Summary Table of Study Protocol

Title	Comprehensive Analysis of Clinical Parameters That May Inform the Choice of Dose Regimen for Carfilzomib 20/27mg/m^2 or 20/56mg/m^2 With and Without Dexamethasone
Protocol version identifier	20200381 Version 1
Date of last version of the protocol	11 September 2020
EU Post Authorization Study (PAS) Register No	Yes
Active Substance	NA
Medicinal Product	NA
Device	NA
Product Reference	NA
Procedure Number	NA
Joint PASS	Yes
Research Question and Objectives	Evaluate the benefit-risk profile of the clinical parameters that are associated with efficacy and safety outcomes for each carfilzomib dosing regimen (20/27mg/m^2 and 20/56 mg/m^2) with or without dexamethasone which may inform the choice of carfilzomib dose
Country(ies) of Study	Global
Author	PPD Amgen Inc Global Clinical Development Thousand Oaks, CA PPD

Marketing Authorization Holder

Marketing authorization holder(s)	NA
MAH Contact	NA

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

Figure 1. Study Design Schema

Step 1: Identify all Amgen acquired or sponsored clinical trial in Onyx-owned or RAVE database until 14 July 2019

Step 2: Within those databases, identify clinical trials that enrolled RRMM subjects

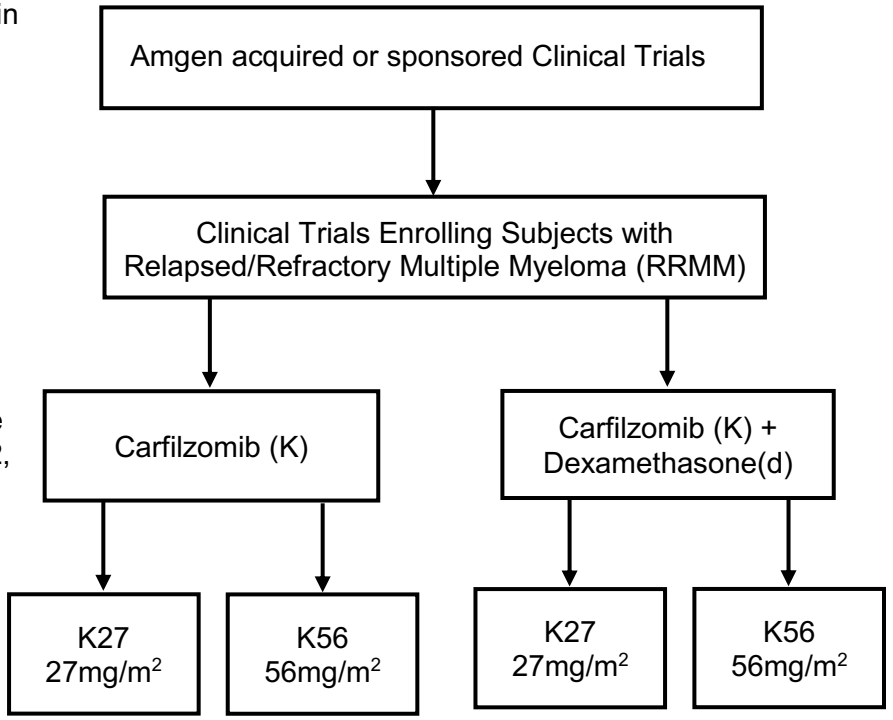
- These subjects may have received any number of prior lines of therapy

Step 3: Among those clinical trials, identify all subjects with RRMM treated with K dosing frequency of twice a week at the start of each week for three of the four-week cycles (days 1, 2, 8, 9, 15, 16 for each 28-day cycle) for all cycles of treatment.

Step 4: Separate those subjects based on treatment of K27, Kd27, K56, or Kd56

- If the regimen in the individual clinical trial dictates that the first and/or second cycle of K therapy is 15mg/m^2 or 20mg/m^2, but 27mg/m^2 is specified for subsequent K cycles of therapy, then the clinical trial will be included for subjects who receive K at 27mg/m^2 with or without dexamethasone.
- If the regimen in the clinical trial dictates that the first cycle of K therapy is 27mg/m^2, but 56mg/m^2 is specified for subsequent K cycles of therapy, then the clinical trial will be included for subjects who receive K at 56 mg/m^2 with or without dexamethasone.
- Therapeutic dexamethasone dosing will be based on

The subject receiving at least 20mg per week.



1. Table of Contents

Summary Table of Study Protocol 1

1. Table of Contents 3

2. List of Abbreviations 6

3. Responsible Parties 7

4. Abstract 9

5. Rationale and Background 12
   - 5.1 Diseases and Therapeutic Area 12
   - 5.2 Rationale 13
   - 5.3 Feasibility and Futility Considerations 14
   - 5.4 Statistical Inference 14

6. Research Question and Objectives 14
   - 6.1 Primary 14
   - 6.2 Secondary 14
   - 6.3 Exploratory 14

7. Research Methods 14
   - 7.1 Study Design 14
   - 7.2 Setting and Study Population 15
     - 7.2.1 Subject Eligibility 15
       - 7.2.1.1 Inclusion Criteria 15
       - 7.2.1.2 Exclusion Criteria 15
     - 7.2.2 Matching 15
     - 7.2.3 Baseline Period 16
   - 7.3 Variables 16
     - 7.3.1 Rationale of Variables Pertaining to Subject Characteristics: Age, Gender, Race, Ethnicity, Body Mass Index, ECOG Performance Status, Creatinine Clearance 17
     - 7.3.2 Rationale of Variables Pertaining to Subject Co-morbidities: Diabetes, Dyslipidemia/hypercholesterolemia, Hypertension, Left Ventricular Hypertrophy, Chronic Kidney Disease, Coronary Artery Disease 18
     - 7.3.3 Rationale of Variables Pertaining to Disease Characteristics: Time From Dnitial diagnosis, Stage of Disease, Lactate Dehydrogenase, Presence of Pasmacytoma, Number of Prior Lines of Therapy, Prior Stem Cell Transplant, Prior Exposure to Lenalidomide, Prior Exposure to Bortezomib, Refractory to Lenalidomide, Refractory to Bortezomib, Refractory to Prior Treatment, Time From Last Relapse of Last Treatment 19

7.3.4 Rationale of Variable Pertaining to Treatment Patterns: Year of treatment initiation 19
7.3.5 Validity and Reliability 19
7.4 Data Sources 20
7.5 Study Size 20
7.6 Data Management 20
7.6.1 Obtaining Data Files 21
7.6.2 Review and Verification of Data Quality 21
7.7 Data Analysis 21
7.7.1 Planned Analyses 21
7.7.1.1 Primary Analysis 27
7.7.2 Planned Method of Analysis 27
7.7.2.1 General Considerations 27
7.7.2.2 Missing or Incomplete Data 28
7.7.2.3 Descriptive Analysis 28
7.7.2.4 Analysis of the Primary, Secondary, and Exploratory Endpoint(s) 28
7.7.2.5 Sensitivity Analysis 30
7.7.3 Analysis of Safety Endpoint(s)/Outcome(s) 31
7.8 Quality Control 31
7.9 Limitations of the Research Methods 31
7.9.1.1 Confounding 31
7.9.2 Analysis Limitations 32
7.9.3 Limitations Due to Missing Data and/or Incomplete Data 32
7.10 Other Aspects 33

8. Protection of Human Subjects 33
8.1 Informed Consent 33
8.2 Institutional Review Board/Independent Ethics Committee (IRB/IEC) 33
8.3 Subject Confidentiality 33

9. Collection, Recording, and Reporting of Safety Information and Product Complaints 33

10. Administrative and Legal Obligations 33

11. Plans for Disseminating and Communicating Study Results 34

12. References 35

13. Appendix 38

List of Tables

Table 1. Summary of Individual Clinical Trials to Derive Subject Data for Pooled Analysis 22
Table 2. Clinical Trials for Primary Data Analysis 27
Table 3. Clinical Trials for Sensitivity Data Analysis 31

List of Figures

Figure 1. Study Design Schema 2

List of Listings

List 1. Planned Variables to be Analyzed that May Inform the Choice of Carfilzomib Dosing Regimen 11
List 2. Adverse Events of Special Interest (in alphabetical order) 29

