added to the second longest dimension that is perpendicular to the longest dimension. Sum of perpendicular dimensions of bone lesions will be measured only for evidence of progression. The SPD for a bone lesion is defined the same as it is for a plasmacytoma. An increase of 50% or more from the nadir in the size of any bone lesion provides evidence for PD, see Section 12.8 for more details.

9.2.2.4 Progressive Disease Assessment

Progressive disease (including PD due to development of hypercalcemia attributed solely to recurrence/progression of multiple myeloma) will be based on local laboratory evaluation. Confirmation of PD (using 2 consecutive assessments) will be required only when it is determined by laboratory evaluations and not if identified via imaging as per IMWG criteria. The assessments outlined in Section 12.8 are required for determination of PD. Subjects should be considered to have PD if they meet the criteria for progression by a variable that was not considered measurable at baseline; however, for subjects who had a measurable serum or urine M-spike at baseline, progression should not be defined by increases in SFLC alone (Kumar et al, 2016).

9.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (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 Common Terminology Criteria for Adverse Events (CTCAE) and is described in Section 12.4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after signing of the ICF through the 30 (+3) days after the last dose of study drug(s) are reported using the Event CRF.

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 ICF through 30 (+3) days after the last dose of study drug(s) are reported using the Event CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours, as indicated in Section 12.4. 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 Section 12.4.

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 Section 12.4.

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 CRF.

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, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions 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, if appropriate according to local requirements.

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

9.2.6 Clinical Outcome Assessments

9.2.6.1 European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30)

The European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30) is a questionnaire developed to assess the quality of life of cancer patients (Bjordal et al, 2000).

EORTC QLQ-C30 includes 30 items grouped into:

- five quality of life categories: physical, social, emotional, cognitive and role performance;
- three scales of symptoms: fatigue, pain, and nausea and vomiting;
- a global scale of quality-of-life and individual items related to the symptoms of the disease and its treatment; dyspnea, insomnia, loss of appetite, constipation, diarrhea and
- an item on economic impact

The responses to the scale items refer to "last week," with the exception of the subject's physical performance scale, where the timeframe involved is the present.

9.2.6.2 European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Multiple Myeloma Module (EORTC QLQ-MY20)

In addition to the QLQ-C30, a number of disease-specific modules have been produced by the EORTC. This modular approach was adopted by EORTC in recognition of the limitations of generic patient-reported outcome instruments to provide an appropriate coverage of disease-specific concerns. Modules specific to tumor site, treatment modality, and quality of life have been developed. These were designed to be administered alongside the core questionnaire (QLQ-C30); like the core questionnaire, the modules were designed for use in cancer clinical trials. The MM module (the QLQ-MY20) was developed by EORTC in 1999 (Bjordal et al, 2000). A summary of the QLQ-C30 and QLQ-MY20 subscales are provided in Section 12.16.

[redacted]

[redacted]

10. Statistical Considerations

10.1 Sample Size Determination

The study is descriptive in nature. Approximately 75 subjects will be enrolled in the study with approximately 25 subjects in each treatment arm.

The sample size is assessed in terms of the expected levels of precision for estimating the proportion of subjects completing 12 cycles of treatment, relative dose intensity (%), and incidence of adverse events.

With a sample size of 25 subjects for each treatment arm, assuming 50%, 75%, or 90% of subjects will complete 12 cycles of treatment, the expected half-widths of the 95% CI for estimating the proportion of subjects completing 12 cycles of treatment are calculated as below.

Sample Size	95% Confidence Interval Half-width (%)		
	50%	75%	90%
25	20.5	18.1	13.5

In the A.R.R.O.W. trial, the mean (standard deviation) of relative dose intensity of carfilzomib is 92.2 (11.2) in Once-weekly subjects. In this study with a sample size of 25 subjects in each treatment arm, assuming standard deviation ranges from 5% to 15%, the expected half-widths of the 95% CI for estimating the mean relative dose intensity are calculated as below.

Sample Size	95% Confidence Interval Half-width (%)		
	SD = 5	SD = 10	SD = 15
25	2.0	3.9	5.9

For subject incidence of adverse events of 1%, 5%, 10%, 50%, 80%, the expected half-widths of the 95% confidence interval (CI) for estimating the subject incidences of adverse events are calculated as below.

