CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202714Orig1s021

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	202714/S-021
Priority or Standard	Priority
Submit Date(s)	August 24, 2018
Received Date(s)	August 24, 2018
PDUFA Goal Date	February 24, 2019
Division/Office	Division of Hematology Products (DHP)/Office of Hematology and Oncology Products (OHOP)
Review Completion Date	September 27, 2018
Established Name	carfilzomib
Trade Name	Kyprolis®
Pharmacologic Class	Proteasome inhibitor
Applicant	Onyx Pharmaceuticals, Inc., a wholly-owned subsidiary of Amgen Inc.
Formulation(s)	Lyophilized powder: 10 mg, 30 mg, and 60 mg
Dosing Regimen	20/70 mg/m^2 once weekly with dexamethasone
Applicant Proposed Indication(s)/Population(s)	Carfilzomib 20/70 mg/m^2 once weekly with dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Carfilzomib 20/70 mg/m^2 once weekly with dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy

Table of Contents

Table of Tables

Table of Figures

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
QT-IRT= QT Interdisciplinary Review Team

Glossary

ADR	adverse drug reaction
$AUC_{C1,avg}$	average daily area under the concentration-time curve in cycle 1
AUC_{inf}	area under the concentration-time curve from time zero to infinity
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	European Quality of Life-5 Dimensions
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
HR	hazard ratio
HRQoL	health-related quality of life
IMiD	immunomodulatory drug
IRC	Independent Review Committee
ISE	Integrated Summary of Efficacy
ITT	intent to treat
IV	intravenously
Kd	carfilzomib plus dexamethasone
KRd	carfilzomib, lenalidomide, plus dexamethasone
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
ORCA	Onyx Response Computational Assessment
ORR	overall response rate
OS	overall survival
PBRER	Periodic Benefit-Risk Evaluation Report
PFS	progression-free survival
PRO	patient-reported outcome
QLQ-C30	Quality of Life Core Module
QLQ-MY20	Quality of Life Multiple Myeloma Module 20
ΔQTcF	change from baseline in corrected QT interval by Fredericia criteria
SAP	statistical analysis plan
sIPTW	stabilized inverse probability of treatment weighting
SMQN	standardized MedDRA query, narrow scope
sNDA	supplemental New Drug Application
SSAP	supplemental statistical analysis plan

TTR	time to response
US	United States
USPI	United States Prescribing Information
Vd	bortezomib plus dexamethasone

1 Executive Summary

1.1. Product Introduction

Carfilzomib (Kyprolis®) is a proteasome inhibitor that is currently approved for the following indications:

1. In combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.
2. As a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy.

Carfilzomib is dosed on two consecutive days each week for three weeks, followed by 12 days of rest. There are two dosing regimens approved for monotherapy use:

1. 20/27 mg/m^2: 20 mg/m^2 on Days 1 and 2, and if tolerated, 27 mg/m^2 on Days 8, 9, 15 and 16 of each 28-day cycle.
2. 20/56 mg/m^2: 20 mg/m^2 on Days 1 and 2, and if tolerated, 56 mg/m^2 on Days 8, 9, 15 and 16 of each 28-day cycle.

From Cycle 13 on, Day 8 and 9 dosing of carfilzomib is omitted.

Carfilzomib is approved for use in combination with dexamethasone with the following dosing regimen:

1. 20/56 mg/m^2: 20 mg/m^2 on Days 1 and 2, and if tolerated, 56 mg/m^2 on Days 8, 9, 15 and 16 of each 28-day cycle.
    - Dexamethasone is administered on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day cycle.
    - From Cycle 13 on, Day 8 and 9 dosing of carfilzomib is omitted.

Carfilzomib is approved for use in combination with lenalidomide and dexamethasone with the following dosing regimen:

1. 20/27 mg/m^2: 20 mg/m^2 on Days 1 and 2, and if tolerated, 27 mg/m^2 on Days 8, 9, 15 and 16 of each 28-day cycle.
    - Lenalidomide 25 mg PO daily on Days 1 -21.
    - Dexamethasone 40 mg PO/IV on Days 1, 8, 15 and 22 of each 28-day cycle
    - From Cycle 13 on, Day 8 and 9 dosing of carfilzomib is omitted.

The Applicant proposed the following indication in the current supplement:

Carfilzomib 20/70 mg/m^2 once weekly with dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends approval of Kyprolis (carfilzomib), according to 21 Code of Federal Regulations (CFR) 314.126(a)(b), for the indication that the Applicant proposed:

Carfilzomib 20/70 mg/m^2 once weekly with dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.

Carfilzomib is currently approved as monotherapy (20/27 mg/m^2 twice weekly and 20/56 mg/m^2 twice weekly), in combination with dexamethasone (Kd) (20/56 mg/m^2 twice weekly), and in combination with lenalidomide and dexamethasone (KRd) (20/27 mg/m^2 twice weekly). Approval of the 20/70 mg/m^2 once weekly dose regimen is based on a favorable benefit-risk profile based on the results from the ARROW study, supported by a propensity score analysis conducted on data from studies evaluating Kd 20/70 mg/m^2 once-weekly (CHAMPION-1) and the labeled Kd 20/56 mg/m^2 twice-weekly dose regimen (ENDEAVOR).

ARROW was a phase 3, open-label, randomized study comparing Kd 20/70 mg/m^2 once weekly with Kd 20/27 mg/m^2 twice weekly in subjects with relapsed/refractory multiple myeloma who received 2-3 prior lines of therapy. Subjects were stratified based on ISS stage, age and whether or not they were refractory to bortezomib treatment. The study met the primary endpoint of progression free survival (PFS) for the intention-to-treat (ITT) population. The data provided demonstrated that subjects who were treated with Kd 20/70 mg/m^2 once weekly had significantly better efficacy, measured by PFS and overall response rate (ORR), than those treated with Kd 20/27 mg/m^2 twice weekly. For subjects who received 20/70 mg/m^2 once weekly, the median PFS was 11.3 months (95% CI: 8.6, 13.2). This compared favorably to the median PFS for subjects who received 20/27 mg/m^2 twice weekly (7.6 months [95% CI: 5.7, 8.7]), (HR=0.69, 95% CI: 0.54 -0.88). The ORR for subjects who received 20/70 mg/m^2 once weekly was 62.9% (95% CI: 56.5, 69.0), which compared favorably to the ORR for subjects who received 20/27 mg/m^2 twice weekly (40.8% [95% CI: 34.5, 47.3]). The differences in PFS and ORR between the two treatment groups were statistically significant and clinically meaningful.

To support the efficacy of the Kd 20/70 mg/m^2 once-weekly dosing regimen in the context of the labeled Kd dose (20/56 mg/m^2 twice weekly), an exploratory analysis using external control arms from the CHAMPION-1 and ENDEAVOR clinical studies for patients who had received 1-3 lines of therapy. Because of the differences in the patient populations between ARROW and ENDEAVOR, propensity score analyses were used as the primary analytical method. The dosing regimen 20/70 mg/m^2 once weekly may have favorable efficacy results when compared to the 20/56 mg/m^2 twice weekly dosing regimen. However, the magnitude of the effect based on the

PFS is not clear, and caution should be taken when interpreting the cross-study comparison analyses results due to the limitations of the propensity score analyses. The FDA concluded that the cross-study comparisons are considered to be post-hoc analyses and the magnitude of the treatment effect cannot be adequately characterized. The FDA did consider the propensity score analysis, along with the efficacy results from CHAMPION-1, as supportive evidence for the 20/70 mg/m^2 dose in the population of patients with one prior line of therapy.

The primary source of safety data was a within-study comparison of the 20/70 mg/m^2 once weekly dosing regimen and the 20/27 mg/m^2 twice-weekly dosing regimen from the ARROW study. Safety analyses demonstrated that the overall safety profiles of the two dosing regimens were comparable. A similar number of subjects in each treatment group experienced treatment-emergent adverse events, serious adverse events and treatment-emergent adverse events leading to treatment discontinuation. The most common adverse events in both treatment groups were anemia, hypertension, pyrexia and fatigue. The majority of these events were Grade 1 and 2 in severity. Overall, the incidence of adverse events was balanced between the treatment groups, with only pyrexia occurring more frequently in the 20/70 mg/m^2 once weekly group (23.1% vs. 16.2%). Anemia and insomnia occurred more frequently in the 20/27 mg/m^2 twice weekly group (31.9% vs. 26.5% and 20% vs. 14.7%, respectively). There were no other clinically meaningful differences in the common treatment-emergent adverse events between the two treatment groups.

Adverse events of special interest included cardiac events, renal and hepatic impairment, allergic and anaphylactic reactions, thrombotic/embolic events, hemorrhagic events, neurologic events and myelosuppression. Adverse events of cardiac failure (all grades) were more common in the twice weekly dosing regimen (18% vs. 13%). Overall, the remainder of the adverse events of special interest were balanced between the two treatment groups and there were no other meaningful differences. Safety analyses were also conducted comparing Kd 20/70 mg/m^2 once weekly with 20/56 mg/m^2 twice weekly, the currently labeled dose. These analyses demonstrated that the safety profile for Kd 20/70 mg/m^2 once weekly is similar to Kd 20/56 mg/m^2 twice weekly. There were no new safety findings with the 20/70 mg/m^2 once weekly dosing regimen. The safety profile of Kd 20/70 mg/m^2 once weekly is consistent with the known safety profile for carfilzomib and is acceptable for this patient population with a serious and life-threatening disease.

The efficacy and safety results of ARROW, along with supportive analyses from ENDEAVOR and CHAMPION-1, demonstrate an acceptable benefit-risk profile to support the 20/70 mg/m^2 once weekly dosing regimen. Based on the above, and the recommendation of the team members, I recommend regular approval for this supplemental NDA.

Vishal Bhatnagar, MD
Cross-Disciplinary Team Leader

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Multiple myeloma is a plasma cell malignancy that accounts for approximately 1-2% of all cancers and approximately 17% of hematologic malignancies in the United States.[1] In 2018, it is estimated that there will be 30,770 new cases of myeloma in the United States and 12,770 deaths from the disease.[2] In 2015, there were an estimated 124,733 people living with myeloma in the United States. Multiple myeloma is diagnosed most frequently among people aged 65-74 with a median age at diagnosis of 69 years.[2]

The clinical presentation of multiple myeloma is often related to the infiltration of plasma cells into the bone or other organs, as well as kidney damage from excess light chains. The most common symptoms at the time of diagnosis include anemia, bone pain, fatigue, weakness and weight loss. Despite the availability of multiple treatments, myeloma is thought to be an incurable disease, with the majority of patients experiencing recurring remissions and relapses. The goal of treatment is often aimed at creating longer periods of time without disease progression. Improving outcomes in patients with relapsed/refractory disease is an unmet medical need.

There are multiple treatment regimens approved for use in multiple myeloma including alkylating agents, corticosteroids, immunomodulatory drugs (IMiDs), proteasome inhibitors and monoclonal antibodies. Carfilzomib is a proteasome inhibitor that is currently approved in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy.

The Applicant submitted a supplemental new drug application (sNDA) for a new dosing regimen for carfilzomib 20/70 mg/m^2 once weekly in combination with dexamethasone (Kd) for the treatment of patients with relapsed/refractory multiple myeloma after 1-3 prior lines of therapy.

The benefit-risk assessment in this sNDA is primarily based on results from the A.R.R.O.W. study. A.R.R.O.W. was a phase 3, open-label, randomized study comparing Kd 20/70 mg/m^2 once weekly to Kd 20/27 mg/m^2 twice weekly in subjects with relapsed/refractory multiple myeloma who had received 2-3 prior lines of therapy. The primary endpoint was progression free survival (PFS) determined by ORCA. The estimated median PFS in the Kd 20/70 mg/m^2 once weekly treatment arm was 11.2 months compared to 7.6 months in the Kd 20/27 mg/m^2

twice weekly treatment arm (HR=0.693, 95% CI: 0.544-0.883). For subjects who received 20/70 mg/m^2 once weekly, the ORR was 63.8% (95% CI: 57.3, 69.8), compared to 41.2% (95% CI: 34.9, 47.7) for subjects who received 20/27 mg/m^2 twice weekly. Overall survival data are immature.

To evaluate the efficacy of the Kd 20/70 mg/m^2 once-weekly dosing regimen in the context of the labeled Kd dose (20/56 mg/m^2 twice weekly), cross-study comparisons were performed using data from the CHAMPION-1 and ENDEAVOR clinical studies. Because of the differences in the patient populations between these studies, propensity score analyses were used as the primary analytical method. The dosing regimen 20/70 mg/m^2 once weekly appears to have favorable efficacy results when compared to the 20/56 mg/m^2 twice weekly dosing regimen. However, the magnitude of the effect based on the PFS is not clear.

Overall, the Kd 20/70 mg/m^2 once weekly dosing regimen was tolerable, with adverse reactions that were similar to those already known with carfilzomib. The most common adverse events were anemia, hypertension, pyrexia and fatigue. Overall, the incidence of adverse events was balanced between the treatment groups, with only pyrexia occurring more frequently in the Kd 20/70 mg/m^2 once weekly group (23.1% vs. 16.2%). Anemia and insomnia occurred more frequently in the Kd 20/27 mg/m^2 twice weekly group (31.9% vs. 26.5% and 20% vs. 14.7%, respectively). There were no other clinically meaningful differences in the common treatment-emergent adverse events between the two treatment groups.

In conclusion, the dosing regimen of Kd 20/70 mg/m^2 once weekly demonstrated a statistically significant improvement in PFS and ORR when compared to Kd 20/27 mg/m^2 twice weekly in a randomized phase 3 study. There were no new safety findings with the once weekly dosing regimen and adverse events were consistent with the known safety profile of carfilzomib. Therefore, the benefit-risk profile is favorable to support approval of:

Carfilzomib 20/70 mg/m^2 once weekly with dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In 2018, it is estimated that there will be 30,770 new cases of multiple myeloma in the United States. • Multiple myeloma is incurable with a 5-year survival rate of 50.7%	**Relapsed/refractory multiple myeloma is a serious and life-threatening condition.**
Current Treatment Options	• Multiple drugs approved for use in relapsed/refractory multiple myeloma, and numerous combination regimens are considered standard of care. • Potential treatments include alkylating agents, corticosteroids, immunomodulatory drugs (IMiDs), proteasome inhibitors and monoclonal antibodies.	**There is an unmet medical need to improve the outcomes of patients with relapsed/refractory multiple myeloma.**
Benefit	• The clinical benefit of the carfilzomib 20/70 mg/m^2 once weekly dosing regimen was determined by the efficacy results of the A.R.R.O.W. study as well as cross-study comparisons from the CHAMPION-1 and ENDEAVOR studies. • A.R.R.O.W. was a phase 3, open-label, randomized study in patients with relapsed/refractory multiple myeloma who had received 2-3 prior lines of therapy. Patients were randomized one-to-one to receive either carfilzomib 20/70 mg/m^2 once weekly with dexamethasone or carfilzomib 20/27 mg/m^2 twice weekly with dexamethasone. The primary endpoint was PFS assessed by ORCA. ORR assessed by ORCA was the major secondary efficacy endpoint - PFS in the Kd 20/70 mg/m^2 once weekly treatment arm was 11.2 months, compared to 7.6 months in the Kd 20/27 mg/m^2 twice weekly treatment arm. A statistically significant difference was observed between two treatment groups (HR=0.69, 95% CI: 0.54 - 0.88; p=0.0014). - ORR in the Kd 20/70 mg/m^2 once weekly treatment arm was	**Evidence of effectiveness was supported by a statistically significant and clinically meaningful improvement in PFS and ORR with the Kd 20/70 mg/m^2 once weekly dosing regimen when compared to the Kd 20/27 mg/m^2 twice weekly dosing regimen in patients with relapsed/refractory multiple myeloma.** **Supportive results from propensity score adjusted analyses based on external control arms from the CHAMPION-1 and ENDEAVOR studies further substantiate the evidence of the benefit of the Kd 20/70 mg/m^2 dosing regimen.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	62.9% (95% CI: 56.5, 69.0), compared to 40.8% (95% CI: 34.5, 47.3) in the Kd 20/27 mg/m^2 twice weekly treatment arm. The odds ratio was 2.49 (95% CI: 1.72-3.60; p<0.0001). • A supportive, cross-study comparison was performed using data from the CHAMPION-1 and ENDEAVOR clinical studies. Because of the differences in the patient populations between these studies, propensity score weighted analyses were used as the primary analytical method to balance baseline covariates. • The dosing regimen 20/70 mg/m^2 once weekly appears to have favorable efficacy results when compared to the 20/56 mg/m^2 twice weekly dosing regimen. However, the magnitude of the effect based on the PFS is not clear and caution should be taken when interpreting the cross-study comparison analyses results due to the limitation of the propensity score analyses.	
Risk and Risk Management	• The safety profile of carfilzomib is well known. • Potential risks associated with carfilzomib use include cardiac toxicities, acute renal failure, tumor lysis syndrome, pulmonary toxicity, hypertension, venous thrombosis, infusion reactions, hemorrhage, thrombocytopenia, hepatic toxicity, thrombotic microangiopathy, posterior reversible encephalopathy syndrome (PRES), and embryo-fetal toxicity. • The most common treatment-emergent adverse events that occurred in patients who received Kd 20/70 mg/m^2 were similar to other dosing regimens and included anemia, hypertension, pyrexia, fatigue and diarrhea. • There is no proposal or indication for a risk management plan.	**There were no new safety findings with this dosing regimen when compared to 20/27 mg/m^2 once weekly and 20/56 mg/m^2 once weekly. The safety profile of carfilzomib 20/70 mg/m^2 once weekly with dexamethasone is acceptable for the intended population.** **The Warnings and Precautions section of the label details the potential risks with carfilzomib use.**