List of Appendices

Appendix A. ENCePP Checklist for Study Protocol 39

2. List of Abbreviations

Abbreviation or Term	Definition or Explanation
AE	Adverse event
BIW	Bi-weekly (twice a week)
CI	Confidence Interval
CrCl	Creatinine clearance
CRF	Clinical Research Form
ECOG PS	Eastern Cooperative Oncology Group Performance status
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
HLT	High Level Term
HR	Hazard Ratio
ISS	International Staging System
K	Kyprolis® (carfilzomib)
K27	Carfilzomib (monotherapy) at a priming dose of 20mg/m^2 followed by a therapeutic dose of 27mg/m^2
K56	Carfilzomib (monotherapy) at a priming dose of 20mg/m^2 followed by a therapeutic dose of 56mg/m^2
Kd	Carfilzomib in combination with dexamethasone
Kd27	Carfilzomib at a priming dose of 20mg/m^2 followed by a therapeutic dose of 27mg/m^2 in combination with dexamethasone
Kd56	Carfilzomib at a priming dose of 20mg/m^2 followed by a therapeutic dose of 56mg/m^2 in combination with dexamethasone
KM	Kaplan-Meier
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
ORR	Relapsed or Refractory Multiple Myeloma
PFS	Overall Response Rate
PI	Progression-free Survival
PT	Proteasome Inhibitor
QW	Preferred Term
SAP	Once-weekly
SMQB	Statistical Analysis Plan
SMQN	Standard MedDRA Queries, Broad (Scope)
SOC	Standard MedDRA Queries, Narrow (Scope)
TEAE	System Organ Class
	Treatment-Emergent Adverse Event

3. Responsible Parties

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4. Abstract

- Study Title

  Comprehensive Analysis of Clinical Parameters that May Inform the Choice of Dose Regimen for Carfilzomib 20/27mg/m^2 or 20/56mg/m^2 With and Without Dexamethasone

- Study Background and Rationale

  Prior attempts to evaluate different carfilzomib (K) and carfilzomib in combination with dexamethasone (Kd) dosing regimens demonstrated limitations of the collected data on clinical parameters and outcomes. The aim of this analysis is to pool data from Amgen-sponsored clinical trials to describe the benefit-risk profile of clinical parameters associated with efficacy and safety outcomes of subjects treated with one of four different dosing regimens to inform the choice of carfilzomib regimen. The dosing regimens of carfilzomib include a therapeutic dose of 27mg/m^2 or 56mg/m^2, each as monotherapy or in combination with dexamethasone (K27, K56, Kd27, Kd56).

- Study Feasibility and Futility Considerations

  Upon initial review of Amgen-sponsored K clinical trials, there was a limited number of subjects receiving K56 (N=45 subjects). This does not allow a robust comparison of data from this regimen to data from the K27 regimen. Statistical models will be used to determine a favorable or unfavorable association of clinical parameters and choice of carfilzomib regimen.

- Research Question and Objectives

Objectives	Endpoints
Primary	
• Describe the benefit-risk profile for each pre-specified K regimen (K27, Kd27, K56, Kd56) based on the clinical parameters that are associated with efficacy and safety outcomes from the pooled data meeting the criteria for sample size and completeness of covariates	• Efficacy outcomes: Progression free survival (PFS) and Objective Response • Safety outcomes: ○ Grade 3 or higher adverse events and Serious Adverse Events (SAE) for the following key risks that may impact the overall benefit risk profile of carfilzomib: ▪ Cardiac failure (SMQN) ▪ Acute Renal failure (SMQN) ▪ Hypertension (SMQN) ▪ Cardiac events [totaling the incidence using cardiac failure (SMQN), ischaemic heart disease (SMQN), torsades des pointes including QT prolongation (SMQN)] ○ Fatal adverse events
Secondary	
• Compare efficacy and safety outcomes for K dosing regimens with dexamethasone (Kd27 versus Kd56)	• Same efficacy and safety endpoints in the primary objective
Exploratory	
• Compare efficacy and safety outcomes for K27 dosing regimens without and with dexamethasone (K27 versus Kd27)	• Same efficacy and safety endpoints in the primary objective

  – Hypothesis(es)/Estimation

    No formal hypothesis testing is planned for the efficacy and safety comparison between K dosing regimens (Kd56 versus Kd27; Kd27 versus K27). All analyses will be descriptive.

- Study Design/Type

  This is a retrospective, post-hoc, pooled analysis of interventional carfilzomib studies using internal data from Onyx-owned databases and the RAVE database, which is used for all clinical trials conducted by Amgen that span across the globe.

- Study Population or Data Resource

  The study population is all subjects with relapsed or refractory relapsed multiple myeloma (RRMM) who received consistent twice-weekly K treatment with K27, Kd27, K56, or Kd56 via an Amgen-sponsored clinical trial.

- Summary of Eligibility Criteria
  - Amgen acquired or sponsored clinical trial
  - Clinical trial that enrolled subjects with RRMM
  - Subjects treated with K administered as twice weekly in the following regimens: K27, Kd27, K56, or Kd56
- Variables

  Selection of current treatments depend on a plethora of clinical parameters that vary in important and might affect the choice of K regimen for a particular patient. Given that the benefit-risk assessment is a cornerstone of decision making in medicine, and benefit-risk assessment is based upon efficacy outcomes and safety outcomes (Reaney et al, 2019; Curtin et al, 2011), special consideration will be given to clinical parameters known to impact efficacy and safety outcomes in those treated with carfilzomib. Specified below are the clinical parameters for analysis (List 1) for efficacy outcomes such as progression-free survival (PFS) and objective response rate and safety outcomes such as fatalities, grade 3 or higher AEs of special interest for carfilzomib, and serious AEs of special interest for carfilzomib. Variables common to both efficacy and safety outcomes are listed first.

List 1. Planned Variables to be Analyzed that May Inform the Choice of Carfilzomib Dosing Regimen

Variables for efficacy outcomes	Variables for safety outcomes
Age	Age
Gender	Gender
Race	Race
Ethnicity	Ethnicity
Body mass index	Body mass index
ECOG* performance status	ECOG performance status
Creatinine clearance	Creatinine clearance
Time from initial diagnosis	Diabetes
Stage of disease (International Staging System)	Dyslipidemia/hypercholesterolemia

Lactate dehydrogenase	Hypertension
Presence of plasmacytoma	Left ventricular hypertrophy
Number of prior lines of therapy	Chronic kidney disease
Prior stem cell transplant	Coronary artery disease
Prior exposure to lenalidomide	Year of treatment initiation
Prior exposure to bortezomib	
Refractory to lenalidomide	
Refractory to bortezomib	
Refractory to last treatment	
Time from last relapse or last treatment	
Year of treatment initiation	

* Eastern Cooperative Oncology Group

- Study Sample Size

For the carfilzomib regimens K27, K56, Kd27, and K56, the approximate number of subjects for the pooled analysis are 559, 45, 586, and 627 respectively from 13 different Amgen-sponsored clinical trials. The sample size is based on the eligibility criteria.

- Data Analysis

In response to the anticipated variations in the sample sizes and data variables collected for these clinical trials, there will be a primary analysis to avoid the introduction of extra-variation to the pooled data and a subsequent sensitivity analysis. The primary analysis will consist of all studies that meet the eligibility criteria with an adequate sample size of at least 20 subjects and at least 80% completeness of data for each variable in List 1. The subsequent sensitivity analysis will consist of all studies that meet the eligibility criteria.

5. Rationale and Background

5.1 Diseases and Therapeutic Area

Multiple myeloma is the second most common hematological malignancy with more than 150,000 new diagnoses per year globally (Bray et al, 2018). Certain populations are at higher risk of developing MM, namely the elderly with the peak number of new diagnoses in individuals aged 65 to 74 years. African Americans are twice as likely to develop MM than Caucasian-Americans. Men are slightly more likely to develop MM compared to women (Ailawadhi et al, 2019). As the most common malignant plasma cell disorder, MM is characterized by neoplastic proliferation of a predominant clone of plasma cells that produce a monoclonal immunoglobulin protein. Each person with MM

tends to harbor subclones of plasma cells, which can evolve and mutate. This genetic heterogeneity of abnormal plasma cells is hypothesized to drive disease progression and treatment resistance. As a result, MM is characterized by periods of remission and relapse, but remains ultimately fatal (Durie, 2018).

The introduction of novel treatment agents has revolutionized the treatment landscape such that the median survival now extends to approximately 5 years (SEER Database 2010-2016). One of the novel treatment agents is K, a second-generation proteasome inhibitor (PI) that the FDA granted accelerated approval in 2012 for use in individuals with RRMM. Phase 1 studies with K noted better tolerance when administered 2 consecutive days at the start of each week for three weeks of each four-week cycle compared to 5 consecutive days at the start of each two-week cycle. As monotherapy, K at a dose of 27mg/m^2 demonstrated efficacy. The absence of a maximally tolerated dose lead to subsequent escalation studies, which suggested improved efficacy without significant additional toxicity at a dose of 56mg/m^2 when infused over a duration of 30 minutes instead of 10 minutes, a regimen which was also approved by the FDA. When combined with the therapeutic dose for dexamethasone, Kd demonstrated improved efficacy with a comparable safety profile to previous phase 1 and 2 trials. It was the pivotal phase 3 ENDEAVOR clinical trial that established K 20/56 with dexamethasone (Kd 20/56) as a cornerstone for treatment in RRMM (O'Connor et al, 2009; Packet insert for Kyprolis, 2019; Goren et al, 2019).