Sample Size	95% Confidence Interval Half-width (%)				
	1%	5%	10%	50%	80%
25	7.8	10.8	13.5	20.5	16.9

Abbreviation or Term	Definition/Explanation
IMWG	International Myeloma Working Group
Interactive Voice/Web Response System (IXRS)	telecommunication/web-based technology that is linked to a central computer in real time as an interface to collect and process information
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Boards
IV	intravenous
K	Kyprolis
Kd	carfilzomib with dexamethasone regimen
Kd56	Kd 56 mg/m^2 twice weekly
Kd70	Kd 70 mg/m^2 once weekly
KPd	carfilzomib with pomalidomide and dexamethasone regimen
KPd27	KPd 27 mg/m^2 twice weekly
KPd56	KPd 56 mg/m^2 once weekly
KRd	carfilzomib with lenalidomide and dexamethasone regimen
KRd27	KRd 27 mg/m^2 twice weekly
KRd56	KRd 56 mg/m^2 once weekly
MM	multiple myeloma
MR	minimal response
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET/CT	positron emission tomography/computed tomography
PFS	progression-free survival
PI	proteasome inhibitor
PR	partial response
PRES	posterior reversible encephalopathy syndrome
RBC	red blood cell
RRMM	relapsed or refractory multiple myeloma
SAP	Statistical Analysis Plan
sCR	stringent complete response
SFLC	serum free light chain
SIFE	serum immunofixation

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 case report form (CRF). • The investigator must assign the following adverse event attributes: o Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms); o Dates of onset and resolution (if resolved); o Severity (or toxicity grade defined below); o Assessment of relatedness to carfilzomib; and o 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 CRF. • It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor in lieu of completion of the Event CRF 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, 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/or study-mandated procedure 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.
- New or updated information will be recorded in the originally completed Event CRF.
- The investigator will submit any updated serious adverse event data to Amgen 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 electronic data capture (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 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 a paper Serious Adverse Event Report Form (see Figure 12-1).

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

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to IP)**

1. **Site Information**

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. **Subject Information**

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the serious adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

   Serious Adverse Event Diagnosis or Syndrome* –

   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria)rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

   Is event serious?* – Indicate Yes or No. This is a mandatory field.

   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:

   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   Relationship to IP – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

   Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**

   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

   If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**

   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

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12.8 Appendix 8. 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 biopsy by immunohistochemistry (κ/λ ratio ≤ 4:1 or ≥ 1:2 for κ and λ patients, respectively, after counting ≥ 100 plasma cells)
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 (0.26 to 1.65)
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 (requires a 24-hour urine collection) • 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

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Footnotes defined on next page

12.10 Appendix 10. Eastern Cooperative Oncology Performance Status

GRADE	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, 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

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

12.16 Appendix 16. Overview of QLQ-C30 and QLQ-MY20 Scales

	QLQ-C30	QLQ-MY20
Total number of items	30	20
Subscales	▪ 5 functional scales – Physical functioning – Role functioning – Emotional functioning – Cognitive functioning – Social functioning ▪ 3 symptom scales – Fatigue – Pain – Nausea and vomiting ▪ A global health status (GHS)/Quality of life (QOL) scale ▪ Single items – Additional symptoms (dyspnoea, appetite loss, insomnia, constipation, and diarrhoea) – Financial difficulties	▪ Disease symptoms ▪ Side effects of treatment ▪ Body image ▪ Future perspectives
Response scales	4- or 7-point scales	4-point scale
Score range	0-100 (high score = high response) ▪ Functional scales: High score = better functioning, ▪ GHS/QOL: High score = better GHS/QOL, ▪ Symptom scales and single symptom items: High score = worse symptoms	0-100 (high score = high response) ▪ Disease symptoms and side effects of treatments scales: High score = worse symptoms ▪ Body image and future perspectives scales: High score = better functioning
Recall period	Past week	Past week

QOL = quality of life.

Source: Bjordal et al, 2000.