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

✓	The patient experience data that was submitted as part of the application, include:	Patient reported outcome data was included in the Applicant submission. It is located in module 5.3.5.1 of the eCTD, entitled "CSR 20140355 PRO report"
	✓ Clinical outcome assessment (COA) data, such as	
	✓ **Patient reported outcome (PRO):** The Sponsor included PRO information from the EORTC QLQ-C30 and EQ-5D performed during the A.R.R.O.W. study. Per the Sponsor analysis: "The results of the exploratory MMRM analyses demonstrate that patients treated with once weekly carfilzomib 20/70mg/m^2 dosing in combination with dexamethasone (Kd70) had better scores than those treated with twice-weekly carfilzomib 20/27 mg/m^2 dosing in combination with dexamethasone (Kd27) overall for some of the PRO subscales. These were EORTC QLQ-C30 Physical Functioning, Role Functioning, Fatigue, Pain, Insomnia; EORTC QLQ-MY20 Disease Symptoms; EQ-5D-5L Index and VAS score. The differences between the arms, however, were small and did not reach the thresholds for clinical significance overall. Sensitivity analysis confirmed these findings. No differences were observed between arms for the other pre-specified subscales of QLQ-C30 Global Health Status/QoL, QLQ-MY20 Side effects of treatment and QLQ-MY20 Future perspectives. Time to deterioration in PRO scales was longer in the once-weekly arm for the EORTC QLQ-C30 Fatigue, EORTC QLQ-MY20 Disease Symptoms and EQ-5D Index and VAS scores, with hazard ratios ranging from 0.577 to 0.768. A limitation when interpreting these results is that the majority of patients were censored (>50% for all subscales), and calculation of median time to deterioration was not possible for all subscales."	Patient reported outcome data for this supplement was supportive in nature, had limitations as described in the Sponsor analysis, and was not used as primary support for the approval of the 20/70 mg/m^2 dosing regimen.
	□ Observer reported outcome (ObsRO)	

	☐ Clinician reported outcome (ClinRO)	
	☐ Performance outcome (PerfO)	
	☐ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	
	☐ Observational survey studies designed to capture patient experience data	
	☐ Natural history studies	
	☐ Patient preference studies (e.g., submitted studies or scientific publications)	
	☐ Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.	

Vishal Bhatnagar, MD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Multiple myeloma, an oligoclonal neoplastic proliferation of plasma cells, is the second most common hematologic malignancy and is responsible for approximately 80 000 annual deaths worldwide (1% of cancer deaths; Ferlay et al, 2015). The estimated incidence of multiple myeloma in 2012 worldwide was 114 000 persons, which represents 0.8% of all cancers. The 5-year prevalence of multiple myeloma worldwide was estimated at 229 000 persons. Multiple myeloma is a disease of older adults, with a median age at diagnosis of 69 years (Surveillance, Epidemiology, and End Results Cancer Stat Facts, 2018).

Multiple myeloma is characterized by a recurring pattern of remission and relapse (Laubach et al, 2016; Durie et al, 2012; Jakubowiak et al, 2012). With successive lines of treatment, patients have lower response rates and a shorter duration of response (Kumar et al, 2012), remissions become increasingly transient, and the disease eventually becomes refractory (nonresponsive to the most recent therapy or progression within 60 days of discontinuation from the most recent therapy) (Laubach et al, 2016).

Therefore, the primary goals of treatment for relapsed or refractory multiple myeloma are to achieve deep and durable response, which is associated with improved outcome, and subsequently longer overall survival (OS) with an acceptable level of toxicity (Stewart et al, 2015; Harousseau et al, 2010). Additional goals are to prevent or delay disease-related morbidity (including bone fractures and renal insufficiency), to provide relief of pain and other disease-related symptoms, and to maintain the best possible quality of life for cancer survivors (World Health Organization, 2018).

The FDA's Assessment:
FDA agrees with the Applicant's assessment of multiple myeloma.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Regimens used and/or approved for the treatment of multiple myeloma incorporate conventional agents such as alkylating agents, other cytotoxics such as anthracyclines and corticosteroids, as well as novel agents, including immunomodulatory drugs (IMiDs), proteasome inhibitors, monoclonal antibodies, and histone deacetylase inhibitors (National

Comprehensive Cancer Network [NCCN], 2018). The novel and conventional agents are typically combined as doublet or triplet regimens (Table 1) and are sequenced across multiple lines of therapy.

A carfilzomib-containing regimen is recommended by the International Myeloma Working Group for patients with relapsed multiple myeloma who are refractory to lenalidomide or bortezomib (Laubach et al, 2016). Regimens including carfilzomib (Kyprolis®) have significantly improved clinical outcomes and represent valuable treatment options for patients with relapsed or refractory multiple myeloma. Notably, carfilzomib has demonstrated, in 2 large randomized phase 3 studies (Study PX-171-009 [ASPIRE] and Study 2011-003 [ENDEAVOR]), statistically significant, 9-month improvements in median progression-free survival (PFS) and statistically significant, 8-month improvements in median OS, representing 21% reductions in the risk of death with carfilzomib-based therapy (Siegel et al, 2018; Dimopoulos et al, 2017; Dimopoulos et al, 2016; Stewart et al, 2015). Marketing authorization and label updates for carfilzomib in combination with lenalidomide (Revlimid®) plus dexamethasone (KRd) and in combination with dexamethasone (Kd) were granted by the United States (US) Food and Drug Administration (FDA) based on these findings.

The approved dose administration for carfilzomib is intravenously (IV) over 10 to 30 minutes (for doses of 20/27 and 20/56 mg/m^2, respectively) on 2 consecutive days each week for 3 weeks of a 28-day cycle (i.e., on days 1, 2, 8, 9, 15, and 16). Carfilzomib is usually administered in the clinic; adherence to this twice-weekly schedule can disrupt work and social lives, and thus, can be burdensome in terms of time and costs for patients, caregivers, and healthcare providers. A once-weekly Kd dose regimen may represent an important option for potentially lessening the burden of treatment for all stakeholders. Indeed, the most recent NCCN guidelines included Kd once-weekly for the treatment of relapsed or refractory multiple myeloma as a treatment option (NCCN, 2018). Evidence suggests a once-weekly dosing schedule could have at least 2 important benefits: reduced administration time and costs for patients, caregivers, and providers, and better adherence to treatment with IV antimyeloma agents (Section 1.2.1 of A.R.R.O.W. Module 2.5, Clinical Overview).

Table 1. Summary of NCCN Category 1 Preferred Regimens for Relapsed or Refractory Multiple Myeloma

Product(s) Name	Year of Approval	Dosing/Administration	Efficacy Information[a]	Important Safety and Tolerability Issues
Carfilzomib/ dexamethasone	January 2016	Carfilzomib 20/56 mg/m^2 IV days 1, 2, 8, 9, 15, 16 of 28-day cycles (20 mg/m^2 cycle 1 days 1 and 2)	<u>Kd vs Vd</u> **PFS:** 18.7 (15.6, NE) vs 9.4 (8.4, 10.4); HR = 0.53 (0.44, 0.65) **OS:** 47.6 (42.5, NE) vs 40.0 (32.6, 42.3); HR = 0.79 (0.65, 0.96) **ORR:** 77% vs 63%	Cardiac toxicities, acute renal failure, tumor lysis syndrome, pulmonary toxicity, pulmonary hypertension, dyspnea, hypertension, venous thrombosis, infusion reactions, hemorrhage, thrombocytopenia, hepatic toxicity and hepatic failure, thrombotic microangiopathy, and PRES
Carfilzomib/ lenalidomide/ dexamethasone	July 2015	Carfilzomib 20/27 mg/m^2 IV days 1, 2, 8, 9, 15, 16 of 28-day cycles (20 mg/m^2 cycle 1 days 1 and 2)	<u>KRd vs Rd</u> **PFS:** 26.3 (23.3, 30.5) vs 17.6 (15.0, 20.6); HR = 0.69 (0.57, 0.83) **OS:** 48.3 (42.4, 52.8) vs 40.4 (33.6, 44.4); HR = 0.79 (0.67, 0.95) **ORR:** 87% vs 67%	
Daratumumab/ bortezomib/ dexamethasone	November 2016	Daratumumab 16 mg/kg IV weekly for weeks 1 to 9, every 3 weeks for weeks 10 to 24, every 4 weeks for week 25+ Bortezomib 1.3 mg/m^2 SC days 1, 4, 8, 11 of 21-day cycles (cycles 1 to 8)	<u>DVd vs Vd</u> **PFS:** NE vs 7.2; HR = 0.39 (0.28, 0.53) **ORR:** 79.3% vs 59.9% **OS:** not reported	<u>Daratumumab:</u> Infusion reactions, neutropenia, and thrombocytopenia <u>Bortezomib:</u> Peripheral neuropathy, hypotension, cardiac toxicity, pulmonary toxicity, PRES, gastrointestinal toxicity, thrombocytopenia/neutropenia, tumor lysis syndrome, and hepatic toxicity
Daratumumab/ lenalidomide/ dexamethasone	November 2016	Daratumumab 16 mg/kg IV weekly for weeks 1 to 8, every other week for weeks 9 to 24, and every 4 weeks for week 25+	<u>DRd vs Rd</u> **PFS:** NE vs 18.4; HR = 0.37 (0.27, 0.52) **ORR:** 91.3% vs 74.6% **OS:** not reported	Infusion reactions, neutropenia, and thrombocytopenia

Product(s) Name	Year of Approval	Dosing/Administration	Efficacy Information[a]	Important Safety and Tolerability Issues
Elotuzumab/ lenalidomide/ dexamethasone	November 2015	Elotuzumab 10 mg/kg IV weekly of 28-day cycles (cycles 1 and 2), then every other week (cycles 3+)	ERd vs Rd **PFS:** 19.4 (16.6, 22.2) vs 14.9 (12.1, 17.2); HR = 0.70 (0.57, 0.85) **ORR:** 78.5% vs 65.5% **OS:** 43.7 (40.3, NE) vs 39.6 (33.3, NE); HR = 0.77 (0.61, 0.97)	Infusion reactions, infections, second primary malignancies, and hepatotoxicity
Ixazomib/ lenalidomide/ dexamethasone	November 2015	Ixazomib 4 mg orally days 1, 8, and 15 of 28-day cycles	IRd vs Rd **PFS:** 20.6 (17.0, NE) vs 14.7 (12.9, 17.6); HR = 0.74 (0.59, 0.94) **ORR:** 78% vs 72% **OS:** not reported	Thrombocytopenia, gastrointestinal toxicities, peripheral neuropathy, peripheral edema, cutaneous reactions, hepatotoxicity

DRd = daratumumab, lenalidomide, plus dexamethasone; DVd = daratumumab, bortezomib, plus dexamethasone; ERd = elotuzumab, lenalidomide, plus dexamethasone; HR = hazard ratio; IRd = ixaxomib lenalidomide, plus dexamethasone; IV = intravenously; Kd = carfilzomib plus dexamethasone; KRd = carfilzomib, lenalidomide, plus dexamethasone; NCCN = National Comprehensive Cancer Network; NE = not estimable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PRES = posterior reversible encephalopathy syndrome; Rd = lenalidomide plus dexamethasone; SC = subcutaneously; USPI = United States Prescribing Information; Vd = bortezomib plus dexamethasone

[a] PFS and OS are presented as median (95% CI) in months; HR is presented with 95% CI.

Source: Darzalex USPI, 2018; Kyprolis USPI, 2018; NCCN 2018; Empliciti USPI, 2017; Velcade USPI, 2017; Ninlaro USPI, 2016

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of current treatment options for the relevant multiple myeloma population studied in the clinical studies contained in the Applicant submission.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Carfilzomib for injection was granted accelerated approval by the US FDA on 20 July 2012 as monotherapy, with full approval granted in January 2016. Carfilzomib is currently approved in the US as monotherapy (20/27 and 20/56 mg/m^2 twice-weekly), in combination with dexamethasone (Kd at 20/56 mg/m^2 twice-weekly), and in combination with lenalidomide plus dexamethasone (KRd at 20/27 mg/m^2 twice-weekly).

The FDA's Assessment:

The FDA agrees with the Applicant's history of the approval of carfilzomib (NDA 202714). Carfilzomib was initially granted accelerated approval as monotherapy in July 2012. In July 2015, carfilzomib was granted regular approval for use in combination with lenalidomide and dexamethasone (KRd). In January 2016, 20/27 mg/m^2 monotherapy was converted from accelerated to regular approval, the 20/56 mg/m^2 30 minute-infusion monotherapy regimen was approved and the Kd 20/56 mg/m^2 combination therapy was approved.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

A summary of key interactions with the FDA regarding Study 20140355 (A.R.R.O.W.), the subject of this marketing application, is provided in Table 2. Briefly, input from the FDA was received through formal interactions on the study protocol and regarding the acceptability of the proposed data package to support the addition of a Kd 20/70 mg/m^2 once-weekly dosing regimen in the indicated population of patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy. Based on the key outcomes from these meetings, Amgen proceeded with the submission, including the additional safety, efficacy, and pharmacokinetic analyses requested. The filing package is consistent with the advice received during these discussions with the FDA.

Table 2. Key Regulatory Interactions for A.R.R.O.W.

Interaction/Meeting	Summary
Type C meeting (20 October 2014) FDA Meeting Minutes dated 24 October 2014	The purpose of this meeting was to obtain FDA guidance on the design of the proposed phase 3 A.R.R.O.W. study supporting a new once-weekly dosing regimen. • The Agency acknowledged that the proposed dose and regimen of the 2 treatment groups appeared acceptable. • The Agency agreed that the selected patient population who have received at least 2 but no more than 3 prior therapies is appropriate. In response to the FDA's inquiry, the sponsor updated the protocol to require exposure to both a proteasome inhibitor and an IMiD. • The Agency agreed that response rate is an acceptable endpoint for accelerated approval in patients with relapsed or refractory multiple myeloma; however, the acceptability of using ORCA will be a review issue. • The Agency recommended a fixed hierarchical testing of endpoints starting with ORR, then PFS, and finally, OS, and recommended an interim OS analysis when 70% of the PFS information is available. Finally, the Agency stated that it is acceptable to perform an analysis of ORR 3 months after the last subject is randomized. • The Agency acknowledged that inclusion of the once-weekly regimen in the prescribing information will be a review issue at the time of sNDA submission.
Request for Comments and Advice for Protocol 20140355 Amendment 3 (Serial No. 0739)	Amgen sought Agency advice on whether it would be appropriate to exclude 19 subjects, who may not have consented fully, from all safety and efficacy analyses in the clinical study report. On 02 February 2017, the Agency recommended the inclusion of the 19 subjects who died before reconsent.
A.R.R.O.W. Protocol Amendment 4 (Serial No. 0749)	Advances in antimyeloma therapy altered the landscape for accelerated approval such that PFS was considered to be the more relevant regulatory endpoint in the relapsed/refractory setting. To support a potential sNDA seeking approval of a once-weekly carfilzomib dosing regimen at 20/70 mg/m^2 and to protect the integrity of the PFS data, the primary endpoint was amended to PFS, with ORR as a key secondary endpoint. The purpose and timing of the interim PFS analysis were also amended to monitor efficacy and to allow the possibility of stopping the study early for efficacy.
FDA comments on the draft SAP for A.R.R.O.W. received by email on 19 April 2017 Amgen responses submitted on 08 May 2017 (Serial No. 0763)	Amgen clarified that the planned sample size for ORR was 460 subjects and that the analysis of OS is not event-driven, but rather driven by the timing of the PFS analysis. The details of the timing and censoring for the PFS primary analysis were provided with the submission and additional analyses to evaluate the proportional hazard assumption for time-to-event endpoints were included in the SAP.