Interest in identifying the optimal dosing for K as monotherapy or in combination with other agents has sparked several clinical trials, including the SWOG-sponsored S1304 clinical trial (or 20159848). However, prior attempts to evaluate different K and Kd dosing regimens demonstrated limitations of the collected data on clinical variables and outcomes.

5.2 Rationale

Given the anticipated limitations from other investigator-sponsored studies, only Amgen-sponsored K clinical trials at any phase in the RRMM setting will be reviewed for this pooled analysis. The aim of this post-hoc analysis pooled from Amgen-sponsored clinical trials is to describe the benefit-risk profile of clinical parameters associated with efficacy and safety outcomes of subjects treated with K27, Kd27, K56, or Kd56 to inform the choice of carfilzomib regimen.

5.3 Feasibility and Futility Considerations

Upon initial review of Amgen-sponsored K clinical trials, there was limited data for K56 (N=45 subjects) and does not allow for a robust comparison of data from this regimen to data from the K27 regimen. Statistical models will be used to determine a favorable or unfavorable association of clinical parameters and choice of carfilzomib regimen.

5.4 Statistical Inference

This study is descriptive in nature and will not test any hypotheses.

6. Research Question and Objectives

6.1 Primary

Describe the benefit-risk profile for each pre-specified K regimen (K27, Kd27, K56, Kd56) based on the clinical parameters that are associated with efficacy and safety outcomes from the pooled data meeting the criteria for sample size and completeness of covariates

6.2 Secondary

Compare efficacy and safety outcomes for K dosing regimens with dexamethasone (Kd27 versus Kd56)

6.3 Exploratory

Compare efficacy and safety outcomes for K27 dosing regimens without and with dexamethasone (K27 versus Kd27)

7. Research Methods

7.1 Study Design

This is a retrospective cohort study using the data entered Onyx-owned databases and Amgen RAVE database, which is used for all clinical trials conducted by Amgen.

7.2 Setting and Study Population

Eligible subjects will be derived from clinical trials that have yielded data as of 14 July 2019, when drafting of this protocol and corresponding statistical analysis plan began.

7.2.1 Subject Eligibility

7.2.1.1 Inclusion Criteria

Step 1: Identify all Amgen acquired or sponsored studies in Onyx-owned or RAVE database until 14 July 2019.

Step 2: Within those databases, identify all clinical studies that enrolled subjects with RRMM

- These subjects may have received any number of prior lines of therapy

Step 3: Among those clinical studies, identify all subjects treated with K dosing frequency of twice a week at the start of each week for three of the four-week cycles (days 1, 2, 8, 9, 15, 16 for each 28-day cycle) for all cycles of treatment.

Step 4: Separate these subjects based on treatment of K27, Kd27, K56, or Kd56.If the regimen in the individual clinical trial dictates that the first and/or second cycle of K therapy is 15mg/m^2 or 20mg/m^2, but 27mg/m^2 is specified for subsequent K cycles of therapy, then the clinical trial will be included for subjects who receive K at 27mg/m^2 with or without dexamethasone.

- If the regimen in the clinical trial dictates that the first cycle of K therapy is 27mg/m^2, but 56mg/m^2 is specified for subsequent K cycles of therapy, then the clinical trial will be included for subjects who receive K at 56 mg/m^2 with or without dexamethasone.
- Therapeutic dexamethasone dosing will be based on the subject receiving at least 20mg per week.

7.2.1.2 Exclusion Criteria

Exclude any subjects duplicated among the different carfilzomib regimens

7.2.2 Matching

The propensity score matching approach for the comparison of outcomes among carfilzomib regimens is detailed in Section 9.5.2.1 of the SAP. Briefly, to generate the propensity score for each subject, all the variables or covariates specified in List 1 will be included in the propensity score model (logistic regression model) with the dosing regimen as the binary response. There will be propensity score matching for the datasets of Kd27 versus Kd56 and for K27 versus Kd27. For the evaluation of these

secondary and exploratory objectives, the propensity score matching creates mutually exclusive sets of observations that have similar propensity scores. The Greedy nearest neighbor 1:1 matching without replacement will be used to sequentially match each subject in the Kd56 regimen with one subject in the Kd27 regimen if the difference in the logits of the propensity score for pairs of subjects from the two groups is less than or equal to 0.1 times the pooled estimate of the standard deviation (Austin, 2014). The threshold 0.1 was chosen so that the resulting matched samples have balanced distributions of baseline covariates. Same method will be used to create a propensity score matched samples for subjects with Kd27 or K27.

7.2.3 Baseline Period

The baseline period is defined as the period from screening up to the time before the first dose of protocol-specified treatment was given, during which the data obtained for each variable or covariate in List 1. If multiple values were obtained during this time period, then the most recent value prior to the first dose of protocol-specified treatment will be used as the baseline parameter.

7.3 Variables

Selection of current treatments depend on a plethora of clinical parameters that vary in important and might affect the choice of K regimen for a particular patient. Given that the benefit-risk assessment is a cornerstone of decision making in medicine, and benefit-risk assessment is based upon efficacy outcomes and safety outcomes (Reaney et al, 2019; Curtin et al 2011), special consideration will be given to clinical parameters known to impact efficacy and safety outcomes. Further consideration will be given to those clinical parameters that may be unique to efficacy and safety outcomes in those treated with carfilzomib. Specified below are the clinical parameters for analysis (List 1) for efficacy outcomes such as progression-free survival (PFS) and objective response rate and safety outcomes such as fatalities, grade 3 or higher AEs of special interest for carfilzomib, and serious AEs of special interest for carfilzomib. Variables common to both efficacy and safety outcomes are listed first. Further details are specified in the SAP.

List 1. Planned Variables to be Analyzed that May Inform the Choice of Carfilzomib Dosing Regimen

Variables for efficacy outcomes	Variables for safety outcomes
Age	Age
Gender	Gender
Race	Race
Ethnicity	Ethnicity
Body mass index	Body mass index
ECOG* performance status	ECOG performance status
Creatinine clearance	Creatinine clearance
Time from initial diagnosis	Diabetes
Stage of disease (International Staging System)	Dyslipidemia/hypercholesterolemia
Lactate dehydrogenase	Hypertension
Presence of plasmacytoma	Left ventricular hypertrophy
Number of prior lines of therapy	Chronic kidney disease
Prior stem cell transplant	Coronary artery disease
Prior exposure to lenalidomide	Year of treatment initiation
Prior exposure to bortezomib	
Refractory to lenalidomide	
Refractory to bortezomib	
Refractory to last treatment	
Time from last relapse or last treatment	
Year of treatment initiation	

* Eastern Cooperative Oncology Group

7.3.1 Rationale of Variables Pertaining to Subject Characteristics: Age, Gender, Race, Ethnicity, Body Mass Index, ECOG Performance Status, Creatinine Clearance

Established prognostic patient characteristics, not only for myeloma but the majority of oncological diseases, include age (Bringhen S et al, 2013; Chretien M-L et al, 2014; Qian J et al, 2017;) and performance status (ECOG-ACRIN Cancer Research Group, 2020; Jang RW et al, 2014). While body habitus, as measured via body mass index, is a known MM risk, it is potentially a prognostic risk (Beason et al, 2013; Tamayo RR et al, 2014). Given the discrepancy of the incidence of MM and outcomes between genders (Boyd KD et al, 2011) and among different races and ethnicities (Fillmore NR et al, 2019; Waxman AJ et al, 2010), these demographics were deemed important to include. For decades, renal dysfunction has been part of the CRAB criteria (acronym for

hyper**c**alcemia, **r**enal failure, **a**nemia, and **b**one disease) for end-organ damage to diagnosis MM (Rajkumar et al, 2014). With at least 50% of patients with MM having renal dysfunction at presentation due to the proteins secreted by the malignant cells (Yaday et al, 2016), creatinine clearance is a recommended diagnostic evaluation per NCCN guidelines and serves an important eligibility criterion in MM clinical trials (Bringhen S et al, 2013; National Comprehensive Cancer Network Clinical Practice (NCCN) Guidelines in Oncology, 2020).