Table 2-1. Schedule of Activities

PROCEDURE	Screening[a] [b] (up to 21 days before Day 1)	Treatment Period												Safety FU[c] (30 [+3] days post last dose)	Notes
		Cycle 1-2								Cycle 3-12					
		Day 1	2	8	9	15	16	22	23	1	8	15	21		
Fasting lipid panel	X														Total cholesterol, HDL, LDL, triglycerides (fasting ≥ 12 hours)
NT-proBNP (or BNP)	X														At screening and as clinically indicated (see Section 12.9)
HbA1c	X														
Fasting glucose	X														Fasting ≥ 12 hours
Estimated GFR	X														Estimated GFR calculated using CKD-EPI equation (see Section 12.13)
Urinalysis	X														For calculation of albumin creatinine ratio per exclusion criteria 206, see Section 6.2
DISEASE-SPECIFIC ASSESSMENTS															
LDH	X														
Beta-2 microglobulin	X														
Corrected calcium	X														
SPEP/UPEP/SFLC/SIFE/UIFE[e]	X	X[f]								X					UPEP requires 24-hour urine collection. Evaluated by investigator based on IMWG criteria (see Section 12.8)
Myeloma Response Assessment[e]		(X)[g]												X	Disease assessment to be performed every 28 ± 7 days until confirmed PD regardless of cycle duration, including dose delays. Disease assessments at the safety follow-up visit are not required for subjects who discontinue early due to confirmed PD or if assessments were performed within 14 days prior to the safety follow-up visit.

Footnotes defined on last page of this table.

AMGEN
Study # 20170596
carfilzomib

Electronic Serious Adverse Event Contingency Report Form

For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. SERIOUS ADVERSE EVENT

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

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

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Objectives/Endpoints

Objectives	Endpoints
Primary	
Describe adherence and treatment safety across all 12 cycles of carfilzomib based regimens in subjects with relapsed or refractory multiple myeloma with 1-3 prior lines of therapy at study entry.	• proportion of subjects completing 12 cycles of treatment • proportion of actual cumulative dose received to the full intended cumulative dose in cycles 1-12 • relative dose intensity in cycles 1-12 • dose modifications and reasons in cycles 1-12 • treatment-emergent adverse events and serious adverse events
Secondary	
Assess subject health-related quality-of--life (HRQoL) with the Kd, KRd, and KPd regimens.	• European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire (EORTC QLQ) Core 30 (C30) and EORTC QLQ Multiple Myeloma Module (MY20) scores through cycle 12 or up to disease progression
Assess response to the Kd, KRd, and KPd regimens.	• response rate (stringent complete response [sCR], complete response [CR], very good partial response [VGPR], partial response [PR], minimal response [MR], stable disease [SD], progressive disease [PD], Not evaluable [NE]). • progression-free survival (PFS) at 1 year • response rate and PFS by line of prior therapy 1 vs $\geq$ 2

Hypotheses

Carfilzomib combinations (Kd, KRd, and KPd) have acceptable tolerability and adherence in subjects with RRMM in a community-based setting.

Overall Design

This is a phase 2, multicenter, open-label study in subjects with RRMM in US community oncology centers. Subjects with 1-3 prior lines of therapy at study entry are eligible to be screened for participation. Subjects refractory to their last line of treatment are eligible to participate as long as their last line of treatment did not include a proteasome inhibitor (PI). The study will consist of a screening period of up to 28 days for bone marrow aspirate, bone lesion assessment, and plasmacytoma assessment and up to 21 days for all other assessments, up to 12 cycles of treatment, and a 30-day safety follow-up period following the last dose of study drug.

OS analysis reducing the risk of death by 21% compared to Vd (median OS 47.6 months vs 40.0 months, HR = 0.791, one-sided p = 0.010). Grade 3 or worse adverse events were reported in 81% of subjects in the Kd group and 71% of subjects in the Vd group. The most frequent grade 3 cardiopulmonary events of interest reported in the Kd and Vd groups, respectively, included hypertension 15% vs 3%, pneumonia 9% vs 9%, dyspnea 6% vs 2%, and congestive heart failure in 6% vs 2%.

Based on the results of the ENDEAVOR study, the FDA approved carfilzomib in combination with dexamethasone for the treatment of patients with RRMM who have received 1 to 3 lines of therapy. The dose of carfilzomib to be used in combination with dexamethasone is 56 mg/m^2 twice weekly following an initial treatment with 20 mg/m^2 on the first 2 days of treatment (Kyprolis USPI).