Interaction/Meeting	Summary
Type B meeting (20 March 2018) FDA Meeting Minutes dated 14 March 2018	The purpose of this meeting was to seek Agency feedback regarding the adequacy of the available data package to support the planned sNDA submission for a new Kd 20/70 mg/m^2 once-weekly dosing regimen for the treatment of patients with relapsed or refractory multiple myeloma after 1 to 3 prior therapies based on results from the phase 3 A.R.R.O.W. study. Major feedback was as follows: • The Agency commented that in general, between-study comparisons are strongly discouraged and cross-study comparisons are considered exploratory, and cautioned that the propensity score method may not adequately control for unknown covariates. The adequacy of the data package to support the proposed indication will be a review issue. • The Agency noted that integrated analyses should be conducted of all relevant safety data from A.R.R.O.W., ENDEAVOR, and CHAMPION-1; specifically, the comparison of Kd 20/70 mg/m^2 once-weekly dosing (A.R.R.O.W. and CHAMPION-1) with Kd 20/27 mg/m^2 twice-weekly (from A.R.R.O.W.) and Kd 20/56 mg/m^2 twice-weekly (ENDEAVOR) for subjects with 1 to 3 and 2 to 3 prior lines of therapy, regardless of refractory status. • The Agency noted that the proposed approach for exposure-response analysis will be a review issue and requested additional clinical pharmacology analyses. • The Agency commented that safety narratives should be submitted for all serious adverse events. • The Agency acknowledged that the proposal for the USPI will be a review issue. • The Agency agreed that the proposed dataset formats appear acceptable. • The Agency agreed with Amgen's proposal for BIMO and asked Amgen to provide BIMO clinical site summary for both A.R.R.O.W. and CHAMPION 1.

BIMO = Bioresearch Monitoring Program; FDA = Food and Drug Administration; IMiD = immunomodulatory drug; Kd = carfilzomib plus dexamethasone; ORCA = Onyx Response Computational Assessment; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; SAP = statistical analysis plan; sNDA = supplemental New Drug Application; USPI = United States Prescribing Information

The FDA's Assessment:

The Applicant has sufficiently described the pre-submission regulatory activities related to the A.R.R.O.W. study.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The FDA's Assessment:
Clinical sites were not inspected for this sNDA.

4.2. Product Quality

The FDA's Assessment:
Not applicable

4.3. Clinical Microbiology

The FDA's Assessment:
Not applicable

4.4. Devices and Companion Diagnostic Issues

The FDA's Assessment:
Not applicable

5 Clinical Pharmacology

5.1. Executive Summary

The FDA's Assessment:

The proposed carfilzomib dosing regimen in the current supplement is 20/70 mg/m^2 once weekly (20 mg/m^2 on Day 1 of Cycle 1, and 70 mg/m^2 on Days 8 and 15 of Cycle 1 and on Days 1, 8 and 15 of subsequent cycles) in 28-day treatment cycles with dexamethasone. The currently approved carfilzomib dosing regimen with dexamethasone (Kd) is 20/56 mg/m^2 twice weekly. The evidence of efficacy and safety was supported by a cross-study comparison of data between 20/70 mg/m^2 once weekly and Kd 20/56 mg/m^2 twice weekly in patients with relapsed or refractory multiple myeloma from the following clinical studies:

- Phase 3, randomized, open-label Studies 20140355 (A.R.R.O.W.: Kd 20/70 mg/m^2 once weekly, 2-3 prior lines of therapy)
- Phase 3, randomized, active-controlled Study 2011-003 (ENDEAVOR: Kd 20/56 mg/m^2 twice weekly, 1-3 prior lines of therapy), and
- Phase 1/2 dose finding Study 20130403 (CHAMPION-1: Kd 20/70 mg/m^2 once weekly, 1-3 prior lines of therapy).

This review includes exposure-response analysis for efficacy and safety using pooled data from Trials A.R.R.O.W., ENDEAVOR, and CHAMPION-1, and the updated population pharmacokinetic (PK) analysis with data from A.R.R.O.W. and CHAMPION-1. The key review issue focuses on the appropriateness of the proposed Kd 20/70 mg/m^2 once weekly dosing regimen compared to the Kd 20/56 mg/m^2 twice weekly dosing regimen based on exposure-response analysis in patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.

The results of the exploratory exposure-efficacy analysis from the pooled datasets from A.R.R.OW., ENDEAVOR, and CHAMPION-1 indicated trends towards increasing overall response rate (ORR) and progression-free survival (PFS) with increasing average area under curve in Cycle 1 (AUCC1avg). However, exposure was a not a significant predictor of ORR after adjusting for baseline risk factors. Further, there were no apparent trends with increasing exposure for PFS in the individual studies. The conclusions that can be inferred from the exposure-efficacy analysis from the pooled datasets is limited considering the limitations of the analysis (i.e., limited dose range, high variability carfilzomib pharmacokinetics and overlapping exposure).

The updated population pharmacokinetic analysis, including A.R.R.O.W and CHAMPION-1 data for the Kd 20/70 mg/m^2 once weekly regimen, were consistent with previous analysis.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 202714, Supplement 21. This sNDA is approvable from a clinical pharmacology perspective. The key

review issues with the specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness[†]	The pivotal evidence of effectiveness stems from cross study comparison of Trials A.R.R.O.W., ENDEAVOR, and CHAMPION-1 demonstrated comparable progression-free survival between Kd 20/70 mg/m^2 once weekly and Kd 20/56 mg/m^2 twice weekly.
General dosing instructions	20/70 mg/m^2 once weekly (20 mg/m^2 on Day 1 of Cycle 1, and 70 mg/m^2 on Days 8 and 15 of Cycle 1 and on Days 1, 8 and 15 of subsequent cycles)
Dosing in patient subgroups (intrinsic and extrinsic factors)	No revisions.
Labeling	Generally acceptable. The review team has recommendations for revision of specific content and format.
Bridge between the to-be-marketed and clinical trial formulations	Not Applicable.

5.2. Summary of Clinical Pharmacology Assessment

5.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

The objective of the clinical pharmacology program supporting this supplemental New Drug Application (sNDA) was to provide supportive evidence of the comparability of safety and efficacy, in terms of exposure, between carfilzomib at 20/70 mg/m^2 once-weekly and carfilzomib at 20/56 mg/m^2 twice-weekly (see Section 5.2.2.3). However, the analyses were confounded by the similarities in the total weekly dose during cycle 1 of the treatment regimens, differences in infusion lengths among the dose regimens, and the high between-subject variability observed in carfilzomib pharmacokinetics. While conclusions that can be drawn from the pharmacokinetic and pharmacodynamic analyses were limited, the results were generally consistent with the clinical data, which showed the Kd 20/70 mg/m^2 once-weekly dose regimen has comparable efficacy to Kd 20/56 mg/m^2 twice-weekly without any new safety concerns (see Section 7.1.3 and Section 7.2.4).

A.R.R.O.W. Pharmacokinetics
Carfilzomib exposures as measured by maximum plasma concentrations (C_{max}) and area under the concentration-time curve from time zero to infinity (AUC_{inf}) in cycle 1 were similar between the Kd 20/70 mg/m^2 once-weekly and Kd 20/27 mg/m^2 twice-weekly groups by noncompartmental analyses (Section 2.1.1 of A.R.R.O.W. Module 2.7.2, Summary of Clinical Pharmacology). The similarities in exposures for 20/70 mg/m^2 once-weekly and 20/27 mg/m^2 twice-weekly, respectively, were not unexpected given the similarities in total doses administered in each cycle (160 versus 148 mg/m^2) and relatively short infusion durations (i.e., 20/70 mg/m^2 administered over 30 minutes and 20/27 mg/m^2 administered over 10 minutes.

Population Pharmacokinetics
An update of a previously developed carfilzomib population pharmacokinetic model, including data from the phase 3 A.R.R.O.W. study and phase 1/2 Study 2012-002 (CHAMPION-1) was consistent with the previous analyses (Section 3.1.5 of A.R.R.O.W. Module 2.7.2, Summary of Clinical Pharmacology). Only body surface area was identified as a significant covariate on clearance, corresponding to a 47% decrease in subjects with the lowest body surface area (1.1 m^2) or 64% increase in subjects with the highest body surface area (2.8 m^2); none of other evaluated intrinsic or extrinsic factors were found to significantly impact carfilzomib pharmacokinetics.

Pharmacodynamics
Results from a pharmacodynamic analysis comparing data from CHAMPION-1 to ENDEAVOR demonstrated that inhibition of chymotrypsin-like proteasome activity is deep and durable for both Kd 20/70 mg/m^2 once-weekly and Kd 20/56 mg/m^2 twice-weekly dose regimens; however, no overall differences in dose effect on proteasome activity were observed (Section 3.2 of A.R.R.O.W. Module 2.7.2, Summary of Clinical Pharmacology).

Exposure-response Analyses
Three sets of exposure-response analyses were conducted to rigorously evaluate the data:
- an update of the previous exposure-response analyses
- exposure-response analyses of the A.R.R.O.W., ENDEAVOR, and CHAMPION-1 studies individually (i.e., studies evaluating Kd regimens)
- pooled exposure-response analysis of studies evaluating Kd regimens (A.R.R.O.W., ENDEAVOR, and CHAMPION-1) (see also Section 6.1)

An update to a previously conducted exposure-response analyses, including data from A.R.R.O.W. and CHAMPION-1, was consistent with the results of the previous exposure-response analyses (Section 3.3.5.1 of A.R.R.O.W. Module 2.7.2, Summary of Clinical Pharmacology). A relationship was found between carfilzomib average daily area under the concentration-time curve in cycle 1 (AUC_{C1avg}) and overall response rate (ORR), with increasing AUC associated with higher probability of response over the larger dose range evaluated.

Exposure-response analyses of the A.R.R.O.W., ENDEAVOR, and CHAMPION-1 studies individually did not reveal any significant relationships between carfilzomib exposure metrics and efficacy endpoints (Sections 2.1.2, Section 2.2.2, and Section 2.3.3 of A.R.R.O.W. Module 2.7.2, Summary of Clinical Pharmacology).

The pooled exposure-response analysis of Kd regimens showed a high degree of overlap in cycle 1 exposures of carfilzomib over the 20/27 mg/m^2 twice-weekly, 20/70 mg/m^2 once-weekly, and 20/56 mg/m^2 twice-weekly dose range, which can be attributed to the differences in total cycle 1 doses between the treatment regimens of < 40% and the high inter-subject variability in carfilzomib pharmacokinetics (≥ 40% coefficient of variation) (Section 3.3.5.1 of A.R.R.O.W. Module 2.7.2, Summary of Clinical Pharmacology). Positive trends were observed between carfilzomib exposure metrics and PFS, suggesting that higher carfilzomib exposures tend to result in longer PFS; however, no significant exposure-response relationships were identified. While a relationship was identified between ORR and $AUC_{C1,avg}$, with increasing $AUC_{C1,avg}$ associated with higher ORR in the dose range of the 3 studies (i.e., 20/27 mg/m^2 twice-weekly, 20/70 mg/m^2 once-weekly, and 20/56 mg/m^2 twice-weekly), this relationship was not significant after adjustment for baseline characteristics and prognostic factors (i.e., only 1 prior therapy).

The pooled exposure-response analyses were confounded by the limited dose range of Kd regimens of this analysis, the high inter-subject variability in carfilzomib pharmacokinetics, and the 20 mg/m^2 step-up dose administered in week 1 for all dose regimens, which contributed to a high degree of overlapping AUC_{C1avg} values. Overall, this exposure-response analysis suggests that both the Kd 20/70 mg/m^2 once-weekly and Kd 20/56 mg/m^2 twice-weekly dose regimens are efficacious doses, which is consistent with the clinical data (Section 7.1.3).

In the exposure-response analysis of safety, no correlations were observed between increasing carfilzomib exposure and increased risk of any grade adverse event of interest (dyspnea, cardiac failure [standardized Medical Dictionary for Regulatory Activities [MedDRA] query, narrow scope [SMQN], ischemic heart disease, hepatic failure, pulmonary hypertension, interstitial lung disease, chronic kidney disease, renal failure [SMQN or grade ≥ 3] or chronic kidney disease [SMQN or grade ≥ 3]) (Section 3.3.5.2 of A.R.R.O.W. Module 2.7.2, Summary of Clinical Pharmacology).

The FDA's Assessment:

The Applicant's characterization of carfilzomib PK, and PD is generally acceptable. The total dose and mean total exposure in Cycle 1 for 20/70 mg/m^2 once daily regimen is ~40% lower compared to that for 20/56 mg/m^2 twice weekly regimen, but as pointed out by the Applicant there is overlap due to variability in pharmacokinetics of carfilzomib and both regimens were efficacious. The FDA agrees with Applicant's description of the limitations of the exposure-response analysis using pooled data across clinical studies.

5.2.2. General Dosing and Therapeutic Individualization

5.2.2.1. General Dosing

The Applicant's Position:

The proposed dose regimen consists of carfilzomib administered IV over 30 ± 5 minutes in 28-day cycles as once-weekly doses in combination with dexamethasone. Carfilzomib will be administered at 20/70 mg/m^2 on days 1, 8, and 15 (i.e., 20 mg/m^2 on cycle 1 day 1, increased to 70 mg/m^2 on cycle 1 day 8 and thereafter).

Carfilzomib at 20/70 mg/m^2 once-weekly in combination with dexamethasone was identified as the maximum tolerated dose in the phase 1/2 CHAMPION-1 study and the dose regimen was evaluated for efficacy and safety in the phase 3 A.R.R.O.W. study.

The FDA's Assessment:
FDA agrees with the Applicant's proposed dose.

5.2.2.2. Therapeutic Individualization

The Applicant's Position:

No change is proposed to the currently approved US Prescribing Information (USPI) based on intrinsic or extrinsic factors (Kyprolis USPI, 2018).

The carfilzomib dose should be calculated using the patient's actual body surface area at baseline. In patients with a body surface area > 2.2 m^2, the dose should be calculated based upon a body surface area of 2.2 m^2. None of other evaluated intrinsic or extrinsic factors were found to significantly impact carfilzomib pharmacokinetics in the updated population pharmacokinetic model, including data from A.R.R.O.W. and CHAMPION-1, which warranted dose adjustment (see Section 5.2.1).

Consistent with the currently approved USPI, the carfilzomib dose should be reduced by 25% in patients with mild or moderate hepatic impairment (Kyprolis USPI, 2018).

The FDA's Assessment:
FDA agrees with the Applicant's position on no changes to the currently approved labeling regarding intrinsic and extrinsic factors, specifically regarding 25% dose reduction in patients with mild to moderate hepatic impairment. The FDA agrees with the conclusion that no additional intrinsic or extrinsic factors were found to significantly affect the population PK of carfilzomib in as much as the data will support it. This conclusion is reasonable for age, gender, race, protein expression (ALB, ALT, AST, BILI), renal impairment category, and liver function

category.

5.2.2.3. Outstanding Issues

The Applicant's Position:

Because Kd 20/56 mg/m^2 twice-weekly was not approved in any region at the time of study initiation and through most of the enrollment period (Section 1.3.1.1 of A.R.R.O.W. Module 2.5, Clinical Overview), a direct comparison of the pharmacokinetics and pharmacodynamics of Kd 20/70 mg/m^2 once-weekly to the labeled Kd 20/56 mg/m^2 twice-weekly dose regimen is not available. Instead, robust cross-study exposure-response analyses were conducted between Kd 20/70 mg/m^2 once-weekly and Kd 20/56 mg/m^2 twice-weekly from ENDEAVOR (Section 5.2.1). The dose regimens were evaluated in different but overlapping patient populations; therefore, data were also included from the phase 1/2 CHAMPION-1 study, which evaluated the same dose as A.R.R.O.W. but a similar patient population as ENDEAVOR (see Section 7.1.3).