7.3.2 Rationale of Variables Pertaining to Subject Co-morbidities: Diabetes, Dyslipidemia/hypercholesterolemia, Hypertension, Left Ventricular Hypertrophy, Chronic Kidney Disease, Coronary Artery Disease

Additional variables will include those that are associated with baseline co-morbidities, which are evolving prognostic variables and appear to influence treatment patterns in RRMM (Kleber et al, 2011). Notable ones are cardiac and renal comorbidities, as these may be aggravated not only from the MM itself, but also from disease treatments, including carfilzomib (Ritts et al, 2016; Bruno et al, 2019). These may be overlapping as renal insufficiency and have been shown to increase the risk of cardiovascular disease up to four-fold (Gansevoort et al, 2013). Diabetes, dyslipidemia or hypercholesterolemia, and hypertension are known to be more prevalent in those with multiple myeloma at the time of diagnosis compared to age- and gender-matched healthy individuals. Specifically, the respective prevalence for diabetes, dyslipidemia, and hypertension is approximately 27%, 41%, and 53% for those with MM at the time of diagnosis compared to approximately 11%, 32%, and 41% for the matched healthy individuals (Markus et al, 2020). Other baseline comorbidities of left ventricular hypertrophy, coronary artery disease, and chronic kidney disease are also important covariates to include given that carfilzomib is associated with cardiac and renal toxicity and have been previously explored with need for further investigation (Carfilzomib Investigator's Brochure, 2019; Bruno et al, 2019; Dimopoulous et al, 2017). To date, there are still no known predictive factors for such adverse events and the carfilzomib mechanism causing toxicity remains unclear.

7.3.3 Rationale of Variables Pertaining to Disease Characteristics: Time From Initial diagnosis, Stage of Disease, Lactate Dehydrogenase, Presence of Plasmacytoma, Number of Prior Lines of Therapy, Prior Stem Cell Transplant, Prior Exposure to Lenalidomide, Prior Exposure to Bortezomib, Refractory to Lenalidomide, Refractory to Bortezomib, Refractory to Prior Treatment, Time From Last Relapse of Last Treatment

Prognostic disease characteristics have been identified by the International Staging System (ISS) and Revised-ISS, which as of 2015 the latter consists of albumin and β2 microglobulin from the ISS, along with the addition of lactate dehydrogenase (LDH), and chromosomal abnormalities detected by interphase fluorescent in situ hybridization (iFISH) (Greipp et al, 2005; Palumbo A et al, 2015). ISS and LDH will be evaluated as separate covariates. Another important and frequent complication at presentation is the presence of extramedullary plasmacytomas, which tend to be resistant to conventional treatments and seems to be biologically distinct from high-risk molecular and histological features (Chen HF et al, 2012; Sevcikova S et al, 2019). One of the most important disease characteristics in the RRMM setting is the duration of disease control, which can be evaluated by time from initial diagnosis and time from last relapse/treatment (Kumar SK et al, 2018; Durie BGM, 2018; Lancman G et al; 2017; Dingli et al, 2017). The duration of disease control is likely determined by the disease biology, but may also be determined by previous treatment and drug exposures. With further guidance from recent literature review and input from subject matter experts regarding prognostic baseline clinical parameters in rapidly evolving RRMM treatment landscape, prior stem cell transplant, prior exposure and/or refractoriness to bortezomib, prior exposure and/or refractoriness to lenalidomide, and refractoriness to prior treatment are included as covariates (Dingli et al, 2017; Dimopoulous et al, 2015; Barlogie et al, 2011; Rajkumar et al, 2001).

7.3.4 Rationale of Variable Pertaining to Treatment Patterns: Year of treatment initiation

It is recognized that the implementation of these Amgen acquired or sponsored clinical trials spanned nearly a decade, whereby the understanding of the myeloma disease greatly has improved and the clinical development of K proceeded from preclinical to robust clinical studies. As the RRMM treatment combinations and patterns are dynamic, an additional clinical parameter to consider is the year of treatment initiation.

7.3.5 Validity and Reliability

All the clinical trials included in this pooled study have completed the clinical study report and the analysis datasets and variables have been validated by sponsor. In this pooled

analysis, each individual trial will follow its own derivations of the endpoints and variables, which are specified in its own SAP.

7.4 Data Sources

All subject data in the selected clinical trials were recorded on the Clinical Research Form (CRF) unless transmitted to the sponsor electronically. The investigator verified the accurate data entries by signing the CRF. Clinical monitors performed source data verification to confirm that CRF data are accurate. The sponsor data management department performed the edit check outlined in the data management plan on file. The analysis datasets and variables of each individual clinical trials in this pooled analysis have been validated by sponsor. Variables from each individual trial will follow its own derivations specified in its own SAP. All data among sources can be linked based on the unique identifier for each subject. For further details, please see Sections 8.1 and 8.2 of the SAP.

7.5 Study Size

As of 14 July 2019, there are approximately 604 subjects from 9 clinical trials for K monotherapy and 1,213 subjects from 9 clinical trials for Kd The sample size for the primary analysis described in Section 7.7.1.1 is 564 subjects from 5 clinical trials for K monotherapy and 1,199 subjects from 6 clinical trials for Kd (Table 1). The sample size for the subsequent sensitivity analysis described in Section 7.7.2.5 is 604 subjects from 9 clinical trials for K monotherapy and 1,213 subjects from 9 clinical trials for Kd (Table 2).

The sample size is based on the inclusion criteria specified in Section 7.2.1. In this pooled analysis, the primary objective is to describe the benefit-risk profile for each K dosing regimen based on the clinical parameters that are associated with efficacy and safety outcomes. All analyses will be descriptive.

7.6 Data Management

As noted in Section 8.7 of the SAP, programs will be developed and maintained and output will be verified in accordance with current risk-based quality control procedures. Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs. The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

7.6.1 Obtaining Data Files

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. The data of individual clinical trial were entered in Onyx owned clinical databases and Amgen RAVE database. The data handling and electronic transfer of data are described in the data management plan on file. No linking of data files is necessary. For further details, please see Section 8 of the SAP.

7.6.2 Review and Verification of Data Quality

The database of each individual clinical trial was subject to edit checks outlined in the data management plan. Data inconsistencies and suspicious values were reviewed and resolved before the database was locked for analyses in clinical study report. The analysis datasets and variables in each individual clinical trial had been validated by sponsor. In this pooled study, each individual trial will follow its own derivations of the endpoints and variables, which are specified in its own SAP.

7.7 Data Analysis

7.7.1 Planned Analyses

The planned analysis will be based on the subjects pooled from the clinical trials that meet the eligible criteria outlined above, which is further described in Table 1.

Table 1. Summary of Individual Clinical Trials to Derive Subject Data for Pooled Analysis

Study Number	Study Title	Subject Population	Design	Objectives	Drug Combination/ K Dose Schedule[a]	Eligible Subjects (K regimen: subject #)
20160275	A Randomized, Open-label, Phase 3 Study Comparing Carfilzomib, Dexamethasone, and Daratumumab to Carfilzomib and Dexamethasone for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma (CANDOR)	Relapsed or refractory MM	Phase 3, randomized, active-controlled	Efficacy; safety	Carfilzomib + dexamethasone + daratumumab (Dara) vs carfilzomib + dexamethasone K 20/56 mg/m^2 (30 min) Dara 16 mg/kg up to 4 years	Kd: 153 subjects
20140355 (CFZ014)	A Randomized, Open-label, Phase 3 Study in Subjects With Relapsed and Refractory Multiple Myeloma Receiving Carfilzomib in Combination With Dexamethasone, Comparing Once-weekly Versus Twice-weekly Carfilzomib Dosing (A.R.R.O.W.)	Relapsed and refractory MM	Phase 3, randomized	Efficacy; safety	Carfilzomib + dexamethasone K 20/70 mg/m^2 QW (30 min) K 20/27 mg/m^2 BIW (10 min)	Kd27: 235 subjects

Page 1 of 5

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Table 1. Summary of Individual Clinical Trials to Derive Subject Data for Pooled Analysis

Study Number	Study Title	Subject Population	Design	Objectives	Drug Combination/ K Dose Schedule[a]	Eligible Subjects (K regimen: subject #)
20140242 (CFZ005)	An Open-label, Single-arm, Phase 3 Study of Carfilzomib in Combination With Dexamethasone in Subjects With Relapsed and Refractory Multiple Myeloma in China	Relapsed and refractory MM; ≥ 2 prior tx	Phase 3, single arm	Efficacy	Carfilzomib + dexamethasone K 20/27 mg/m^2 (30 min) dex 20 mg	Kd27: 123 subjects
20140122 (PX-171-002 Part 1 and Part 2)	A Phase 1 Study of the Safety and Pharmacokinetics of Escalating Intravenous Doses of the Proteasome Inhibitor PR-171 in Patients with Hematological Malignancies: Four-week Cycle	MM, NHL, WM, or HD; relapsed or refractory after ≥ 2 prior tx	Phase 1, dose escalation/ expansion	Safety and tolerability; establish MTD; PK	Carfilzomib Part 1:1.2 to 27 mg/m^2 (2 min) Part 2: 20/27 mg/m^2 (10 min) up to 12 cycles	K27: 7 subjects Kd27: 3 subjects
20140120 (PX-171-005)	Phase 2 Study of the Safety and Pharmacokinetics of carfilzomib in Subjects with relapsed and Refractory Multiple Myeloma and Varying Degrees of Renal Function	Relapsed and refractory MM; ≥ 2 prior tx; varying degrees of renal function	Phase 2, single arm, parallel cohorts by CrCL grouping	PK; safety and tolerability; PDn; QTc; efficacy	Carfilzomib 15/20/27 mg/m^2 (2 to 10 min)	K27: 8 subjects Kd27: 20 subjects