The safety and efficacy of the 70 mg/m^2 dose has been evaluated in the phase 2 (CHAMPION-1) and phase 3 (A.R.R.O.W.) studies. Carfilzomib pharmacokinetics in the CHAMPION-1 study with the 70 mg/m^2 once weekly dose showed higher maximum concentration than that with the 56 mg/m^2 twice-weekly dose (2390 ng/mL vs 2079 ng/mL, respectively). However, the area under the curve was higher with 56 mg/m^2 twice a week (1896 ng•hr/mL vs 1030 ng•hr/mL per week).

The CHAMPION-1 study, a phase 1/2 trial, provided additional safety data for the 70 mg/m^2 weekly dosing of carfilzomib in combination with dexamethasone. In that study, 104 subjects were treated for a median of 7.7 months at the MTD of 70 mg/m^2 weekly in combination with dexamethasone 40 mg weekly in a similar patient population as the proposed study. At 70 mg/m^2, the most common grade $\geq$ 3 adverse events were fatigue (11%) and hypertension (7%). For specific adverse events of interest, the rates of grade $\geq$ 3 hypertension, dyspnea, cardiac failure, and peripheral neuropathy were 7%, 5%, 2%, and 1%, respectively. Discontinuations due to adverse events were reported to occur in 12% of subjects. Discontinuations due to adverse events and the incidence of specific cardiovascular events of interest were all lower than that reported in the phase 3 ENDEAVOR trial (Berenson et al, 2016).

The MTD defined in the CHAMPION-1 trial was used in the phase 3 A.R.R.O.W. trial, in which subjects with RRMM were treated with Kd with carfilzomib dosed either at 27 mg/m^2 twice-weekly or 70 mg/m^2 once-weekly. The study included 478 subjects with RRMM who received 2 or 3 prior lines of therapy, including a PI and an IMiD. Subjects treated with the once-weekly Kd regimen achieved a statistically significant superior PFS with a median of 11.2 months compared to 7.6 months for those treated with the

Other Medical Conditions

208 History of other malignancy within the past 3 years, with the following exceptions:

- Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before enrollment and felt to be at low risk for recurrence by the treating physician
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated cervical carcinoma in situ without evidence of disease
- Adequately treated breast ductal carcinoma in situ without evidence of disease
- Prostatic intraepithelial neoplasia without evidence of prostate cancer
- Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ
- Treated medullary or papillary thyroid cancer
- Similar neoplastic conditions with an expectation of > 95% five-year disease-free survival

209 Known 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 or core antibody that achieve sustained virologic response with antiviral therapy directed at hepatitis B are allowed).

210 Active acute or chronic graft-versus-host disease (any grade).

211 Acute active infection requiring systemic antibiotics, antifungal, antiviral (except antiviral therapy directed at hepatitis B) agents within 14 days prior to enrollment.

212 Known cirrhosis.

213 Significant neuropathy (grades 3 to 4, or grade 2 with pain) within 14 days prior to enrollment.

214 Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 14 days prior to enrollment.

Cardiopulmonary Conditions

215 Uncontrolled hypertension, defined as an average systolic blood pressure ≥ 160 mmHg or diastolic ≥ 100 mmHg (see Section 12.12 for more details). Subjects with controlled hypertension are eligible.

216 Active congestive heart failure with or without reduced ejection fraction (NYHA Class III to IV), symptomatic ischemia, uncontrolled arrhythmias, clinically significant electrocardiogram (ECG) abnormalities, screening ECG with corrected QT interval (QTc) of > 470 msec, pericardial disease, myocardial infarction within 4 months prior to enrollment.

217 Known chronic obstructive pulmonary disease.

218 Known interstitial pneumonitis.

percentage dose reduction as they were reduced during cycle 2, see Table 7-2 for dose level reductions.

Carfilzomib is to be administered as an IV infusion over 30 (± 5) minutes. Subjects should receive 250 mL of normal saline or equivalent IV fluid prior to and after each dose during cycle 1. After cycle 1, at the discretion of treating physician, subjects may receive up to but no more than 250 mL of normal saline or equivalent fluid prior to each dose of carfilzomib. For subjects at risk of TLS, see Section 7.1.4.3.

Mechanical infusion pumps are recommended, but gravity-dependent infusions are permitted if the 30-minute infusion duration can be reliably maintained. Carfilzomib infusion must occur at a facility capable of managing hypersensitivity reactions.