Another uncertainty is that pharmacodynamic data could not be evaluated from A.R.R.O.W. because all samples were beyond the storage stability date. Therefore, to understand the pharmacodynamic activity of Kd 20/70 mg/m^2 once-weekly, pharmacodynamic data of Kd 20/70 mg/m^2 once-weekly from CHAMPION-1 were reanalyzed and compared with data of Kd 20/56 mg/m^2 twice-weekly from ENDEAVOR (Section 5.2.1).

The FDA's Assessment:
The FDA agrees with Applicant's position on the limitations of the comparability of PK and PD between the Kd 20/70 mg/m^2 once weekly and Kd 20/56 mg/m^2 twice weekly. There are no outstanding issues from a clinical pharmacology perspective.

5.3. Comprehensive Clinical Pharmacology Review

5.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

The Kd 20/70 mg/m^2 once-weekly dose regimen has pharmacokinetic properties that are consistent with currently approved dose regimens. CHAMPION-1 data demonstrated that carfilzomib exposure (C_{max} and AUC_{inf}) increased approximately dose proportionally from 20 to 88 mg/m^2 (Section 2.3.1 of A.R.R.O.W. Module 2.7.2, Summary of Clinical Pharmacology). Additional clinical pharmacology analyses conducted to support the Kd 20/70 mg/m^2 once-weekly dose regimen are described in Section 5.2.1.

The FDA's Assessment:
The FDA agrees with the Applicant on the general pharmacokinetics of Kd 20/70 mg/m^2.

5.3.2. Clinical Pharmacology Questions

5.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

The clinical pharmacology program supporting this sNDA provides evidence to support the observed clinical efficacy of Kd 20/70 mg/m^2 once-weekly. Due to limitations as described in Section 5.2.1 and Section 5.2.2.3, conclusions that can be drawn are limited.

The results of the population pharmacokinetic analysis, including A.R.R.O.W. and CHAMPION-1 data (i.e., Kd 20/70 mg/m^2 once-weekly), were consistent with previous analyses.

The exposure-response analyses based on A.R.R.O.W., ENDEAVOR, and CHAMPION-1 data demonstrated positive trends in the data, which suggest that higher exposures tend to result in longer PFS, consistent with the therapeutic benefit of carfilzomib. In addition, an update to the previously conducted exposure-response analysis, which incorporated A.R.R.O.W. and CHAMPION-1 data, had consistent findings of a relationship between carfilzomib AUC_{C1avg} and ORR, with increasing AUC associated with a higher probability of response.

The pharmacodynamic data demonstrated deep and durable chymotrypsin-like proteasome inhibition for both Kd 20/70 mg/m^2 once-weekly and Kd 20/56 mg/m^2 twice-weekly.

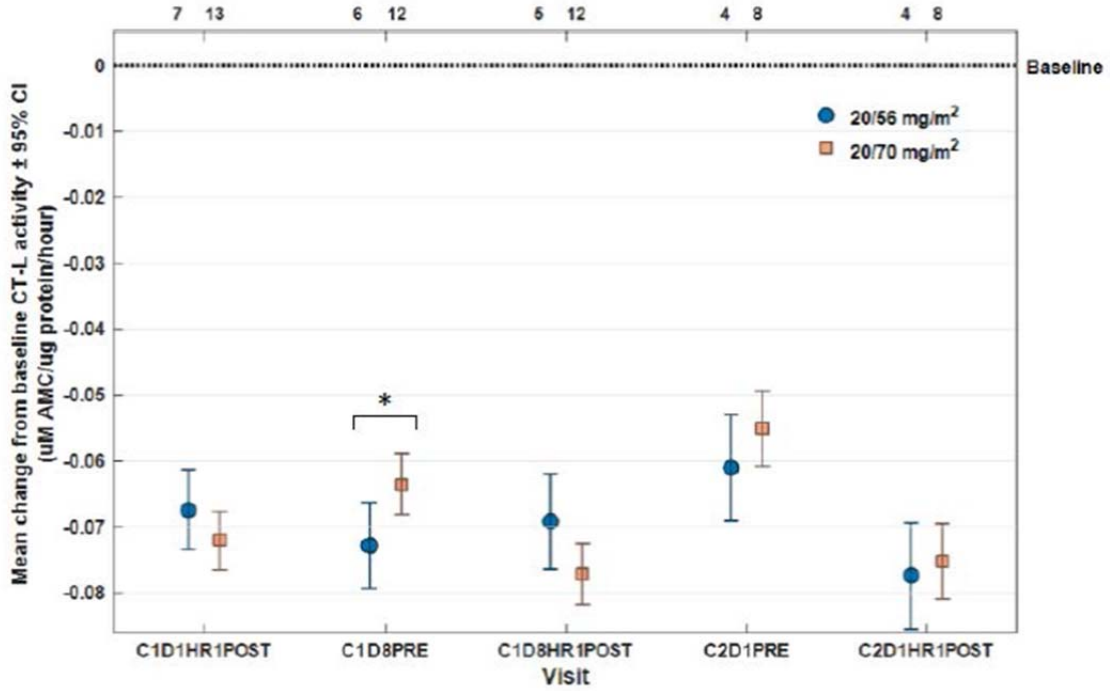
The conclusions that can be drawn from the pharmacokinetic and pharmacodynamic analyses were limited; however, the data are generally consistent with the robust clinical data, which showed the Kd 20/70 mg/m^2 once-weekly dose regimen has comparable efficacy to Kd 20/56 mg/m^2 twice-weekly without any new safety concerns (see Section 7.1.3 and Section 7.2.4).

The FDA's Assessment:
The FDA does not completely agree with the Applicant's exposure response assessment with regards to the pooled assessment. In a univariate assessment after pooling studies, there did appear to be increasing numerical trends with increasing exposure for PFS and ORR. However, this is limited because of potential confounding factors across studies. After adjusting for significant baseline risk factors in a multivariate assessment, exposure was not a significant predictor for ORR. Additionally, when considering the results from each study individually, there were no apparent trends with increasing exposure (over the range studied) for PFS. See

the reviewer's assessment in Appendix 17.3 for further details.

The Agency does not agree with the use of the subjective adjectives "deep" and "durable" with regards to the chymotrypsin assessment. Change from baseline in Chymotrypsin-like (CT-L1) activity can be characterized by the Applicant's plot (Figure 1) of CT-L activity change from baseline against study visit.

Figure 1. Comparison of Proteasome Activity (CT-L) in Whole Blood From CHAMPION-1 and ENDEAVOR



(Source: Applicant's Summary of Clinical Pharmacology, Figure 7)

5.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

The proposed Kd 20/70 mg/m^2 once-weekly dose regimen is considered appropriate for the currently indicated patient population (i.e., subjects with relapsed or refractory multiple myeloma who have received 1 to 3 lines of therapy) (see Section 5.2.1). The population pharmacokinetic model did not identify any new intrinsic or extrinsic factors that significantly impacted carfilzomib pharmacokinetics. In addition, multiple exposure-response analyses provide supportive evidence for the safety and efficacy of the Kd 20/70 mg/m^2 once-weekly dose regimen, and include evaluation of the relevant drug combination, Kd, over a range of

doses (20/27 mg/m^2 twice-weekly, 20/70 mg/m^2 once-weekly, and 20/56 mg/m^2 twice-weekly), and with the population for which the indication is being sought (patients with relapsed or refractory multiple myeloma after 1 to 3 prior therapies).

The FDA's Assessment:
The proposed dose of Kd 20/70 mg/m^2 once-weekly appears reasonable based on the following considerations:

1. The statistical comparison across studies suggests similar efficacy between 20/70 mg/m^2 once-weekly and 20/56 mg/m^2 twice-weekly. See the efficacy assessment Section 7.1 for more details.
2. There is lack of a clear exposure-response relationship at the evaluated exposure levels. This permits the reduced exposure that was seen with the 20/70 mg/m^2 regimen without reducing the anticipated efficacy of the product. See the reviewer's assessment in Appendix 17.3 for further details.

5.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The Applicant's Position:

Adjustment of the carfilzomib dose is required based on body surface area, as stated in the current and proposed USPI (Kyprolis USPI, 2018). Consistent with previous population pharmacokinetic models for carfilzomib, the current population pharmacokinetic model, which includes A.R.R.O.W. and CHAMPION-1, identified body surface area as a significant covariate on carfilzomib clearance (Section 5.2.1). Results of covariate analyses suggested that no other covariates except body surface area were found to be significant or a clinically relevant predictor of carfilzomib clearance. As the carfilzomib dose was already given based on body surface area in all studies, within the range of covariate values investigated, further adjustment of carfilzomib dosing based on these covariates was deemed unwarranted.

In addition, consistent with the currently approved USPI, the carfilzomib dose should be reduced by 25% in patients with mild or moderate hepatic impairment.

The FDA's Assessment:
FDA agrees with the Applicant's position on no alternative recommendation for dosing regimen or management strategy than what is stated in the current drug labeling for intrinsic and extrinsic factors.

5.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:

No evidence of food-drug or drug-drug interactions have been identified for carfilzomib; no new information is provided in the current submission.

The FDA's Assessment:

FDA agrees with the Applicant's position on new information regarding food-drug or drug-drug interactions in the current submission

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6 Sources of Clinical Data

6.1. Table of Clinical Studies

The Applicant's Position:

The primary study supporting the once-weekly dose regimen of carfilzomib is A.R.R.O.W., which compared Kd 20/70 mg/m^2 once-weekly with Kd 20/27 mg/m^2 twice-weekly.

In addition, cross-study comparisons were conducted on data from studies evaluating Kd 20/70 mg/m^2 once-weekly and the labeled Kd 20/56 mg/m^2 twice-weekly dose regimen. Data were analyzed from the phase 3 A.R.R.O.W. study (Kd 20/70 mg/m^2 once-weekly in subjects with relapsed and refractory multiple myeloma who had 2 to 3 prior lines of therapy and were refractory to the last prior line of therapy), the phase 3 ENDEAVOR study (Kd 20/56 mg/m^2 twice-weekly in subjects with relapsed or refractory multiple myeloma who had 1 to 3 prior lines of therapy), and the phase 1/2 CHAMPION-1 study (Kd 20/70 mg/m^2 once weekly in subjects with relapsed or refractory multiple myeloma who had 1 to 3 prior lines of therapy). CHAMPION-1 served as a bridge because it evaluated the same dose regimen as in A.R.R.O.W. but a similar patient population as in ENDEAVOR.

The clinical studies supporting the Kd 20/70 mg/m^2 once-weekly dose regimen (i.e., A.R.R.O.W., ENDEAVOR, and CHAMPION-1) are summarized in Table 3. A detailed description of the A.R.R.O.W. study and its results are provided in Section 7.1.1 and Section 7.1.2, respectively. The results of ENDEAVOR, which was the subject of previous marketing applications, and CHAMPION-1, a phase 1/2 dose finding study, are described below. Additional information is provided in their respective clinical study reports.

Table 3. Listing of Clinical Trials Relevant to This Supplemental New Drug Application

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
20140355 (A.R.R.O.W.)	NCT02412878	Phase 3, multicenter, open-label, randomized (1:1), active-controlled study of Kd QW vs Kd BIW	Kd 20/70 mg/m^2 QW vs Kd 20/27 mg/m^2 BIW	Primary: PFS Secondary: ORR, OS, safety and tolerability, PK	Until PD[a]	478	Relapsed and refractory MM; 2-3 prior tx	118 centers in 20 countries
2011-003 (20130398; ENDEAVOR	NCT01568866	Phase 3, multicenter, open-label, randomized (1:1), active-controlled study of Kd vs Vd	Kd 20/56 mg/m^2 BIW vs Vd	Primary: PFS Secondary: OS, ORR, neuropathy events, safety and tolerability	Until PD[a]	929	Relapsed or refractory MM; 1-3 prior tx	198 centers in 27 countries
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
2012-002 (20130403; CHAMPION-1	NCT01677858	Phase 1/2, multicenter, open-label, single-group, dose-escalation/ expansion study of Kd QW	Kd 20/45, 20/56, 20/70, and 20/88 mg/m^2 QW	Primary: MTD (phase 1), ORR (phase 2) Secondary: safety and tolerability, PK, and CBR, PFS, TTP, and DOR (phase 2 only)	Until PD[a]	118[b]	Relapsed or refractory MM; 1-3 prior tx	32 centers in the US

BIW = twice-weekly; CBR = clinical benefit rate; DOR = duration of response; Kd = carfilzomib plus dexamethasone; MM = multiple myeloma; MTD = maximum tolerated dose; NCT = National Clinical Trial; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetics; QW = once-weekly; TTP = time to progression; tx = lines of therapy; US = United States; Vd = bortezomib plus dexamethasone

[a] Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, or death

[b] Of these, 104 subjects were treated with Kd 20/70 mg/m^2 once-weekly.

In ENDEAVOR, treatment with Kd 20/56 mg/m^2 twice-weekly resulted in a statistically significant and clinically meaningful doubling of PFS and 21% reduction in the risk of death compared with treatment with bortezomib (Velcade®) plus dexamethasone (Vd). At the first preplanned interim analysis (i.e., primary analysis; data cutoff of 10 November 2014), treatment with Kd demonstrated a significant and clinically meaningful improvement in PFS compared with Vd (hazard ratio [HR; 95% CI]: 0.53 [0.44, 0.65]; 1-sided $p < 0.0001$), with median (95% CI) PFS of 18.7 (15.6, not estimable) months versus 9.4 (8.4, 10.4) months, respectively (Section 2.2 of A.R.R.O.W. Module 2.7.3, Summary of Clinical Efficacy). Overall response rates in the Kd and Vd groups were 76.9% and 62.6%, respectively (1-sided $p < 0.0001$). The incidence of grade ≥ 2 peripheral neuropathy was significantly lower in the Kd group (6.0%) than in the Vd group (32.0%) (1-sided $p < 0.0001$). The median duration of response (DOR) was twice as long for subjects in the Kd group versus the Vd group (21.3 and 10.4 months, respectively). At a preplanned second interim analysis (data cutoff of 03 January 2017), treatment with Kd demonstrated a statistically significant and clinically meaningful improvement in OS compared with Vd (HR [95% CI]: 0.79 [0.65, 0.96]; 1-sided $p = 0.0100$, which was lower than the stopping boundary of 0.0123), with median (95% CI) OS of 47.6 (42.5, not estimable) months versus 40.0 (32.6, 42.3) months, respectively. Prespecified subgroups and sensitivity analyses showed a consistent benefit for subjects in the Kd group for PFS, ORR, and OS across nearly all subgroups studied.

In CHAMPION-1, the maximum tolerated dose of carfilzomib once-weekly in combination with dexamethasone was determined to be 70 mg/m^2 (Section 2.3 of A.R.R.O.W. Module 2.7.3, Summary of Clinical Efficacy). For subjects treated with Kd 20/70 mg/m^2 once-weekly, ORR (95% CI) was 76.9% (67.6, 84.6) and the clinical benefit rate (95% CI) was 83.7% (75.1, 90.2). Median (95% CI) PFS was 16.2 (10.2, 21.0) months. Median (95% CI) time to progression and DOR were 17.2 (10.6, 21.7) months and 18.0 (14.5, 21.9) months, respectively.

The FDA's Assessment:

FDA agrees with the summary of the A.R.R.O.W Study, CHAMPION-1 Study and ENDEAVOR Study as presented in the table above. The FDA review was based on data from A.R.R.O.W, CHAMPION-1 and FDA's review of the literature. A propensity score analysis was conducted to evaluate the cross-study comparisons. During a Type B meeting on March 20, 2018, the Agency commented that in general, between-study comparisons were strongly discouraged and cross-study comparisons were considered exploratory. The FDA cautioned that the propensity score method may not adequately control for unknown covariates. The FDA considers the cross-study comparisons on data from studies evaluating Kd 20/70 mg/m^2 once-weekly and the labeled Kd 20/56 mg/m^2 twice-weekly dose regimen as supportive.