Page 2 of 5

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Table 1. Summary of Individual Clinical Trials to Derive Subject Data for Pooled Analysis

Study Number	Study Title	Subject Population	Design	Objectives	Drug Combination/ K Dose Schedule[a]	Eligible Subjects (K regimen: subject #)
20140119 (PX-171-004 – Part 1 and Part 2)	An Open-label, Single-arm, Phase 2 Study of Carfilzomib in Patients with Relapsed and Refractory Multiple Myeloma	Relapsed or refractory MM; 1 to 3 prior tx	Phase 2 Part 1: single arm Part 2: 2 dosing cohorts	Safety; efficacy; PK	Carfilzomib Part 1: 20 mg/m^2 (10 min) Part 2: 20 or 20/27 mg/m^2 (10 min) up to 12 cycles	K27: 78 subjects
20140118 (PX-171-003 – Part 1 (A0) and Part 2 (A1))	An Open-label, Single-arm, Phase 2 Study of Carfilzomib in Patients with Relapsed and Refractory Multiple Myeloma	Relapsed and refractory MM; ≥ 2 prior tx	Phase 2, single arm	Efficacy; safety; PK; PDn	Carfilzomib Part 1: 20 mg/m^2 (2 min) Part 2: 20/27 mg/m^2 (10 min) up to 12 cycles	K27: 200 subjects
20130402 (CFZ002)	An Open-label, Single Arm, Phase 1 Study of the Pharmacokinetics and Safety of Carfilzomib in Subjects with Advanced malignancies and varying Degrees of Hepatic Impairment	Relapsed or progressive advanced malignancies; ≥ 2 prior tx; varying degrees of hepatic function	Phase 1, comparative PK with 4 cohorts based on liver function	Assess hepatic impairment on AUC	Carfilzomib + dexamethasone K 20/27/56 mg/m^2 (30 min) dex 8 mg BIW	K56: 2 subjects

Page 3 of 5

Footnotes defined on last page of the table

Table 1. Summary of Individual Clinical Trials to Derive Subject Data for Pooled Analysis

Study Number	Study Title	Subject Population	Design	Objectives	Drug Combination/ K Dose Schedule[a]	Eligible Subjects (K regimen: subject #)
20130401 (CFZ001)	An Open-label, Single Arm, Phase 1 Study of the Pharmacokinetics and Safety of Carfilzomib in Subjects with Relapsed Multiple Myeloma and End-stage Renal Disease	Relapsed or refractory MM; ≥ 1 prior tx; normal renal function or ESRD on hemodialysis	Phase 1, comparative PK with 2 cohorts based on CrCL	Assess influence of ESRD on AUC	Carfilzomib + dexamethasone K 20/27/56 mg/m^2 (30 min) dex 8 mg BIW	K27: 4 subjects K56: 19 subjects Kd56: 3 subjects
20130398 (2011-003)	A Randomized, Open-label, Phase 3 Study of Carfilzomib Plus Dexamethasone Versus Bortezomib Plus Dexamethasone in Patients With Relapsed Multiple Myeloma (ENDEAVOR)	Relapsed MM; 1 to 3 prior tx	Phase 3, randomized, active-control	Efficacy; safety	Carfilzomib + dexamethasone vs bortezomib (V) + dexamethasone K 20/56 mg/m^2 (30 min) dex 20 mg V 1.3 mg/m^2	Kd56: 463 subjects
20130396 (PX-171-011)	A Randomized, Open-label, Phase 3 Study of Carfilzomib vs Best Supportive Care in Subjects with Relapsed and Refractory Multiple Myeloma (FOCUS)	Relapsed and refractory MM; ≥ 3 prior tx	Phase 3, randomized, active-control	Efficacy; safety	Carfilzomib vs best supportive care K 20/27 mg/m^2 (10 min) Corticosteroid (prednisolone 30 mg or dex 6 mg every other day) Optional CYC 50 mg QD	K27: 157 subjects

Page 4 of 5

Footnotes defined on next page of the table

Table 1. Summary of Individual Clinical Trials to Derive Subject Data for Pooled Analysis

Study Number	Study Title	Subject Population	Design	Objectives	Drug Combination/ K Dose Schedule[a]	Eligible Subjects (K regimen: subject #)
20130393 (PX-171-007)	Phase 1b/2, Multicenter Open-label Study of the Safety and Activity of Carfilzomib in subjects with Relapsed Solids Tumors, Multiple Myeloma, or Lymphoma	Relapsed or refractory MM; ≥ 2 prior tx	Phase 1b/2, dose escalation	Safety and tolerability	Carfilzomib 20/36 to 20/70 mg/m^2 (30 min)	K56: 24 subjects Kd56: 8 subjects
					Carfilzomib + dexamethasone K 20/45 or 20/56 mg/m^2 (30 min)	
2011-002	Carfilzomib Multiple Myeloma Expanded Access protocol (C-MAP) for Subjects with Relapsed and Refectory Disease (C-MAP)	Relapsed or refractory MM; ≥ 4 prior tx; unable to enroll in another US CFZ study	Phase 2, single arm; expanded access program	Safety	Carfilzomib 20/27 mg/m^2 (10 min)	K27: 105 subjects Kd27: 205 subjects

Page 5 of 5

ALL = acute lymphoblastic leukemia; AUC = area under the concentration-time curve; BIW = twice weekly; BTZ = bortezomib; CFZ = carfilzomib; C-MAP = Carfilzomib Multiple Myeloma Expanded Access Protocol; CrCL = creatinine clearance; CYC = cyclophosphamide; Dara = daratumumab; DDI = drug-drug interaction; DEX = dexamethasone; ESRD = end-stage renal disease; HD = Hodgkin's disease; LEN = lenalidomide; MEL = melphalan; Mito = mitoxantrone; MM = multiple myeloma; MTD = maximum tolerated dose; NHL = non-Hodgkin's lymphoma; PDn = pharmacodynamics; PEG = polyethylene glycol; PK = pharmacokinetics; POM = pomalidomide; PRED = prednisone; QD = once daily; QTc = corrected QT interval; QW = once weekly; R3 = dexamethasone, mitoxantrone, PEG-asparaginase, and vincristine; SCLC = small-cell lung cancer; tx = therapy(ies); US = United States; VCR = vincristine; VXLD = vincristine, dexamethasone, PEG-asparaginase, and daunorubicin; WM = Waldenström's macroglobulinemia

Studies 2011-003 (ENDEAVOR) and 2012-005 (CLARION) are co-sponsored by Amgen and Ono Pharmaceutical Co, Ltd. in Japan and is sponsored solely by Amgen in other participating countries. All other studies are sponsored solely by Amgen.

All studies were open-label.

[a]Unless otherwise noted, carfilzomib was administered in 28-day cycles on days 1, 2, 8, 9, 15, and 16 until progressive disease. Stepped-up dosing was allowed on cycle 1 day 8 for Studies PX-171-009 (ASPIRE), PX-171-011 (FOCUS), 2011-003 (ENDEAVOR), PX-171-007, 2011-002, CFZ001, CFZ002, 20140242 (CFZ005), 20140355 (A.R.R.O.W.), 20160275 (CANDOR); on cycle 2 day 1 for Studies PX-171-002 – Part 2, PX-171-003 – Part 2 (A1), PX-171-004 – Part 2, and PX-171-005. Where applicable, and unless otherwise noted, dexamethasone was administered at 40 mg weekly.

7.7.1.1 Primary Analysis

In response to the anticipated variations in the sample sizes and data variables collected for these 13 clinical trials, there will be a primary analysis and a subsequent sensitivity analysis to avoid the introduction of extra-variation to the pooled data. The primary analysis will consist of all studies that meet the eligibility criteria with an adequate sample size of at least 20 subjects and at least 80% completeness of data for each variable in List 1 (Table 2). This yields 5 clinical trials for K monotherapy totaling 564 subjects and 6 clinical trials for Kd totaling 1,199 subjects.

Table 2. Clinical Trials for Primary Data Analysis

K27 (540 subjects)	K56 (24 subjects)	Kd27 (583 subjects)	Kd56 (616 subjects)
20140119 (78 subjects)	20130393 (24 subjects)	20140355 (235 subjects)	20160275 (153 subjects)
20140118 (200 subjects)		20140242 (123 subjects)	20130398 (463 subjects)
20130396 (157 subjects)		20140120 (20 subjects)	
2011-002 (105 subjects)		2011-002 (205 subjects)	

7.7.2 Planned Method of Analysis

Data from these clinical trials will be pooled for the analysis of clinical parameters that may inform the choice of K dose regimen. Given the anticipated heterogeneity of sample sizes from early phase 1 and robust phase 3 studies and evolving data collection, a primary analysis and a subsequent sensitivity analysis will be performed. The primary analysis will consist of studies with an adequate sample size of at least 20 subjects and at least 80% completeness of data for each variable (List 1) to avoid introduction of extra-variation to the pooled data. In contrast, the sensitivity analysis will consist of all pooled data. For a detailed description of the efficacy and safety analyses, please refer to Section 7.7.2.4 and Section 7.2 of the SAP.