Each subject's first dose will be calculated based upon baseline BSA per the Mosteller formula. 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 change in body weight of ≥ 20% compared to baseline or last calculation of BSA, in which case the BSA and dose should be recalculated. The dose can also be modified in response to toxicity following the dose modification guideline tables (see Section 7.4).

The planned dose, dose administered, start date/time, stop date/time, reason for change in planned dose or schedule, and package lot number of carfilzomib are to be recorded on each subject's CRF.

7.1.1.2.1 Starting Dose in Hepatic Insufficiency

For subjects with mild hepatic insufficiency during screening, the initial dose of carfilzomib on days 1 and 2 of cycle 1 should be reduced by 25% to 15 mg/m^2. For subjects in the Kd arm, starting on day 8 and for all subsequent doses of carfilzomib during cycles 1 and 2, the dose should be 42 mg/m^2 (Brown et al, 2017); the dose in cycle 3 through 12 should be 5**3** mg/m^2. For subjects in the KRd and KPd arms, starting on day 8 and for all subsequent doses of carfilzomib during cycles 1 and 2, the dose should be 20 mg/m^2 as per the protocol and doses in cycles 3 through 12 should be 42 mg/m^2.

If hepatic function returns to normal, the dose in following cycles may be re-escalated to the full dose per the protocol. For dose modification due to subsequent changes in hepatic function, refer to Section 7.4.1.1.3 (Table 7-4).

The planned dose, quantity administered, start date, start time, and reason for dose change are to be recorded on each subject's eCRF.

7.1.3 Medical Devices

No investigational medical devices will be 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 usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

7.1.4 Other Protocol-required Therapies

Protocol-required, suggested, or permitted supportive therapies listed below are commercially available and will not be provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies.

Additional details regarding these protocol-required therapies are provided in the IPIM.

7.1.4.1 Antiviral Prophylaxis

An antiviral is a required concomitant medication for the duration of treatment with carfilzomib. Acyclovir (eg, 400 mg orally 3 times a day, or 800 mg orally 2 times a day, or per institutional standards), famcyclovir (eg, 125 mg orally given for 3 days, 2 times a day, or per institutional standards), or valacyclovir (eg, 500 mg orally 2 times 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 carfilzomib.

7.1.4.2 Thromboprophylaxis

It is strongly suggested that all subjects receive an anticoagulant (eg, enteric-coated aspirin at standard prophylactic dose or other anticoagulant or antiplatelet medication, such as clopidogrel bisulfate, low molecular weight heparin, or warfarin). In addition, a second thromboprophylaxis medication is strongly recommended in subjects with elevated risk of thrombosis, based on an individual benefit/risk assessment (Li et al, 2017); see Section 12.14 for more details.

9.1.3 Safety Follow-up

Once a subject discontinues from the study drug (see Section 8.1), he/she will have a safety follow-up visit 30 (+3) days after the last dose of study drug(s) unless the subject is lost to follow-up, has withdrawn consent, or has died. After the safety follow-up, subjects who remain on study are required to complete disease response assessments and will be followed for subsequent antimyeloma treatment every 28 ± 7 days until up to 12 months from enrollment, death, loss to follow-up, withdrawal of consent or progressive disease (PD), whichever occurs first.

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 must sign and personally date the IRB-approved informed consent before any study-specific procedures are performed.

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 5 years prior to enrollment through signing of the ICF. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF. The current toxicity grade will be collected for each condition that has not resolved. Cardiovascular risk factors are to be recorded for the subject including history of cardiovascular disease (heart attack, stroke, peripheral vascular disease), arrhythmias and previous abnormal ECG findings (eg, ventricular hypertrophy and/or ischemic changes), hypertension (include treatment history), thromboembolism, hyperlipidemia (include statin use), and diabetes. Family history of coronary artery disease in first degree relatives with onset < 65 years of age for female relative or < 55 years of age for male relative should also be recorded.

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

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 (for female subjects) and 90 days (for female partners of male subjects) after the last dose of study drug(s).

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 Section 12.5. 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 Section 12.5.

9.2.3.2 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject at screening should be the same that is used throughout the study and documented on the vital signs CRF. Take at least 2 blood pressure measurements spaced 1 to 2 minutes apart and additional measurements if the first 2 are quite different (Section 12.15). Record the average blood pressure on the vital signs CRF.