7 Statistical and Clinical Evaluation

7.1. Review of Relevant Individual Trials Used to Support Efficacy

7.1.1. A.R.R.O.W. (Study 20140355)

The Applicant's Position:

Trial Design

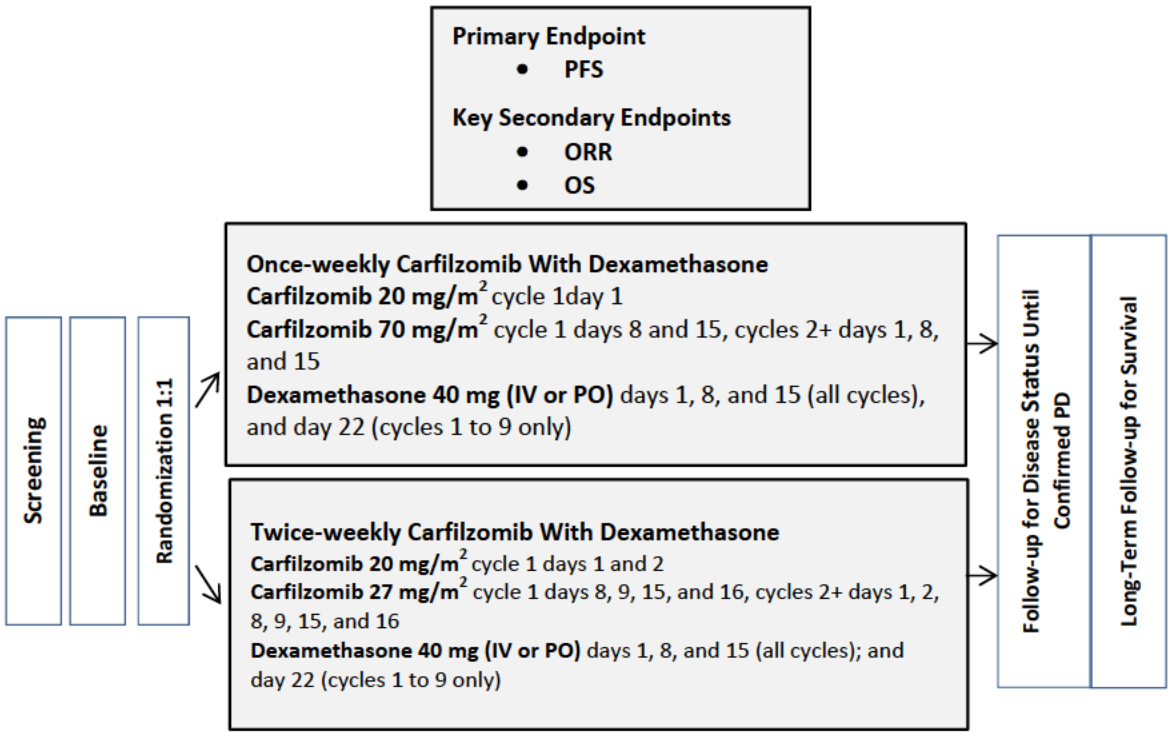
Basic Study Design of A.R.R.O.W.

A.R.R.O.W. (Study 20140355) is a global, phase 3, multicenter, open-label, randomized study in subjects with relapsed and refractory multiple myeloma who had received 2 to 3 prior lines of therapy and were previously treated with a proteasome inhibitor and an IMiD. Subjects were refractory to the last prior therapy. Subjects were randomized in a 1:1 ratio to receive a regimen consisting of either Kd 20/70 mg/m^2 once-weekly or Kd 20/27 mg/m^2 twice-weekly. Randomization was stratified by International Staging System stage (stage 1 versus stages 2 or 3), refractory to bortezomib treatment (yes versus no), and age (< 65 versus ≥ 65 years). Within each stratum defined by the stratification factors, subjects were randomized using a randomly permuted-blocked randomization scheme.

Subjects received the dose regimen determined by randomization until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or death (whichever occurred first). Crossover between the 2 treatment groups was not allowed. Subjects were assessed for response according to the International Myeloma Working Group - Uniform Response Criteria every 28 (± 4) days until progressive disease and/or administration of subsequent antimyeloma therapy. After termination of investigational product, all subjects were followed for disease status (if progressive disease had not been reached), subsequent antimyeloma treatment, and survival.

A schematic of the study design and description of the investigational products is provided in Figure 2.

Figure 2. A.R.R.O.W. Study Design and Treatment Schema



IV = intravenously; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PO = orally

A.R.R.O.W. was open-label to avoid the ethical concern of infusing a placebo solution into immunocompromised subjects in the once-weekly group to mirror the twice-weekly regimen, as well as to assess the convenience of a once-weekly dose regimen. However, the sponsor remained blinded to the by-treatment group results before the interim (primary) analysis. In addition, the primary analyses of response and disease progression were determined by the sponsor using a validated and automatic computer algorithm that was blinded to treatment information (Onyx Response Computational Assessment [ORCA]). An Independent Review Committee (IRC) evaluated disease progression and response in a blinded fashion, which were used as sensitivity analyses. A.R.R.O.W. was also overseen by an independent Data Monitoring Committee, which acted in an advisory capacity to the sponsor with respect to safeguarding the interests of study subjects, assessing interim safety and efficacy data, monitoring the overall conduct of the study, and providing recommendations for continuing, modifying, or stopping the study based on these findings (Section 8.2.5 of Study 20140355).

The A.R.R.O.W. study was conducted in Asia-Pacific, Europe, and North America, including the US. The Applicant finds no cause for concern about the applicability of the results to the US population; the geographical distribution of subject enrollment was similar to that in the ENDEAVOR study, which was the basis of approval for the Kd 20/56 mg/m^2 twice-weekly dose regimen. In A.R.R.O.W., subgroup analyses were conducted by region which provide

reassurance of the efficacy results. In addition, supportive evidence of the safety and efficacy of Kd 20/70 mg/m^2 once-weekly is provided by the CHAMPION-1 study which was conducted solely in the US.

The schedule of activities in A.R.R.O.W. is provided in Table 4.

Table 4. A.R.R.O.W. Schedule of Assessments

Assessment	Screening[a]	Baseline[b]	All Cycles								LTFU
			D1	D2	D8	D9	D15	D16	D22	EOT	
Informed consent	X										
Demographics	X										
Medical and treatment history	X										
Vital signs	X		X	X[c]	X	X[c]	X	X[c]		X	
Physical examination[d]	X		X							X	
ECOG performance status	X									X	
12 lead ECG with QTc interval	X									X	
ECHO/MUGA	X										
Full hematology panel[e]	X		X		X		X			X	
Full serum chemistry panel[e]	X		X		X		X			X	
Coagulation	X									X	
EORTC QLQ-C30, EORTC QLQ-MY20, EQ-5D-5L, and patient-reported convenience and satisfaction[f]			X							X	X
Adverse events and survival status	→										
Concomitant medications	→										
Pregnancy test (FCBP)[g]	X		X							X	
Survival											X

D = day; ECHO = echocardiogram; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; EOT = End of Treatment; EQ-5D-5L = European Quality of Life-5 Dimensions; FCBP = females of childbearing potential; Kd = carfilzomib plus dexamethasone; LTFU = long-term follow-up; MUGA = multigated acquisition; QLQ-C30 = Quality of Life Core Module; QLQ-MY20 = Quality of Life Multiple Myeloma Module 20; QT_C = corrected QT-interval

[a] Screening samples were to be collected within 21 days of randomization.

[b] Baseline samples were to be collected only after subject eligibility was confirmed.

[c] Kd 20/27 mg/m^2 twice-weekly group only

[d] The physical examination from Screening may have been used if it was within 7 days before cycle 1 day 1.

[e] Full hematology and serum chemistry samples from Screening may have been used for cycle 1 day 1 if taken within 3 days before cycle 1 day 1. Beyond cycle 4, labs were performed on days 1 and 15 of each cycle in both groups.

[f] Questionnaires were collected on cycle 1 day 1, then every second cycle (cycle 1, 3, 5, etc.) during treatment and every 12 weeks (every 84 days ± 4 days) until progression or withdrawal of consent during LTFU. Questionnaires were completed by the subject before drug administration during treatment cycles. Patient-reported convenience and satisfaction was collected at cycle 2 and EOT only.

[g] Urine or serum pregnancy test were confirmed negative locally on day 1 of each cycle before dosing and at EOT. At Screening, a confirmed negative serum pregnancy test that was performed centrally was required.

Source: A.R.R.O.W. Protocol Appendix A (Section 16.1.1 of Study 20140355)

Key Inclusion/Exclusion Criteria

The key inclusion/exclusion criteria in A.R.R.O.W. are presented below; the full inclusion/exclusion criteria are listed in A.R.R.O.W. Protocol Section 5 (Section 16.1.1 of Study 20140355). The patient population selected was consistent with the indication of carfilzomib monotherapy approved at the time of study initiation. Since that time, the labeled indication has expanded to include patients with relapsed or refractory multiple myeloma who have received either 1 to 3 prior lines of therapy or 1 or more prior lines of therapy. As such, notable differences exist in the patient populations of A.R.R.O.W. and the phase 3 ENDEAVOR study which was the basis for approval of the Kd 20/56 mg/m^2 twice-weekly dose regimen. To account for these differences when providing information on the efficacy and safety of Kd 20/70 mg/m^2 once-weekly, additional analyses were conducted using different populations to bridge the results of A.R.R.O.W. to the indicated population (see Section 7.1.3 and Section 7.2.1).

The diagnostic criteria and definitions used to enroll subjects in the A.R.R.O.W. study, including the definition of refractory multiple myeloma and measurable disease, are consistent with current diagnostic guidelines for multiple myeloma in the US (Kumar et al, 2016).

Key Inclusion Criteria

- relapsed multiple myeloma
- refractory multiple myeloma, defined as meeting 1 or more of the following:
    - nonresponsive to most recent therapy (stable disease or progressive disease while on treatment), or
    - disease progression within 60 days of discontinuation from most recent therapy
- at least 2 but no more than 3 prior lines of therapies for multiple myeloma
- prior exposure to an IMiD
- prior exposure to a proteasome inhibitor)
- documented response of at least partial response to at least 1 prior line of therapy
- measurable disease with at least 1 of the following assessed at a central laboratory within the 21 days before randomization:
    - serum M-protein ≥ 0.5 g/dL
    - urine M-protein ≥ 200 mg/24 hours
    - in subjects without measurable serum or urine M-protein, serum free light chain ≥ 100 mg/L (involved light chain) and an abnormal serum kappa lambda ratio
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Key Exclusion Criteria:

- cytotoxic chemotherapy or other antineoplastic therapy, aside from immunotherapy or proteasome inhibitors, within the 28 days before randomization
- immunotherapy, such as an IMiD or a proteasome inhibitor within the 21 days before randomization

- prior treatment with either carfilzomib or oprozomib

Study Treatments

The dosing schedules for the Kd 20/70 mg/m^2 once-weekly group and the Kd 20/27 mg/m^2 twice-weekly group in A.R.R.O.W. are presented in

Figure 2.

The dose of the experimental group of A.R.R.O.W., Kd 20/70 mg/m^2 once-weekly, was selected based on the results of the phase 1/2 CHAMPION-1 study. CHAMPION-1 evaluated once-weekly doses of carfilzomib at 20/45, 20/56, 20/70, and 20/88 mg/m^2 in combination with dexamethasone. The maximum tolerated dose was determined to be 20/70 mg/m^2. This dose regimen demonstrated an acceptable safety profile and evidence of clinical response in subjects with relapsed or refractory multiple myeloma.

The control group in A.R.R.O.W. (Kd 20/27 mg/m^2 twice-weekly) is not a labeled dose regimen; however, it is considered to be a standard of care in the US, where it represents 37% of all carfilzomib dose regimens and 78% of all Kd regimens in the treatment of relapsed multiple myeloma, and thus, is considered to be a clinically relevant comparison (see Section 1.3.1.1 of A.R.R.O.W. Module 2.5, Clinical Overview). At the time the A.R.R.O.W. study was designed and initiated (2014), the only approved carfilzomib dose regimen in any region was monotherapy at 20/27 mg/m^2 twice-weekly (in the US) and thus, 20/27 mg/m^2 twice-weekly was the dose selected for the control group. Therapeutic dexamethasone was added with the goal of improving outcomes over monotherapy; equivalent weekly doses of dexamethasone were administered to both treatment groups to enable a clear interpretation of the study's primary comparison between carfilzomib at 20/70 mg/m^2 once-weekly and 20/27 mg/m^2 twice-weekly.

Dose Modification/Discontinuation

In A.R.R.O.W., the dose modification and discontinuation rules for carfilzomib were generally consistent with the USPI.

Dose reductions are presented in Table 5. The reduced carfilzomib dose level was to continue for at least 1 complete cycle. After that, if the reduced dose level was well tolerated, the previous dose level could have been resumed at the investigator's discretion.

Table 5. A.R.R.O.W. Dose Decrements for Carfilzomib and Dexamethasone

	First Dose Reduction Dose -1	Second Dose Reduction Dose -2	Third Dose Reduction Dose -3
Carfilzomib Dose			
70 mg/m^2	56 mg/m^2	45 mg/m^2	36 mg/m^2
27 mg/m^2	20 mg/m^2	15 mg/m^2	11 mg/m^2
Dexamethasone Dose			
40 mg	20 mg	12 mg	NA

NA = not applicable
Source: A.R.R.O.W. Protocol Table 3 and Table 6 (Section 16.1.1 of Study 20140355)

Treatment compliance was recorded in the appropriate electronic case report form.

Concurrent Medications
Lansoprazole (or other proton pump inhibitor) while taking oral dexamethasone was a required concomitant medication.

The following medications/therapies were recommended per protocol-specified procedures, at the investigator's discretion: valacyclovir (or an equivalent antiviral agent), allopurinol (or other approved uric acid-lowering agent), mycostatin or oral fluconazole, antiemetics and antidiarrheal agents, and thromboprophylaxis.

The following medications/therapies were not allowed while subjects received investigational product: therapy with a marketed or investigational anticancer agent that was not required per protocol, radiation to large marrow reserves (focal palliative radiation was allowed with permission from the study medical monitor), prophylactic use of myeloid growth factors (in accordance with American Society of Clinical Oncology guidelines [Smith et al, 2006]), corticosteroids (unless the dose remained less than the equivalent of 4 mg/day of dexamethasone), plasmapheresis, and other investigational agents.

Study Endpoints

The primary endpoint was PFS, defined as the time in months from randomization to the earlier of disease progression or death due to any cause. While the study was originally designed and discussed with the FDA with a primary endpoint of ORR and PFS as a key secondary endpoint, recent advances in antimyeloma therapy have resulted in PFS being considered the more robust regulatory endpoint in a superiority study design of multiple myeloma to support registration. In addition, PFS was the primary endpoint in the phase 3 carfilzomib ASPIRE and ENDEAVOR studies, which led to approval of the KRd 20/27 mg/m^2 twice-weekly and Kd 20/56 mg/m^2 twice-weekly dose regimens, respectively.

To limit bias in the assessment of disease progression, the primary analysis of PFS was determined by a validated and automatic computer algorithm (ORCA) that was blinded to

treatment information, with sensitivity analyses by IRC (blinded) and investigator (unblinded) assessments (see Statistical Analysis Plan and Amendments).

The secondary endpoints which were multiplicity adjusted for statistical testing included additional efficacy parameters, ORR and OS, which are standard endpoints for multiple myeloma studies, including other phase 3 carfilzomib clinical studies. Other secondary endpoints included safety and tolerability and pharmacokinetics of carfilzomib using sparse sampling.

Patient-reported outcomes (PROs), including health-related quality of life (HRQoL) and patient satisfaction and convenience, were exploratory endpoints.

Statistical Analysis Plan and Amendments

The statistical analysis plan (SAP) for A.R.R.O.W. was approved on 09 June 2017, before the A.R.R.O.W. study was unblinded (Section 16.1.9 of Study 20140355). The FDA reviewed the SAP and provided comments on 19 April 2017, with responses provided by the Applicant on 08 May 2017 (see Table 2).

Populations
Analysis sets are described in Table 6.