7.7.2.1 General Considerations

All analyses will be descriptive. No formal hypothesis testing is planned for the efficacy and safety comparison between carfilzomib dosing regimens (Kd27versus Kd56; K27 versus Kd27).

7.7.2.2 Missing or Incomplete Data

The descriptive statistics will identify the extent of missing data. Rules for handling incomplete or missing data related to endpoints are detailed in the SAP of each individual trial. For this analysis, no imputation will be done for the analysis of the safety endpoints and efficacy endpoints. The handling of incomplete or missing dates for adverse events and death are also detailed in the SAP of each individual trial. For this analysis, the missing values for the continuous clinical parameters, or covariates, will not be imputed. The missing values for categorical covariates in each individual trial will be classified into a category called Unknown.

7.7.2.3 Descriptive Analysis

All analyses will be descriptive. Descriptive statistics will be produced to describe the exposure to carfilzomib by treatment group.

- Duration of treatment (weeks) defined as duration (in weeks) (the date of last dose of carfilzomib – the date of first dose of carfilzomib +1) /7
- Number of carfilzomib administrations
- Cumulative dose received of carfilzomib (mg/m2) across all cycles
- Average dose received of carfilzomib (mg/m2): defined as the cumulative dose received divided by the number of doses administered

7.7.2.3.1 Description of Study Enrollment

The subjects will be enrolled based on eligibility criteria outlined in Section 7.2.1 and from clinical trials summarized in Table 1.

7.7.2.4 Analysis of the Primary, Secondary, and Exploratory Endpoint(s)

For the primary endpoint, the analyses will describe the distribution of each clinical parameter and the distribution of each efficacy/safety outcome by each dosing regimen (K27, Kd27, K56, and Kd56) to yield a summary of the favorable versus unfavorable effects for each dosing regimen.

For the secondary and exploratory endpoints, the outcomes for efficacy will use the well-established endpoints of PFS, an approved surrogate marker of overall survival, and ORR, one of the most commonly used endpoints in myeloma clinical trials. Each individual trial will follow its own definition of PFS and ORR, which was specified in its respective SAP, to derive these pooled data. For analyses of PFS, Kaplan-Meier estimates will be used to estimate the median and other quartiles along with corresponding two-sided 95% confidence intervals. For analyses of ORR, the associated 95% exact binomial confidence interval (Clopper-Pearson method) will be

reported for Kd56 versus Kd27 and Kd27 versus K27. Risk ratio (RR) with the corresponding 95% CIs for Kd56 versus Kd27 and Kd27 versus K27 will be estimated using Cochran-Mantel-Haenszel (CMH) method. To account for potential differences in drug exposure duration, exposure-adjusted incidence rate with the corresponding 95% CI will also be calculated.

Also, for the secondary and exploratory endpoints, outcomes for safety will use endpoints of all fatal events as well as grade 3 or higher and serious adverse events (AEs) of special interest (List 2). Classification of the severity of AEs from each trial will be in accordance with the NCI-CTCAE criteria used during that individual clinical trial, which was also specified in its respective SAP. The number and percentage of subjects experiencing the treatment-emergent adverse event (TEAE) by system organ class/preferred term (SOC/PT) will be summarized for the specified safety outcomes and presented side-by-side for the 4 dosing regimens (K27, K56, Kd27, Kd56) overall for both the primary and sensitivity analyses.

List 2. Adverse Events of Special Interest (in alphabetical order)

- Acute renal failure (SMQN)
- Cardiac events (Sum of events for cardiac failure [SMQN] + ischemic heart disease [SMQN] + torsades des points including QT prolongation [SMQB])
- Cardiac failure (SMQN)
- Hypertension (SMQN)

Clinical review for identification of AEs of special interest for this post-hoc analysis spanned the following types of events, in alphabetical order: cardiac, gastrointestinal, haematological (cytopenias), infusion reactions, peripheral neuropathy, pulmonary, renal, tumor lysis syndrome, and viral infections. Specific AEs of special interest consistently identified throughout the individual clinical trials were as follows (SMQNs unless otherwise specified): acute renal failure, cardiac arrhythmia, drug-related hepatic disorder, dyspnea (HL), embolic and thrombotic events – venous, hemorrhage, hepatic failure/fibrosis and cirrhosis/other liver damage-related conditions, hypertension, interstitial lung disease, ischemic heart disease (SMQB), liver related investigations - signs and symptoms, malignant or unspecified tumors, myocardial infarctions (SMQB), pulmonary hypertension, thrombocytopenia (SMQB), and torsade de pointes – QT prolongation (SMQB) (Carfilzomib Investigator's Brochure, 2019). However, AEs of special interest identified for this pooled analysis reflect the AEs of special interest consistently identified in individual clinical trials with increased incidence compared to

the control cohort without K or were notable in safety reports. This approach should capture AEs that lead to non-fatal treatment discontinuations for K, even if the overall incidence for that AE was low. Although thrombocytopenias occur in more than 20% of individuals treated with K, nearly all treatments for MM induce myelosuppression (Package inserts for Cyclophosphamide, 2013; Darzalex, 2016; Empliciti, 2015; Pomalyst, 2017; Revlimid, 2017; Sarclisa, 2020; Thalomid, 2014; Velcade 2008) and supportive measures (eg platelet transfusions) are part of standard-of-care practices, making thrombocytopenia a less critical clinical parameter that may inform the choice of K dose in the RRMM setting. In other words, List 2 focuses on those AEs that has the potential to directly impact the benefit-risk profile for K and thereby inform the choice of K dose regimen.

For the secondary and exploratory endpoints, each propensity score analysis will compare the efficacy (Hazard Ratio (HR)(CI) for PFS and Odds Ratio (OR)(CI) for ORR) and safety outcomes (Risk Ratio (RR)(CI)) overall and in subgroups determined by the clinical parameters from List 1 (covariates). Based on the results, the favorable versus unfavorable effects of Kd27 versus Kd56 and K27 versus Kd27 will be summarized. The comparison of K27 versus K56 will not be included due to the limited sample size of the K56 cohort.

For further details, please refer to Section 9.5 and 9.6 of the SAP.

7.7.2.5 Sensitivity Analysis

For the primary endpoint, the subsequent sensitivity analysis will consist of all studies that meet the eligibility criteria described above without regard to sample size or completeness of data (Table 3). This yields 9 clinical trials for K monotherapy totaling 604 subjects and 9 clinical trials for Kd totaling 1,213 subjects.

Table 3. Clinical Trials for Sensitivity Data Analysis

K27 (559 subjects)	K56 (45 subjects)	Kd27 (586 subjects)	Kd56 (627 subjects)
20140122 (7 subjects)	20130402 (2 subjects)	20140355 (235 subjects)	20160275 (153 subjects)
20140120 (8 subjects)	20130401 (19 subjects)	20140242 (123 subjects)	20130398 (463 subjects)
20140119 (78 subjects)	20130393 (24 subjects)	20140122 (3 subjects)	20130393 (8 subjects)
20140118 (200 subjects)		20140120 (20 subjects)	20130401 (3 subjects)
20130396 (157 subjects)		2011-002 (205 subjects)	
20130401 (4 subjects)			
2011-002 (105 subjects)			

7.7.2.5.1 Subgroup Analysis

Exploratory subgroup analyses may be performed based on the following subgroups determined by the covariates (clinical parameters), if applicable, as per List 1. If there is an insufficient number of subjects in a particular subgroup, defined as less than 10% of subjects in that particular carfilzomib dosing regimen, relevant subgroups may be combined.

7.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

Please refer to Section 7.7.2.4 for the description of the efficacy and safety analyses. The Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or later will be used to code all events.

7.8 Quality Control

Biostatical programmers will write and execute the analytics. A programmer will be assigned to quality control and verify the results from the analyses.

7.9 Limitations of the Research Methods

7.9.1.1 Confounding

All the clinical parameters specified in List 1 are considered to be potential important confounding variables, given the potential association with both the specific K dosing regimens and efficacy and/or safety outcomes. In the analyses of comparison between

the dosing regimens, the propensity score matching method will adjust for the covariates by balancing out their distributions between the dosing regimens.