The temperature location selected for a subject at screening should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

9.2.3.3 Electrocardiograms (ECGs)

Electrocardiograms will be required for all subjects at screening.

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 PI or designated site physician) will review all ECGs. The presence of a low voltage ECG coded on the ECG output, will be entered on the appropriate eCRF. Once signed,

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

Full Analysis Set: The full analysis set will include all enrolled subjects who received at least 1 dose of any study treatment (ie, carfilzomib, dexamethasone. lenalidomide, or pomalidomide).

Safety Analysis Set: The safety population will include all enrolled subjects who received at least 1 dose of any study treatment (ie, carfilzomib, dexamethasone, lenalidomide, or pomalidomide).

The full analysis set will be the same as the safety analysis set for this study.

10.2.2 Covariates

The following covariates will be used to examine primary and secondary endpoints in subgroups as appropriate:

Baseline demographics and characteristics:

- age (as categorical variable: 18 to < 65, 65 to 75, and > 75 years)
- sex (male, female)
- race (white and other categories depending on frequency observed)
- commute distance to treatment center: 0-10, 11-25, > 25 miles

Baseline organ function and comorbid conditions:

- ECOG performance status (0 or 1)
- estimated GFR (< 50 vs ≥ 50 mL/min/1.73 m^2)
- hypertension history (include use of anti-hypertensive medications) (yes, no)
- history of ischemic heart disease (myocardial infarction or coronary artery disease), congestive heart failure (NYHA class ≤ 2), stroke, or history of peripheral vascular disease (yes, no)
- family history of coronary artery disease in first degree relatives with onset < 65 years of age for female relative or < 55 years of age for male relative (yes, no)
- smoking history (yes, no)
- history of hyperlipidemia (yes, no)
- history of diabetes (yes, no)
- history or chronic mild hepatic impairment (yes, no; see Section **7.4.1.1.1**)

Abbreviation or Term	Definition/Explanation
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.
SPD	sum of perpendicular dimensions
SPEP	serum protein electrophoresis
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
TLS	tumor lysis syndrome
TMA	thrombotic microangiopathy
UIFE	urine immunofixation
UPEP	urine protein electrophoresis
ULN	upper limit of normal
US	United States
Vd	bortezomib with dexamethasone regimen
VGPR	very good partial response

Response Subcategory	Multiple Myeloma Response Criteria
Stable Disease	• Not meeting criteria for CR, VGPR, PR, or PD
PD	• Increase of 25% from lowest response value in any of the following: – Serum M-component (absolute increase must be ≥ 0.5 g/dL) – Serum M-protein increase ≥ 1 g/dL, if the lowest M component was ≥ 5 g/dL – Urine M-component (absolute increase must be ≥ 200 mg per 24 hours) – 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) – In patients without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC 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, ≥ 50% increase from nadir in SPD of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion that is > 1 cm in short axis. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD. • 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; CT = computed tomography; MR = minimal response; MRI = magnetic resonance imaging; PD = progressive disease; PET/CT = positron emission tomography/computed tomography; PR = partial response; sCR = stringent complete response; SFLC = serum free light chain; SPD = sum of the products of the maximal perpendicular diameters of measured lesions; 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 institution of any new therapy, as well as no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow, plasmacytoma, and skeletal survey assessments are not required to be confirmed by repeat testing.

For sCR: presence/absence of clonal cells in bone marrow is based upon the normalization of kappa lambda ratio. “Measurable” disease is defined by at least one of serum protein electrophoresis (SPEP) ≥ 1.0 g/dL, urine protein electrophoresis (UPEP) ≥ 200 mg per 24 hours, or in subjects without detectable serum or urine

12.11 Appendix 11. Guidelines for Documenting Prior Treatment

Patients 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 (Rajkumar et al, 2015):

- 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
- For patients with prior carfilzomib therapy, documentation of response (≥ PR) must be available for the most recent previous carfilzomib therapy as well as stop date. Documentation that the patient was not removed from carfilzomib therapy due to toxicity must also be available. For patients with prior therapy with carfilzomib, the start of the 6-month treatment-free interval is when carfilzomib is discontinued even if other portions of the regimen are continued.

[redacted]