Table 6. A.R.R.O.W. Analysis Sets

Analysis Set	Definition
Primary analysis set (ITT Population)	All randomized subjects analyzed according to their randomized treatment assignment, regardless of the treatment received
Safety analysis set	All subjects who received at least 1 dose of investigational product analyzed according to the treatment they received
Per protocol analysis set	All randomized subjects who did not have any important protocol deviations which could have had an impact on the efficacy evaluation of the subject
Health-related Quality of Life Analyses Set	All randomized subjects who filled out EORTC QLQ-C30, EORTC QLQ-MY20, EQ-5D-5L, or patient-reported convenience and satisfaction questionnaire
Pharmacokinetic/Pharmacodynamic Analyses Set	All subjects who participated in the intensive pharmacokinetic/pharmacodynamic substudy or the sparse pharmacokinetic sampling
Interim Analyses Set	All randomized subjects at the time of the interim analysis

ITT = intent-to-treat; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = European Quality of Life-5 Dimensions; QLQ-C30 = Quality of Life Core Module; QLQ-MY20 = Quality of Life Multiple Myeloma Module 20
Source: Table 8-6 of Study 20140355

Exploratory subgroup analyses for the primary endpoint (PFS) and key secondary endpoints (ORR and OS) were performed for each level of the 3 randomization stratification factors: International Staging System stage at study entry (stage 1 versus stage 2 or stage 3), refractory to bortezomib treatment (yes versus no,) and age (< 65 versus ≥ 65 years, < 75 versus ≥ 75 years). Additional subgroup analyses were based on the following factors:

- sex (men versus women)
- race (white versus Asian versus other)
- ethnicity (Hispanic or Latino versus not Hispanic or Latino)
- geographic region (Europe versus North America versus Asia Pacific)
- baseline ECOG (0 versus 1)
- baseline creatinine clearance (30 to < 50 mL/min versus 50 to < 80 mL/min versus ≥ 80 mL/min)
- fluorescence in situ hybridization (FISH) risk group (high risk versus standard risk versus unknown)
- β_2-microglobulin level (< 3.5 versus ≥ 3.5 mg/L)
- International Staging System stage at baseline (stage 1 versus stage 2 and stage 3)
- International Staging System stage at diagnosis (stage 1 versus stage 2 and stage 3 versus unknown)
- corrected calcium at baseline (≤ 11.5 versus > 11.5 mg/dL)
- lines of prior treatment (2 versus 3)
- prior transplant (yes versus no)
- prior lenalidomide (yes versus no)
- refractory to lenalidomide (yes versus no)

The subgroups evaluated were prespecified. Except for stratification variables, subgroups with < 5% of the whole population could have been combined with others, if appropriate.

Interim Analysis and Early Stopping Guidelines

One interim analysis of PFS was planned based on a prespecified number of events (approximately 263 of 350 events [75%]) (A.R.R.O.W. Protocol Section 13.3.2.1 [Section 16.1.1 of Study 20140355]); the interim analysis was conducted with 274 of 350 total PFS events (78% information fraction) (Table 7). The objective of the interim analysis was to monitor for differences between treatment groups for evidence of a substantial benefit in the Kd 20/70 mg/m^2 once-weekly group compared with the Kd 20/27 mg/m^2 twice-weekly group.

To ensure proper control of type I error rate, the analysis of PFS was analyzed under a group sequential design framework with the stopping boundaries constructed using the Lan-DeMets spending function with an O'Brien-Fleming approach. Actual boundaries were calculated based on observed PFS events up to the data cutoff date for the interim analysis (Table 7).

Table 7. A.R.R.O.W. Stopping Boundaries for Progression-free Survival

					Boundary to Reject Null		
Endpoint	Analysis	Information Fraction	Cumulative Events	Alpha Spent	p-value (primary inference)	HR	Power (Incremental)
PFS	Interim	0.78	274	0.011	0.011	0.759	63%
	Final	1.00	350	0.014	0.022	0.806	20%

HR = hazard ratio; PFS = progression-free survival
The boundaries were updated based on the actual numbers of events observed at PFS interim analysis

Efficacy Analyses

The primary analysis of efficacy was performed on the Primary Analysis Set (Intent-to-Treat [ITT] Population) (Table 6). The hypotheses for the primary efficacy endpoint, PFS, and secondary efficacy endpoints (ORR and OS) were tested using a fixed sequence hierarchical testing procedure to control the family-wise type I error rate below a 1-sided 0.025 level. The family of hypotheses was ordered as follows: 1) PFS, 2) ORR, and 3) OS. Starting with the hypothesis of PFS, if any null hypothesis in the sequence was rejected, then the subsequent hypothesis was tested; if any null hypothesis was accepted, then the subsequent hypotheses were not tested. Furthermore, potential multiplicity from testing at 2 possible times of PFS interim analysis and final analysis for ORR and OS were adjusted using the Lan-DeMets spending function with an O'Brien Fleming approach for ORR, and the same spending function with a Pocock approach for OS (Hung et al, 2007).

Primary Endpoint

A 1-sided stratified log-rank test, stratified by the randomization factors, was used to compare PFS between treatment groups as primary inference. In addition, an HR with a 95% CI was estimated from a stratified Cox regression model. The 1-sided p-value from the test was compared against the prespecified alpha value to determine the significance. Kaplan-Meier summaries were performed by treatment group. Censoring rules were based on the FDA Guidance for Industry, 'Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics' (A.R.R.O.W. SAP Table 1 [Section 16.1.9 of Study 20140355]) (FDA, 2007).

The primary analysis of PFS was performed on the ITT Population based on ORCA. Sensitivity analyses were performed using investigator assessments, IRC assessments, and different censoring rules regarding use of new antimyeloma therapy and different analysis population. The discordance between the results regarding progression status and timing from ORCA, investigator, and IRC were summarized. Subgroup analyses were performed to explore the consistency of the treatment effect for subgroups.

Secondary Endpoints
The ORR was analyzed at the time of the PFS analysis because the PFS analysis crossed the stopping boundary. The ORR was calculated by treatment group and the associated 95% CI was estimated using the Clopper-Pearson method. The inferential comparison of ORR between treatment groups was performed using the Cochran Mantel-Haenszel test stratified by the randomization stratification factors. A 1-sided p-value from the test was compared against the prespecified alpha value to determine the significance; because the analysis of ORR was done at the time of the PFS interim analysis, the critical 1-sided p-value boundary was 0.021. Odds ratio and its 95% CI were estimated using the Mantel-Haenszel method. The primary analysis of ORR was based on ORCA for the ITT Population. Sensitivity analyses were performed based on investigator assessments, IRC assessments, unstratified method, and for the Per Protocol Set. The discordance between the results from ORCA, investigator, and IRC were summarized. Subgroup analyses were performed to explore the consistency of the treatment effect for subgroups.

The analysis of OS was conducted at the time of the PFS analysis because both PFS and ORR analyses were significant. The analysis methods used for OS were as described for PFS. Subjects still alive were censored at the date last known to be alive. Because the analysis of OS was done at the time of the PFS interim analysis, the critical 1-sided p-value boundary was 0.018.

Exploratory Endpoints
All European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Core Module (QLQ-C30) and EORTC Quality of Life Multiple Myeloma Module 20 (QLQ-MY20) subscale scores were summarized descriptively by visit, by treatment group, and change from baseline. Data for European Quality of Life-5 Dimensions (EQ-5D-5L) were summarized by frequency and proportion of each level for each dimension by visit and by treatment group. Frequency and proportion of each category from the patient convenience and satisfaction questionnaire was summarized by treatment group at cycle 2 and at the end of treatment visit.

Comparison analyses of HRQoL between treatment groups was implemented in addition to the descriptive analyses; resulting p-values are descriptive.

Protocol Amendments

Table 8 provides a summary of changes related to the conduct of the A.R.R.O.W. study.

The primary endpoint in A.R.R.O.W. is PFS. However, the study was originally designed with ORR as the primary endpoint and PFS as a key secondary endpoint. Although ORR remains a meaningful clinical endpoint, recent advances in antimyeloma therapy have resulted in PFS being considered the more robust regulatory endpoint in a superiority study design to support registration. To support regulatory interactions and protect the integrity of the PFS data, the primary endpoint was amended to PFS in Protocol Amendment 4.0 with ORR as a key

secondary endpoint.

Table 8. Summary of Protocol Amendments for A.R.R.O.W.

Amendment	Major Changes
Original Protocol 19 December 2014	
Amendment 1.0 11 February 2015	• clarified that consent was required from subjects if additional blood samples were collected for pharmacokinetic (sparse sampling) and for the intensive pharmacokinetic/ pharmacodynamic substudy • clarified dexamethasone was to be administrated orally on day 22 in cycles 1 to 9 • clarified that dexamethasone was not to be administered on day 22 after cycle 9 • clarified that events occurring before consent should have been captured as medical history information • clarified the timing of safety labs after cycle 4 • clarified the timing of patient-reported outcome questionnaires
Amendment 1.1 18 March 2015	• administrative updates only
Amendment 2.0 28 April 2015	• added adverse events of pulmonary hypertension and thrombocytopenic thrombotic purpura/hemolytic uremic syndrome to the dose modification guidelines • clarified pharmacokinetic time points for intensive and sparse pharmacokinetic sampling.
Amendment 3.0 22 April 2016	• clarified time points for study procedures • clarified exclusion criteria of antineoplastic therapy use to allow immunotherapy or proteasome inhibitors • added the potential use of an Independent Review Committee • removed information for formulation, physical description, storage, and investigational product accountability to avoid duplication with Investigational Product Instruction Manual • clarified carfilzomib and dexamethasone dosing and procedures for dose interruption • updated text to align with current carfilzomib core safety language • revised hematologic and nonhematologic toxicities for carfilzomib, and dexamethasone-related toxicities • clarified guidance for use of concomitant medications and therapies that were excluded • clarified that cytogenetic abnormalities from prior testing should have been reported as part of multiple myeloma history • added other radiologic modalities permitted for performing skeletal assessment (e.g., low-dose computed tomography scan) • clarified requirements for the discontinuation of subjects for progressive disease • revised definition of adverse events regarding worsening of pre-existing conditions • clarified disease response for IMWG-URC

Amendment	Major Changes
Amendment 4.0 08 February 2017	• changed PFS from a key secondary objective/endpoint to the primary objective/endpoint and ORR from the primary objective/endpoint to a key secondary objective/endpoint • revised the interim PFS analysis to monitor efficacy and allow the possibility of stopping the study early for efficacy; statistical language was aligned • updated stopping boundaries for PFS • updated carfilzomib dose modifications for nonhematologic toxicity • allowed for the possibility of long-term follow-up for overall survival • added sections for end of study, product complaints, and thromboprophylaxis • added sample forms for serious adverse event reporting and pregnancy and lactation notifications • updated background information
Superseding Amendment 4.0 07 March 2017	• corrected an error in the dexamethasone dosing in the study schema

IMWG-URC = International Myeloma Working Group - Uniform Response Criteria; ORR = overall response rate; PFS = progression-free survival

The FDA's Assessment:

The Applicant has described the protocol and the Statistical Analysis Plan (SAP) for A.R.R.O.W above. The SAP for A.R.R.O.W. was approved on June 9, 2017 before the A.R.R.O.W. study was unblinded. The primary endpoint before Protocol Amendment 4.0 was ORR, which was the basis of the sample size calculation that called for a sample of 460 subjects. In Protocol Amendment 4.0, the planned sample size remained the same, but the primary endpoint was changed to PFS. A total of 350 PFS events were needed for the final PFS analysis to have 83% power to detect a significant difference in PFS between the two treatment groups at 1-sided significance level of 0.025. One interim analysis was performed at approximately 75% information time using the lan-DeMets spending function with an O'Brien-Fleming approach, if the underlying hazard ratio was 0.73. With the change of ORR to a secondary endpoint, the power for ORR analysis was approximately 88%, under the assumption that the expected response rate was 35% in the Kd 20/27 mg/m^2 twice-weekly group and 50% in the Kd 20/70 mg/m^2 once-weekly group, the target odds ratio is 1.857. No target number of events was identified for OS analysis. The analysis of OS was conducted at the time of the PFS analysis. The SAP was acceptable to the FDA. Note that the hazard ratio was estimated using a stratified Cox-proportional hazard model.

7.1.2. A.R.R.O.W. Study Results

The Applicant's Position:

Compliance with Good Clinical Practices

The A.R.R.O.W. study was conducted in accordance with the Code of Federal Regulations (CFR)

governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with Good Clinical Practice. The study was conducted under Investigational New Drug 71057.

Financial Disclosure

Financial interests or arrangements with clinical investigators have been disclosed (see Appendix 17.2). Two investigators had significant financial interests with the sponsor (Onyx/Amgen); 1 subject was enrolled at each of these sites. Because of the multicenter nature of the study, the use of objective endpoints, clinical site monitoring and audits, and the independent and centralized assessment of efficacy endpoints, it is unlikely that financial interests could have influenced or biased the results of the A.R.R.O.W. study.

Patient Disposition

A total of 478 subjects were randomized (240 subjects in the Kd 20/70 mg/m^2 once-weekly group and 238 subjects in the Kd 20/27 mg/m^2 twice-weekly group) and comprise the ITT Population (Table 9). Of these, 473 subjects were treated with at least 1 dose of investigational product (238 subjects in the Kd 20/70 mg/m^2 once-weekly group and 235 subjects in the Kd 20/27 mg/m^2 twice-weekly group) and comprise the Safety Population.

Table 9. Subject Disposition in A.R.R.O.W.

	Kd 20/27 mg/m^2 Twice-weekly n (%)	Kd 20/70 mg/m^2 Once-weekly n (%)	Total n (%)
Subjects randomized	238	240	478
Subjects randomized but not dosed	3 (1.3)	2 (0.8)	5 (1.0)
Subjects who received carfilzomib	235 (98.7)	238 (99.2)	473 (99.0)
Subjects continuing carfilzomib	55 (23.1)	80 (33.3)	135 (28.2)
Subjects who discontinued carfilzomib	180 (75.6)	158 (65.8)	338 (70.7)
Death	6 (2.5)	13 (5.4)	19 (4.0)
Adverse event	18 (7.6)	25 (10.4)	43 (9.0)
Subject request	10 (4.2)	10 (4.2)	20 (4.2)
Disease progression	129 (54.2)	97 (40.4)	226 (47.3)
Physician decision	8 (3.4)	3 (1.3)	11 (2.3)
Other	9 (3.8)	10 (4.2)	19 (4.0)
Subjects entered AFU[a]	12 (5.0)	16 (6.7)	28 (5.9)
Continuing in AFU	3 (1.3)	6 (2.5)	9 (1.9)
Completed or discontinued AFU	9 (3.8)	10 (4.2)	19 (4.0)
Subject request	1 (0.4)	0 (0.0)	1 (0.2)
Death	1 (0.4)	0 (0.0)	1 (0.2)
Disease progression	5 (2.1)	9 (3.8)	14 (2.9)
Other	2 (0.8)	1 (0.4)	3 (0.6)
Subjects entered LTFU[b]	126 (52.9)	110 (45.8)	236 (49.4)
Continuing in LTFU	98 (41.2)	91 (37.9)	189 (39.5)
Completed or discontinued LTFU	28 (11.8)	19 (7.9)	47 (9.8)
Withdrawal of consent from study	4 (1.7)	1 (0.4)	5 (1.0)
Death	24 (10.1)	18 (7.5)	42 (8.8)

AFU = active follow-up; Kd = carfilzomib plus dexamethasone; LTFU = long-term follow-up
Percentages are relative to the number of subjects randomized in each column.
Data are reported as of the data cutoff of 15 June 2017.
[a] Active follow up is the long-term follow-up before disease progression as specified in the protocol for subjects who discontinued treatment before disease progression.
[b] Long-term follow-up is the long-term follow-up after disease progression (for survival) as specified in the protocol.
Source: Table 14-1.1 of Study 20140355

Protocol Violations/Deviations

The important protocol deviations were expected to have minimal impact on the overall interpretation of the efficacy or safety results of the study (Table 14-3 of Study 20140355).

Table of Demographic Characteristics

Subject demographics for the ITT Population were generally consistent between treatment groups (Table 10). Overall, 54.4% of subjects were men, 84.1% were white, and the median age was 66 (range: 35 to 85) years. The percentage of Asian subjects was higher in the Kd 20/70 mg/m^2 once-weekly group (12.5%) than in the Kd 20/27 mg/m^2 twice-weekly group (6.3%). The percentage of subjects aged 65 to 74 years was higher in the Kd 20/27 mg/m^2

twice-weekly group (42.9%) than in the Kd 20/70 mg/m^2 once-weekly group (37.5%).