7.9.2 Analysis Limitations

This is a post-hoc pooled analysis to evaluate the benefit-risk profile of the clinical parameters that are associated with efficacy and safety outcomes for each K dosing regimen (K27, Kd27, K56, Kd56) which may inform the choice of carfilzomib dose. To balance the clinical parameters between non-randomized dosing regimens, and thereby reduce bias due to patient selection given that subjects might differ systematically between dosing regimens, the well-established propensity score matching method will be used (Brookhart et al, 2006; D'Agostino, 1998). While there are inherent limitations to the propensity score matching method, including the loss of patients who cannot be matched 1:1 and inability to create a balance for unobserved covariates, there are no superior alternative methods to adjust for differences in populations among the various clinical trials to enhance the robustness of the results. Therefore, at this time, this method is considered the most appropriate method to compare the clinical outcomes overall and in subsequent subgroups.

In response to the anticipated variations in the sample sizes and data variables collected for these 13 clinical trials, and to avoid the introduction of extra-variation to the pooled data, there will be a primary analysis and a subsequent sensitivity analysis, as previously described in Section 7.7.2.

Another limitation is the small sample size of the pooled data for K56. The small sample size prevents robust comparison of K27 vs K56, which is needed to summarize potential clinical parameters that could impact the choice between these two regimens. Supplementation of K56 data from real-world clinical databases would introduce significant volumes of missing data, which would compromise the integrity of the post-hoc analysis. To probe further and better understand carfilzomib monotherapy, which may be a plausible option for subjects with heavily pre-treated myeloma, an exploratory analysis will be performed to compare the efficacy and safety outcomes for K27 dosing regimen without versus with dexamethasone (K27 versus Kd27).

7.9.3 Limitations Due to Missing Data and/or Incomplete Data

As previously noted, the implementation of these studies spanned nearly a decade, whereby the understanding of the myeloma disease has greatly improved. Despite special consideration, data for particular variables in several clinical trials may not exist. For example, as the predictors for outcomes in MM remain complex, the data collection

for two cardiovascular parameters of tobacco exposure and family history of early coronary artery disease have be inconsistent and thus will be excluded. Also, given the recent recommendations for FISH analysis, there would be no data for this clinical parameter of chromosomal abnormalities in earlier years of clinical trials. With the anticipate large volume of unknown data, this clinical parameter will be excluded. These parameters have been excluded to avoid large volumes of empty data fields due to non-existent data that would jeopardize the integrity of the analyses. To address data that is missing (versus non-existent data), please see Section 7.7.2.2.

7.10 Other Aspects

For additional details, please refer to the SAP.

8. Protection of Human Subjects

8.1 Informed Consent

No study subjects will be contacted for the analysis.

8.2 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

This study is a retrospective analysis of existing data; therefore, IRB approval is not necessary.

8.3 Subject Confidentiality

This protocol will comply with all applicable laws regarding subject privacy. No direct subject contact or collection of additional subject data will occur. Only anonymous data will be used for the analysis. Results will be in tabular form and aggregate analyses that omit subject identification. Any publications and reports will not include subject identifiers.

9. Collection, Recording, and Reporting of Safety Information and Product Complaints

Reporting of individual adverse events (AE), product complaints, and other safety findings is not applicable for this pooled retrospective post-hoc analysis, as the safety data from the studies identified have been previously reported to regulatory agencies, institutional review boards, and ethics committees in accordance with local regulations and routine pharmacovigilance practices. No new safety data will be collected or analyzed to complete the objectives of this study.

10. Administrative and Legal Obligations

Amgen may amend the protocol at any time. Amgen reserves the right to terminate the study at any time.

11. Plans for Disseminating and Communicating Study Results

As a regulatory requirement, this report will be submitted to the FDA at the agreed upon timelines; otherwise, there are no current plans to submit results for publication.

12. References

Austin PC. A comparison of 12 algorithms for matching on the propensity score. Statistics in Medicine. 2014;33:1057-1069.

Broglie B, Bolejack V, Schell M, Crowley J. Prognostic factor analyses of myeloma survival with intergroup trial S9321 (INT 0141): examining whether different variables govern different time segments of survival. Ann Hematol. 2011;90(4):423-428.

Beason TS, Chang SH, Sanfilippo KM, et al. Influence of body mass index on survival in veterans with multiple myeloma. Oncologist. 2013;18(10):1074-1079.

Boyd KD, Ross FM, Chiecchio L, et al. Gender disparities in the tumor genetics and clinical outcome of multiple myeloma. Cancer Epidemiol Biomarkers Prev. 2011;20(8):1703-1707.

Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [published correction appears in CA Cancer J Clin. 2020 Jul;70(4):313]. CA Cancer J Clin. 2018;68(6):394-424.

Bringhen S, Mateos MV, Zweegman S, et al. Age and organ damage correlate with poor survival in myeloma patients: meta-analysis of 1435 individual patient data from 4 randomized trials. Haematologica. 2013;98(6):980-987.

Brookhart MA, Schneeweiss S, Rothman KH, et al. Variable selection for propensity score models. Am J Epidemiol. 2006;163(12):149-1156.

Bruno G, Bringhen S, Maffei I, et al. Cardiovascular organ damage and blood pressure level predict adverse events in multiple myeloma patients undergoing carfilzomib therapy. Cancers. 2019;11(662):e1-12.

Chen HF, Wu TQ, Shen HS, et al. Extramedullary plasmacytoma in the presence of multiple myeloma: clinical correlates and prognostic relevance. Onco Targets Ther. 2012;5:329-334.

Chretien ML, Hebraud B, Cances-lauwers V, et al. Age is a prognostic factor even among patients with multiple myeloma younger than 66 years treated with high-dose melphalan: the IFM experience on 2316 patients. Haematologica. 2014;99(7):1236–1238.

Cyclophosphamide [package insert]. Deerfield, IL: Baxter International, Inc; March 2013.

Curtin F, Schulz P. Assessing the benefit: risk ratio of a drug--randomized and naturalistic evidence. Dialogues Clin Neurosci. 2011;13(2):183-190.

D'Agostino RB Jr. Tutorial in Biostatistics propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Statistics in Medicine. 1998;17:2265-2281.

Darzalex (daratumumab) [package insert]. Horsham, PA: Janssen Biotech, Inc; Novemeber 2016.

Dimopoulos MA, Orlowski RZ, Facon T, et al. Retrospective matched-pairs analysis of bortezomib plus dexamethasone versus bortezomib monotherapy in relapsed multiple myeloma. Haematologica. 2015;100(1):100-106.

Dimopoulos MA, Roussou M, Gavriatopoulou M, et al. Cardiac and renal complications of carfilzomib in patients with multiple myeloma. Blood Adv. 2017;1(7):449-454. Dingli D, Ailawadhi S, Bergsagel PL, et al. Therapy for relapsed multiple myeloma: guidelines from the Mayo stratification for myeloma and risk-adapted therapy. Mayo Clin Proc. 2017;92(4):578-598.

Durie BGM. 2018 ed. North Hollywood, CA: International Myeloma Foundation. https://www.myeloma.org/sites/default/files/images/publications/UnderstandingPDF/concisereview.pdf. Accessed 18 June 2020.

ECOG-ACRIN Cancer Research Group. ECOG Performance Status. Updated 2020. https://ecog-acrin.org/resources/ecog-performance-status. Accessed 19 June 2020.

Empliciti (elotuzumab) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; Novemeber 2015.

Fillmore NR, Yellapragada SV, Ifeorah C, et al. With equal access, African American patients have superior survival compared to white patients with multiple myeloma: a VA study Blood. 2019;133(24): 2615-2618.

Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet. 2013;382:339-352.

Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23(15):3412-3420.

Groen K, van de Donk NWCJ, Stege CAM, et al. Carfilzomib for relapsed and refractory multiple myeloma. Cancer Manag Res. 2019;11:2663–2675.

Jang RW, Caraiscos VB, Swami N, et al. Simple Prognostic Model for Patients With Advanced Cancer Based on Performance Status. Journal of Oncology Practice. 2014;10(5):e335-e341. Accessed 24 June 2020.

Kleber M, Ihorst G, Terhorst M, et al. Comorbidity as a prognostic variable in multiple myeloma: comparative evaluation of common comorbidity scores and use of a novel MM-comorbidity score. Blood Cancer J. 2011;1(9):e35.

Kumar SK, Dispenzieri A, Fraser R, et al. Early relapse after autologous hematopoietic cell transplantation remains a poor prognostic factor in multiple myeloma but outcomes have improved over time. Leukemia. 2018;32(4):986-995.

Kyprolis (carfilzomib) [package insert]. Thousand Oaks, CA: Amgen, Inc; February 2019.

Lancman G, Tremblay D, Barley K, et al. The effect of novel therapies in high-molecular-risk multiple myeloma. Clin Adv Hematol *Oncol*. 2017;15(11):870-879.

Markus E, Trestman S, Cohen Y, et al. Components of metabolic syndrome in patients with multiple myeloma and smoldering multiple myeloma. BMC Cancer. 2020;20(48).

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology – Multiple Myeloma (Version 4.2020 May 8, 2020). https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed 8 June 2020.

O'Connor OA, Stewart AK, Vallone M, et al. A phase 1 dose escalation study of the safety and pharmacokinetics of the novel proteasome inhibitor carfilzomib (PR-171) in patients with hematologic malignancies. Clin Cancer Res. 2009;15(22):7085-7091.

Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol. 2015;33(26):2863–2869.

Pomalyst (pomalidomide) [package insert]. Celgene Corporation: Summit, NJ; December 2017.

Qian J, Jin J, Luo H, et al. Analysis of Clinical Characteristics and Prognostic Factors of Multiple Myeloma: A Retrospective Single-Center Study of 787 Cases. Hematology. 2017;22(8):472-476.

Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538-e548. doi:10.1016/S1470-2045(14)70442-5. Accessed 14 June 2020.

Rajkumar SV, Fonseca R, Dispenzieri A, et al. Methods for estimation of bone marrow plasma cell involvement in myeloma: Predictive value for response and survival in patients undergoing autologous stem cell transplantation. Am J Hematol. 2001;68(4):269-275.

Reaney M, Bush E, New M, et al. The Potential Role of Individual-Level Benefit-Risk Assessment in Treatment Decision Making: A DIA Study Endpoints Community Workstream. Ther Innov Regul Sci. 2019;53: 630–638.

Revlimid (lenalidomide) [package insert]. Celgene Corporation: Summit, NJ; February 2017.

Ritts AJ, Lehihan DJ, Cornell RF. Cardiac Considerations for Modern Multiple Therapies. Expert Analysis. American College of Cardiology. July 2016. https://www.acc.org/latest-in-cardiology/articles/2016/07/07/14/59/cardiac-considerations-for-modern-multiple-myeloma-therapies. Accessed 20 August 2020.

Sarclisa (isatuximab-irfc) [package insert]. Bridgewater, NJ: Sonafi-Aventis US, LLC: March 2020.

SEER Database. Cancer Stat Facts - Myeloma 2010-2016. http://seer.cancer.gov/statfacts/html/mulmy.html. Accessed 13 June 2020.

Sevcikova S, Minarik J, Stork M, et al. Extramedullary disease in multiple myeloma – controversies and future directions. Blood Review. 2019;36:32-39.

Tamayo RR, Perez JS, Jmenez-Moleon JJ, et al.Obesity and Multiple Myeloma: What Do the Data Tell Us? J Leuk. 2014;1:e109. Accessed 13 June 2020.

Thalomid (thalidomide) [package insert]. Summit, NJ: Celgene Corporation; June 2014.

Velcade (bortezomib) [package insert]. Cambridge, MA; Millennium Pharmaceuticals, Inc; June 2008.

Waxman AJ, Mink PJ, Devesa SS, et al. Racial disparities in incidence and outcome in multiple myeloma: a population-based study. Blood 2010;116(25):5501-5506.

Yaday P, Cook M, Cockwell P. Current Trends of Renal Impairment in Multiple Myeloma. Kidney Dis (Basel) 2016;1(4):241-257.

13. Appendix

Appendix A. ENCePP Checklist for Study Protocol

Study title: Comprehensive Analysis of Clinical Parameters that May Inform the Choice of Dose Regimen for Carfilzomib 20/27mg/m^2 or 20/56mg/m^2 With and Without Dexamethasone

EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**NA**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☐	X	☐	
1.1.2 End of data collection[2]	☐	X	☐	
1.1.3 Progress report(s)	☐	☐	X	
1.1.4 Interim report(s)	☐	☐	X	
1.1.5 Registration in the EU PAS Register®	☐	X	☐	
1.1.6 Final report of study results.	☐	X	☐	

Section 2: Research question	**Yes**	**No**	**NA**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	X	☐	☐	5.2
2.1.2 The objective(s) of the study?	X	☐	☐	6.1, 6.2, 6.3
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	X	☐	☐	7.2.1.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	X	7.7.2.1
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	X	

Section 3: Study design	**Yes**	**No**	**NA**	**Section Number**
3.1 Is the study design described? (eg, cohort, case-control, cross-sectional, other design)	X	☐	☐	7.1

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**NA**	**Section Number**
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	X	☐	☐	7.1
3.3	Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence)	X	☐	☐	7.7.1, 7.7.1.1, 7.7.2, 7.7.2.5
3.4	Does the protocol specify measure(s) of association? (eg, risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	X	☐	☐	7.7.2.4
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, adverse events that will not be collected in case of primary data collection)	☐	☐	X	9

Section 4: Source and study populations		**Yes**	**No**	**NA**	**Section Number**
4.1	Is the source population described?	X	☐	☐	7.2.1.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☐	☐	X	
	4.2.2 Age and sex	☐	☐	X	
	4.2.3 Country of origin	☐	☐	X	
	4.2.4 Disease/indication	X	☐	☐	7.2.1.1
	4.2.5 Duration of follow-up	☐	☐	X	
4.3	Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	X	☐	☐	7.2.1.1

Section 5: Exposure definition and measurement		**Yes**	**No**	**NA**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	X	☐	☐	7.7.2.3
5.2	Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☐	☐	X	
5.3	Is exposure categorised according to time windows?	☐	☐	X	
5.4	Is intensity of exposure addressed? (eg, dose, duration)	X	☐	☐	7.7.2.3
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	X	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	X	

Section 6: Outcome definition and measurement		**Yes**	**No**	**NA**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	X	☐	☐	7.3, 7.7.2.4
6.2	Does the protocol describe how the outcomes are defined and measured?	X	☐	☐	7.7.2.4
6.3	Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	X	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (eg, HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	X	

Section 7: Bias		**Yes**	**No**	**NA**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (eg, confounding by indication)	X	☐	☐	7.9.1.1
7.2	Does the protocol address selection bias? (eg, healthy user/adherer bias)	X	☐	☐	7.9.2
7.3	Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias)	X	☐	☐	7.3.4

Section 8: Effect measure modification	**Yes**	**No**	**NA**	**Section Number**
8.1 Does the protocol address effect modifiers? (eg, collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	X	☐	☐	7.7.2.5.1

Section 9: Data sources	**Yes**	**No**	**NA**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:	X	☐	☐	7.4, 7.6.1
9.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	X	☐	☐	7.4, 7.6.1
9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	X	☐	☐	7.4, 7.6.1
9.1.3 Covariates and other characteristics?	X	☐	☐	7.4, 7.6.1
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	X	☐	☐	7.4, 7.6.1
9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	X	☐	☐	7.4, 7.6.1
9.2.3 Covariates and other characteristics? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	X	☐	☐	7.4, 7.6.1
9.3 Is a coding system described for:				
9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	X	
9.3.2 Outcomes? (eg, International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	X	☐	☐	7.7.3
9.3.3 Covariates and other characteristics?	X	☐	☐	7.4, 7.6.1
9.4 Is a linkage method between data sources described? (eg, based on a unique identifier or other)	X	☐	☐	7.4, 7.6.1

Section 10: Analysis plan	**Yes**	**No**	**NA**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	X	☐	☐	7.7.2, 7.7.2.1, 7.7.2.2, 7.7.2.4, 7.7.2.5, 7.7.2.5.1 7.7.3
10.2 Is study size and/or statistical precision estimated?	☐	☐	X	7.5
10.3 Are descriptive analyses included?	X	☐	☐	7.7.2, 7.7.2.1, 7.7.2.3,
10.4 Are stratified analyses included?	☐	☐	X	
10.5 Does the plan describe methods for analytic control of confounding?	X	☐	☐	7.9.1.1
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	X	
10.7 Does the plan describe methods for handling missing data?	X	☐	☐	7.7.2.2, 7.9.3
10.8 Are relevant sensitivity analyses described?	X	☐	☐	7.7.2.5

Section 11: Data management and quality control	**Yes**	**No**	**NA**	**Section Number**
11.1 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	X	☐	☐	7.6.1
11.2 Are methods of quality assurance described?	X	☐	☐	7.6, 7.6.2, 7.8
11.3 Is there a system in place for independent review of study results?	☐	☐	X	

Section 12: Limitations	**Yes**	**No**	**NA**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				7.9.2
12.1.1 Selection bias?	X	☐	☐	
12.1.2 Information bias?	☐	☐	X	
12.1.3 Residual/unmeasured confounding?	☐	☐	X	
(eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).				
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	X	☐	☐	5.3

Section 13: Ethical/data protection issues	**Yes**	**No**	**NA**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	X	☐	☐	8.2
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	X	
13.3 Have data protection requirements been described?	X	☐	☐	7.4, 7.6, 7.6.1, 8.3

Section 14: Amendments and deviations	**Yes**	**No**	**NA**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	X	☐	☐	10

Section 15: Plans for communication of study results	**Yes**	**No**	**NA**	**Section Number**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	X	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☐	☐	X	11