Table 10. Demographic Characteristics (A.R.R.O.W. Intent-to-Treat Population)

	Kd 20/27 mg/m^2 Twice-weekly (N = 238)	Kd 20/70 mg/m^2 Once-weekly (N = 240)	Total (N = 478)
Sex (n [%])			
Male	128 (53.8)	132 (55.0)	260 (54.4)
Female	110 (46.2)	108 (45.0)	218 (45.6)
Ethnicity (n [%])			
Hispanic/Latino	5 (2.1)	2 (0.8)	7 (1.5)
Not Hispanic/Latino	226 (95.0)	235 (97.9)	461 (96.4)
Missing[a]	7 (2.9)	3 (1.3)	10 (2.1)
Race (n [%])			
Asian	15 (6.3)	30 (12.5)	45 (9.4)
Black or African American	2 (0.8)	3 (1.3)	5 (1.0)
White	202 (84.9)	200 (83.3)	402 (84.1)
Other	9 (3.8)	4 (1.7)	13 (2.7)
Missing[a]	10 (4.2)	3 (1.3)	13 (2.7)
Age (years)			
Mean	64.8	65.5	65.2
SD	8.8	9.7	9.2
Median	66.0	66.0	66.0
Min, Max	35, 83	39, 85	35, 85
Age group (n [%])			
18 - 64 years	104 (43.7)	104 (43.3)	208 (43.5)
65 - 74 years	102 (42.9)	90 (37.5)	192 (40.2)
75 - 84 years	32 (13.4)	45 (18.8)	77 (16.1)
≥ 85 years	0 (0.0)	1 (0.4)	1 (0.2)
Geographic region (n [%])[b]			
Asia Pacific	17 (7.1)	32 (13.3)	49 (10.3)
Europe	203 (85.3)	192 (80.0)	395 (82.6)
North America	18 (7.6)	16 (6.7)	34 (7.1)
United States	3 (1.3)	0	3 (0.6)

Kd = carfilzomib plus dexamethasone

[a] Data on race and/or ethnicity were not collected for 12 subjects in France who had not signed the French informed consent form V5 authorizing the collection of this data point.

[b] Asia Pacific includes Australia, Japan, and New Zealand; Europe includes Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Norway, Poland, Romania, Spain, Sweden, and United Kingdom; North America includes Canada and the United States.

Source: Table 14-2.1 and Table 14-2.2 of Study 20140355 and A.R.R.O.W. adsl.sas7bdat, 08 November 2017

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Disease characteristics in A.R.R.O.W. were generally well balanced between treatment groups (Table 13).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Antimyeloma therapies taken after discontinuation of investigational product in A.R.R.O.W. were collected because of their potential impact on the efficacy endpoint, OS. A total of 141 subjects (29.5%) had at least 1 antimyeloma therapy after discontinuation of investigational product (26.7% in the Kd 20/70 mg/m^2 once-weekly group, 32.4% in the Kd 20/27 mg/m^2 twice-weekly group) (Table 10-4 in Study 20140355). New antimyeloma medications (Kd 20/70 mg/m^2 once-weekly, Kd 20/27 mg/m^2 twice-weekly) with a > 2% difference between treatment groups included bortezomib (5.4%, 8.4%) and lenalidomide (3.3%, 8.8%). Other new antimyeloma medications were generally balanced between treatment groups.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Subjects in the Kd 20/70 mg/m^2 once-weekly group had a 31% risk reduction in disease progression or death compared with subjects in the Kd 20/27 mg/m^2 twice-weekly group (HR [95% CI]: 0.69 [0.54, 0.88]; p = 0.0014) (Table 11 and Figure 3). This p-value was below the prespecified stopping boundary of 0.011 (Table 7); therefore, the treatment effect was statistically significant and translates into a 3.6-month longer median PFS (based on ORCA) for the Kd 20/70 mg/m^2 once-weekly group.

Results for PFS determined by IRC (HR [95% CI]: 0.68 [0.54, 0.87], p = 0.0010) were consistent with PFS determined by ORCA (Table 14-2.3 of Study 20140355). The PFS results were generally consistent across prespecified subgroups and sensitivity analyses (Section 10.1 of Study 20140355).

Table 11. Overview of Efficacy in A.R.R.O.W. (Intent-to-Treat Population)

	Kd 20/27 mg/m^2 Twice-weekly (N = 238)	Kd 20/70 mg/m^2 Once-weekly (N = 240)
PFS		
Number of subjects with a PFS event (n [%])	148 (62.2)	126 (52.5)
Median (95% CI) (months)[a]	7.6 [5.8, 9.2)	11.2 [8.6, 13.0)
Hazard ratio (QW/BIW) (95% CI)[b]	0.693 (0.544, 0.883)	
p-value (1-sided)[b]	0.0014	
ORR[c]		
Number of subjects with overall response (n)	97	151
ORR (% [95% CI])[d]	40.8 (34.5, 47.3)	62.9 (56.5, 69.0)
Odds ratio (QW/BIW) (95% CI)[e]	2.485 (1.716, 3.598)	
p-value (1-sided)[e]	< 0.0001	
OS		
Number of subjects with an OS event (n [%])	68 (28.6)	58 (24.2)
Median (95% CI) (months)[a]	NE [18.1, NE)	NE [NE, NE)
Hazard ratio (QW/BIW) (95% CI)[b]	0.800 (0.563, 1.138)	
p-value (1-sided)[b]	0.1070	

BIW = twice-weekly; Kd = carfilzomib plus dexamethasone; NE = not estimable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; QW = once-weekly

Stratification factors included International Staging System stage at study entry (stage 1 versus stage 2 or 3), refractory to bortezomib treatment (yes versus no), and age (< 65 versus ≥ 65 years).

Progression-free survival and ORR were based on a validated computational algorithm (Onyx Response Computational Assessment [ORCA]).

[a] Median was estimated using the Kaplan-Meier method. Corresponding CIs were estimated using the method by Klein and Moeschberger (1997) with log-log transformation.

[b] The hazard ratio and 95% CI were from stratified Cox regression, and the p-value was from stratified log-rank test.

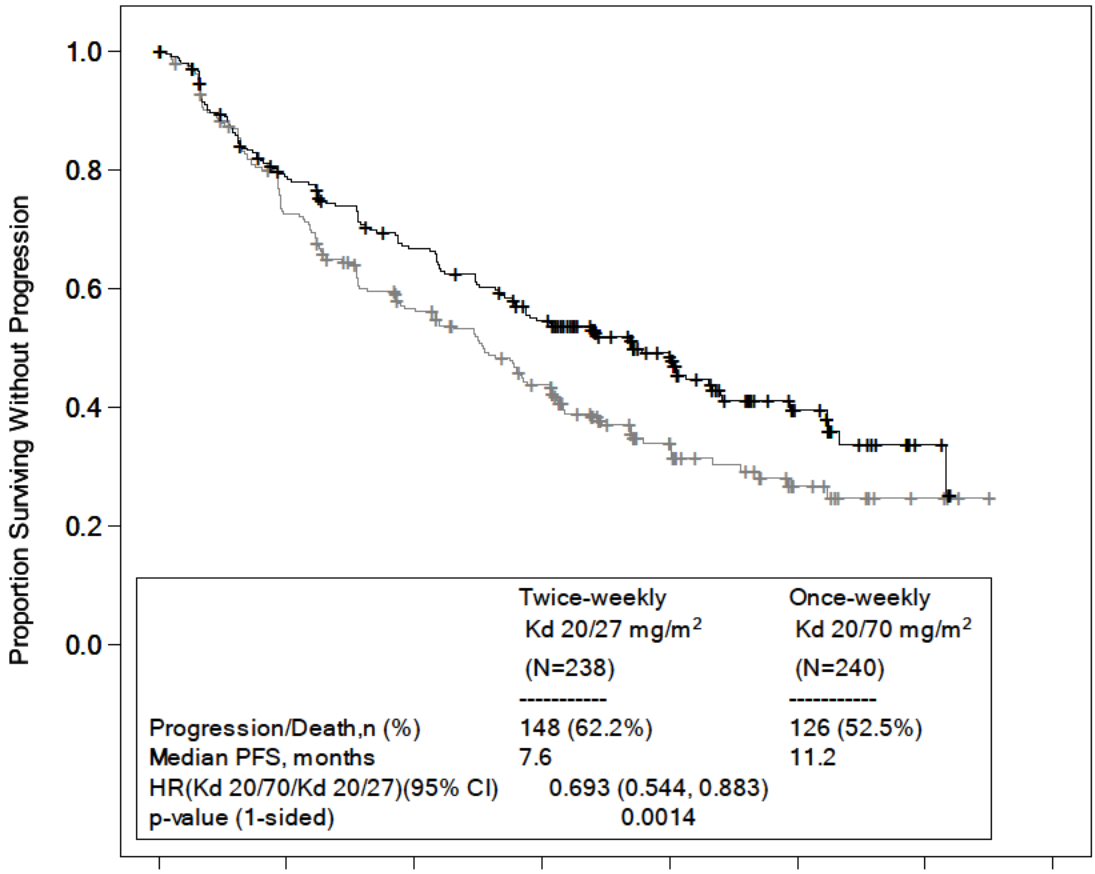
[c] Overall response rate is defined as achieving a best overall response of partial response or better.

[d] Clopper-Pearson interval

[e] The odds ratio and 95% CI were calculated using the Mantel-Haenszel method, and the p-value was from the stratified Cochran-Mantel-Haenszel test.

Source: Table 14-4.1 of Study 20140355

Figure 3. Kaplan-Meier Plot - Progression-free Survival as Assessed by the Sponsor Using ORCA (A.R.R.O.W. Intent-to-Treat Population)



Number of Subjects at Risk:

Kd 20/27	238	164	119	86	41	15	4	0
Kd 20/70	240	178	145	114	69	24	5	0

HR = hazard ratio; Kd = carfilzomib plus dexamethasone; ORCA = Onyx Response Computational Assessment; PFS = progression-free survival
The survival curves and the median PFS were derived by unstratified Kaplan-Meier method, the HR and 95% CI were from Cox proportional hazards model stratified by the randomization stratification factors, and the 1-sided p-value was from the stratified log-rank test.
Source: Figure 14-4.1.1 of Study 20140355

Data Quality and Integrity

No issues were identified with the data quality or integrity from A.R.R.O.W. which could affect the efficacy results.

Efficacy Results – Secondary and other relevant endpoints

Overall Response

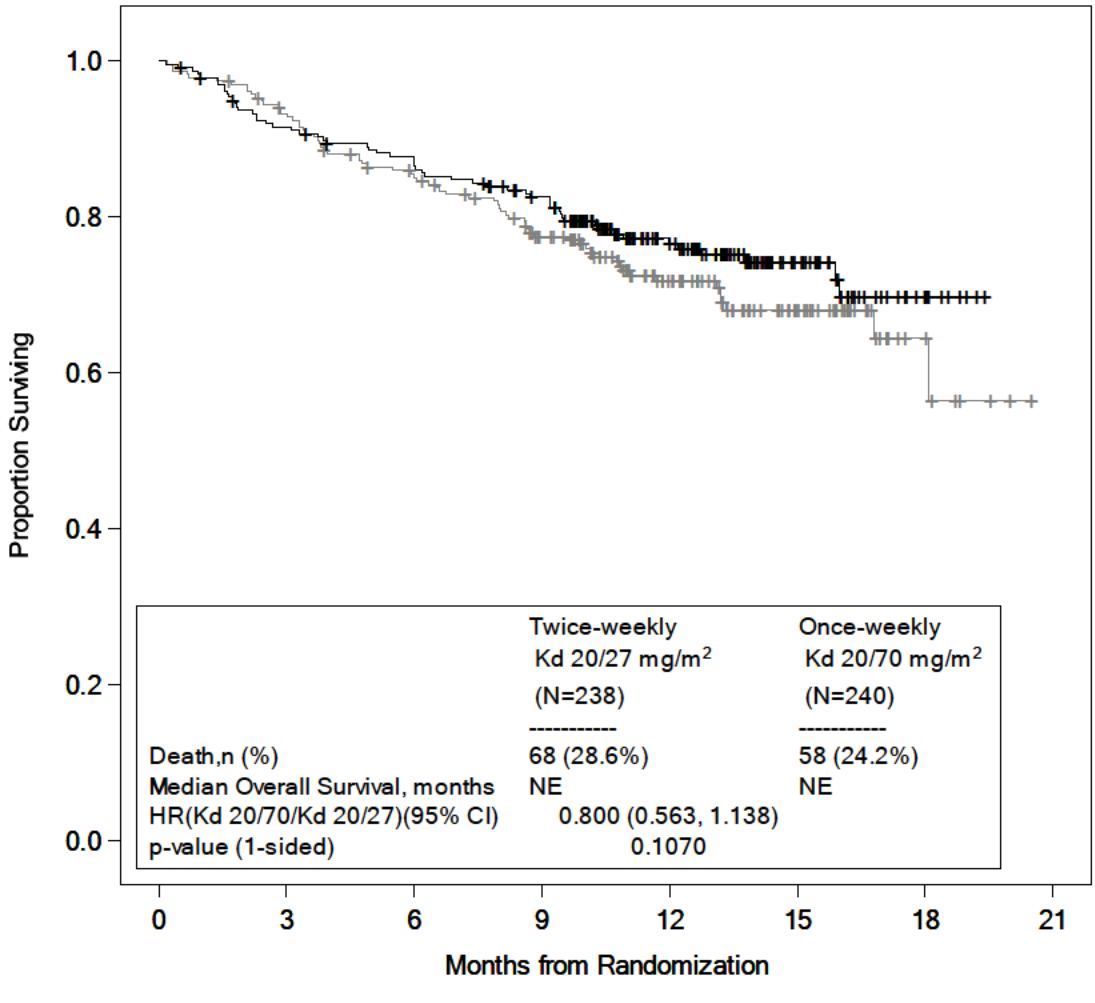
The ORR (95% CI) based on ORCA was significantly higher for the Kd 20/70 mg/m^2 once-weekly group (62.9% [56.5, 69.0]) than for the Kd 20/27 mg/m^2 twice-weekly group (40.8% [34.5, 47.3]; odds ratio [95% CI]: 2.49 [1.72, 3.60]; p < 0.0001) (Table 11). This p-value was below the prespecified significance level of 0.021; therefore, the difference was statistically significant. In addition, more subjects in the Kd 20/70 mg/m^2 once-weekly group achieved deeper responses than those in the Kd 20/27 mg/m^2 twice-weekly group. In the Kd 20/70 mg/m^2 once-weekly and Kd 20/27 mg/m^2 twice-weekly groups, respectively, the best overall responses were stringent complete response (1.7%, 0%), complete response (5.4%, 1.7%), and very good partial response (27.1%, 11.8%) (Table 14-4.3.1 of Study 20140355). Results of ORR were generally consistent across prespecified subgroups and sensitivity analyses, including investigator and IRC assessments (Section 10.2.1 of Study 20140355).

The median (95% CI) DOR was 15.0 (12.2, not estimable) months in the Kd 20/70 mg/m^2 once-weekly group and 13.8 (9.5, not estimable) months in the Kd 20/27 mg/m^2 twice-weekly group (Table 14-4.3.1 of Study 20140355). Median time to response (TTR) was 1.1 months in the Kd 20/70 mg/m^2 once-weekly group and 1.9 months in the Kd 20/27 mg/m^2 twice-weekly group.

Overall Survival

Although not statistically significant, a trend was observed for longer OS in the Kd 20/70 mg/m^2 once-weekly group compared with the Kd 20/27 mg/m^2 twice-weekly group (HR [95% CI]: 0.80 [0.56, 1.14]; p = 0.1070) (Table 11 and Figure 4). As of the data cutoff date, 58 subjects (24.2%) in the Kd 20/70 mg/m^2 once-weekly group and 68 subjects (28.6%) in the Kd 20/27 mg/m^2 twice-weekly group had died. Median OS was not reached in either group; therefore, the OS data were not mature. Results of OS were generally consistent across prespecified subgroups (Section 10.2.2 of Study 20140355).

Figure 4. Kaplan-Meier Plot - Overall Survival (A.R.R.O.W. Intent-to-Treat Population)



Number of Subjects at Risk:

Kd 20/27	238	219	196	165	97	50	9	0
Kd 20/70	240	217	203	186	115	48	10	0

HR = hazard ratio; Kd = carfilzomib plus dexamethasone; NE = not evaluable
The survival curves and the median overall survival were derived by the unstratified Kaplan-Meier method, while other statistics reported were from Cox proportional hazards model stratified by the randomization stratification factors.
Source: Figure 14-4.3.1 of Study 20140355

Dose/Dose Response

Dose response was evaluated using population pharmacokinetic and exposure-response analyses (see Section 5.2.1).

Durability of Response

Durability of response for the Kd 20/70 mg/m^2 once-weekly dose regimen in A.R.R.O.W. was demonstrated by superior PFS versus the control group as well as DOR, and is discussed above under Efficacy Results – Primary Endpoint (Including Sensitivity Analyses) and Efficacy Results – Secondary and other relevant endpoints.

Persistence of Effect

Persistence of effect over time after treatment for the Kd 20/70 mg/m^2 once-weekly dose regimen in A.R.R.O.W. was demonstrated by a trend for prolonged OS (Efficacy Results – Secondary and other relevant endpoints).

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The proportion of subjects who reported the dose schedule "convenient" (i.e., convenient, very convenient, or neutral) at cycle 2 day 1 was higher in the Kd 20/70 mg/m^2 once-weekly group (82.4%) than in the Kd 20/27 mg/m^2 twice-weekly group (65.8%) (odds ratio [95% CI]: 4.98 [2.54, 9.77]; $p < 0.001$ when logistic multivariable regression was adjusted for stratification factors) (A.R.R.O.W. PRO Report [Section 16.1.13.2 of Study 20140355]). The sensitivity analysis, in which neutral was included in the "inconvenient" category, showed the Kd 20/70 mg/m^2 once-weekly regimen was considered by subjects as more convenient than the Kd 20/27 mg/m^2 twice-weekly regimen (odds ratio [95% CI]: 2.61 [1.73, 3.92]; $p < 0.001$).

The proportion of subjects who reported being "satisfied" (i.e., satisfied, very satisfied, or neutral) at cycle 2 day 1 was similar for the Kd 20/70 mg/m^2 once-weekly group (84.7%) and the Kd 20/27 mg/m^2 twice-weekly group (79.6%) (odds ratio [95% CI]: 2.41 [0.97, 6.01]; $p = 0.059$). The sensitivity analysis, in which neutral was included in the "dissatisfied" category, showed subjects were more likely to be satisfied with the Kd 20/70 mg/m^2 once-weekly regimen than the Kd 20/27 mg/m^2 twice-weekly regimen (odds ratio [95% CI]: 1.52 [1.01, 2.29]; $p = 0.047$).

Better scores (indicative of greater functioning and fewer symptoms) were consistently reported by the Kd 20/70 mg/m^2 once-weekly group than by the Kd 20/27 mg/m^2 twice-weekly group on the EORTC QLQ-C30 physical functioning, role functioning, fatigue, pain, and insomnia subscales; EORTC QLQ-MY20 disease symptoms subscale; the EQ-5D-5L index score; and European Quality of Life Visual Analogue scale score.

Additional Analyses Conducted on the Individual Trial

Not applicable.

Integrated Review of Effectiveness

The FDA's Assessment:
The FDA analysis of PFS and ORR align with the results and conclusions presented in this section by Applicant. The efficacy data from the A.R.R.O.W study demonstrated that subjects with relapsed and refractory multiple myeloma treated with Kd 20/70 mg/m^2 once-weekly had significantly better PFS and ORR than those treated with Kd 20/27 mg/m^2 twice-weekly. The FDA reviewer's sensitivity analyses by using different patient population, different method, and different censoring strategies also confirmed the robustness of the primary analysis results. In general, consistent results of PFS and ORR were demonstrated across subgroups by demographics and baseline characteristics.

The FDA also agrees with the Applicant that the OS data was immature at the time of the final PFS analysis. Nevertheless, the data do not indicate any harm or detriment to survival at this juncture. Although not statistically significant, a trend was observed for longer OS in the Kd 20/70 mg/m^2 once-weekly group compared with the Kd 20/27 mg/m^2 twice-weekly group, the hazard ratio was 0.80 with 95% CI of (0.56, 1.14). The presentation of the p-value for OS analysis in Table 11 did not cross the pre-specified boundary (i.e. 1-sided p-value boundary was 0.018) and the p-value should not be included in the labeling.

The Applicant's position on the PRO data presented above was reviewed. The Applicant did not seek a PRO labeling indication or inclusion in the product information. The presentation of the p-value for PRO analyses should be considered nominal only. The FDA notes that measuring factors such as satisfaction and convenience are highly subjective and susceptible to confounding factors, therefore these results should be interpreted with caution.

7.1.3. Assessment of Efficacy Across Trials

The Applicant's Position:

Primary Endpoints

Statistical Approach
To evaluate the efficacy of the Kd 20/70 mg/m^2 once-weekly dose in the context of data for the labeled Kd 20/56 mg/m^2 twice-weekly dose regimen, simply comparing the studies side-by-side would not control for differences in baseline characteristics between treatment groups and could lead to biased estimates of treatment effects (see Section 6.1 and Baseline Characteristics). Therefore, cross-study comparisons were performed based on data from A.R.R.O.W. (study initiation 09 September 2015 to data cutoff 15 June 2017), ENDEAVOR (study initiation 20 June 2012 to primary analysis data cutoff 10 November 2014), and CHAMPION-1

(study initiation 04 September 2012 to data cutoff 22 July 2016), as well as the pooled analysis of A.R.R.O.W. plus CHAMPION-1 (using the data cutoffs for the individual studies).

Because of the differences in population evaluated in the A.R.R.O.W., ENDEAVOR, and CHAMPION-1 studies, propensity score weighting was used as the primary analytical method to balance for potential confounding of the treatment effects and enhance the comparability of the baseline characteristics of the Kd 20/70 mg/m^2 once-weekly and Kd 20/56 mg/m^2 twice-weekly groups. The propensity score, defined as the conditional probability of being treated given the covariates, can be used to balance covariates in 2 non-randomized groups, and therefore reduce the treatment selection bias, such as in this situation, where subjects might differ systematically between treatment groups (Brookhart et al, 2006; D'Agostino, 1998).

Planned Covariates:
Before the analysis, factors associated with the prognosis of relapsed or refractory multiple myeloma were identified by a thorough literature search and consulting external subject matter experts (Dingli et al, 2017; Dimopoulos et al, 2015; Bringhen et al, 2013; Chen et al, 2012; Barlogie et al, 2011; Greipp et al, 2005; Rajkumar et al, 2001). These were prespecified baseline covariates per the Integrated Summary of Efficacy (ISE) supplemental statistical analysis plan (SSAP) (Table 12).

Table 12. Prognostic Factors Included in Propensity Score Model in the Primary Analysis

Prognostic Factor	Included in 1-3 PLAS	Included in 2-3 PLAS
Age group (< 65 years versus ≥ 65 to < 75 years versus ≥ 75 years)	Yes	Yes
ECOG performance status (0 versus 1 to 2)	Yes	Yes
Time from diagnosis (months)	Yes	Yes
International Staging System stage (stage 1 versus stage 2 to 3)	Yes	Yes
Creatinine clearance (< 50 mL/min, ≥ 50 to 80 mL/min, ≥ 80 mL/min)	Yes	Yes
Total number of prior treatments (1 to 2 versus 3)	Yes	Yes
Prior stem cell transplant (yes versus no)	Yes	Yes
Prior exposure to lenalidomide (yes versus no)	Yes	Yes
Prior exposure to bortezomib (yes versus no)	Yes	No
Refractory to bortezomib (yes versus no)	Yes	Yes
Prior exposure to IMiD (yes versus no)	Yes	No
Refractory to last prior treatment (yes versus no)	Yes	No
Time from last relapse (months)	Yes	Yes

1-3 PLAS = 1 to 3 Prior Lines of Therapy Analysis Set (i.e., subjects with relapsed or refractory multiple myeloma after 1 to 3 prior lines of therapy from A.R.R.O.W., CHAMPION-1, and ENDEAVOR); 2-3 PLAS = 2 to 3 Prior Lines of Therapy Analysis Set (i.e., subjects with relapsed and refractory multiple myeloma after 2 to 3 prior lines of therapy from A.R.R.O.W. and ENDEAVOR); ECOG = Eastern Cooperative Oncology Group; IMiD = immunomodulatory drug
Source: Table 1 of A.R.R.O.W. ISE supplemental statistical analysis plan

Cytogenetic risk (at baseline) was also identified as an important prognostic factor from expert opinion but was not included in the propensity score model because of the high proportion of

missing data in the A.R.R.O.W. and CHAMPION-1 studies. No FISH test was done in A.R.R.O.W.; instead, cytogenetic risk status was defined based on historical FISH data, if available.

Furthermore, additional variables considered to be potentially prognostic (i.e., hemoglobin and lactate hydrogenase concentration, platelet count, and the presence of plasmacytoma) were identified and added into the previous propensity score model as sensitivity analyses.

Based on these steps, the Applicant considers the list of identified covariates comprehensive and that they cover the important prognostic factors that are related to the probability of getting a certain treatment and in turn have an impact on the treatment effects assessed in the cross-study comparison.

Propensity Score Method
The propensity score method for the cross-study analyses, including the identification of covariates, was prespecified, and the A.R.R.O.W. ISE SSAP was finalized before the A.R.R.O.W. data were unblinded. A summary of the steps in the propensity score model development follows:

1. A subject's propensity score indicated their propensity to be treated with Kd 20/70 mg/m^2 once-weekly (in the combined A.R.R.O.W. + CHAMPION-1 group) versus Kd 20/56 mg/m^2 twice-weekly. The propensity scores were estimated using a logistic regression model adjusted for baseline characteristics that were considered important for characterizing the population and prognostic of outcomes in multiple myeloma (Brookhart et al, 2006).

2. Upon deriving a propensity score for each subject, a balanced distribution of propensity scores between the treatment groups was confirmed with box plots.

3. The efficacy endpoints were then evaluated adjusting for the propensity score using the stabilized inverse probability of treatment weighting (sIPTW) approach. Scatter plots of each subject's propensity score versus the sIPTW were produced so that the distribution and impact of the weights could be visually ascertained. A trimmed sIPTW method was prespecified to reduce the impact of outliers (Lee et al, 2011).

4. In addition to the primary analyses of the efficacy outcomes, sensitivity analyses and subgroup analyses were conducted to support the robustness of the propensity score adjustment.

Because cross-study comparisons have inherent limitations, numerous analyses were performed on the efficacy data to account for the uncertainty of the propensity model and to ensure the data are reliable and robust. Briefly, the analyses listed below were performed on subjects with relapsed or refractory multiple myeloma after 1 to 3 prior lines of therapy and subjects with relapsed or refractory multiple myeloma after 2 to 3 prior lines of therapy who were refractory to the last prior line:

- Unadjusted efficacy data were analyzed as side-by-side comparisons by study.

- Unadjusted pooled data of Kd 20/70 mg/m^2 once-weekly in A.R.R.O.W. plus CHAMPION 1 were compared with Kd 20/56 mg/m^2 twice-weekly.
- Propensity score adjusted data were analyzed using a trimmed sIPTW method, as the prespecified primary analysis of the cross-study comparison per the A.R.R.O.W. ISE SSAP.
- Ad hoc analyses for the IRC-based PFS and ORR endpoints, including the traditional multiple regression analysis method, propensity scores matching, and propensity stratification, were conducted for subjects with 1 to 3 prior lines of therapy to further assess the robustness of the conclusions from the prespecified propensity score analysis using trimmed sIPTW.

No formal hypothesis testing, including noninferiority or superiority testing, was planned for the cross-study comparisons. Because of the characteristics of cross-study comparison and the lack of multiplicity adjustments, all analyses were descriptive.

Baseline Characteristics

Baseline disease characteristics were different across the A.R.R.O.W., CHAMPION-1, and ENDEAVOR studies; key differences are provided in Table 13 and include the following:

- The A.R.R.O.W. study population included only subjects with 2 or 3 prior lines of therapy whereas half of the ENDEAVOR and CHAMPION-1 study populations included subjects with only 1 prior line of therapy.
- Approximately 40% of subjects in the pooled Kd 20/70 mg/m^2 once-weekly group had 3 prior therapies compared with < 20% of subjects in the Kd 20/56 mg/m^2 twice-weekly group.
- Over 90% of subjects in the pooled Kd 20/70 mg/m^2 once-weekly group were refractory to the last prior therapy compared with only 40% of the Kd 20/56 mg/m^2 twice-weekly group.
- A much higher proportion of subjects in the pooled Kd 20/70 mg/m^2 once-weekly group than in the Kd 20/56 mg/m^2 twice-weekly group had prior exposure to lenalidomide or bortezomib and were refractory to lenalidomide or bortezomib.

These differences indicate that, in general, the pooled Kd 20/70 mg/m^2 once-weekly group in A.R.R.O.W. and CHAMPION-1 had a poorer prognosis than the Kd 20/56 mg/m^2 twice-weekly group from ENDEAVOR.

Table 13. Summary of Key Baseline Disease Characteristics (Full Analysis Set)

	A.R.R.O.W.		CHAMPION-1	A.R.R.O.W. + CHAMPION-1	ENDEAVOR
	Kd 20/27 mg/m^2 Twice-weekly (N = 238)	Kd 20/70 mg/m^2 Once-weekly (N = 240)	Kd 20/70 mg/m^2 Once-weekly (N = 104)	Kd 20/70 mg/m^2 Once-weekly (N = 344)	Kd 20/56 mg/m^2 Twice-weekly (N = 464)
Total number of prior regimens (n [%])					
1	0	0	54 (51.9)	201 (58.4)[a]	232 (50.0)
2	125 (52.5)	116 (48.3)	31 (29.8)		157 (33.8)
3	112 (47.1)	124 (51.7)	19 (18.3)	143 (41.6)	75 (16.2)
> 3	1 (0.4)	0	0	-	0
Prior exposure to lenalidomide (n [%])					
Yes	194 (81.5)	207 (86.3)	56 (53.8)	263 (76.5)	177 (38.1)
No	44 (18.5)	33 (13.8)	48 (46.2)	81 (23.5)	287 (61.9)
Refractory to any prior lenalidomide-including regimen (n [%])					
Yes	170 (71.4)	186 (77.5)	37 (35.6)	-	113 (24.4)
No	24 (10.1)	21 (8.8)	19 (18.3)	-	64 (13.8)
Prior exposure to bortezomib (n [%])					
Yes	237 (99.6)	236 (98.3)	87 (83.7)	323 (93.9)	250 (53.9)
No	1 (0.4)	4 (1.7)	17 (16.3)	21 (6.1)	214 (46.1)
Refractory to any prior bortezomib-including regimen (n [%])					
Yes	90 (37.8)	111 (46.3)	57 (54.8)	168 (48.8)	15 (3.2)
No	147 (61.8)	125 (52.1)	30 (28.8)	176 (51.2)	235 (50.6)
Refractory to last prior treatment (n [%])					
Yes	235 (98.7)	237 (98.8)	74 (71.2)	311 (90.4)	184 (39.7)
No	3 (1.3)	3 (1.3)	30 (28.8)	33 (9.6)	280 (60.3)

Kd = carfilzomib plus dexamethasone; - = not reported
[a] Data are presented as 1 and 2 prior lines of therapy combined.
Source: A.R.R.O.W. ISE Table 14-1.4, and A.R.R.O.W. ISE Table 14-2.2.1

A summary of the unadjusted and propensity score adjusted values for each prognostic factor is provided in Table 14 and Figure 5. After propensity score adjustment using the trimmed sIPTW, baseline characteristics were balanced for the Kd 20/70 mg/m^2 once-weekly and Kd 20/56 mg/m^2 twice-weekly groups for subjects with 1 to 3 prior lines of therapy. Thus, the trimmed sIPTW adjustment created more balanced analysis populations to make the cross-study comparison fairer and more robust.

Table 14. Difference in Patient Characteristics Between Once-weekly and Twice-weekly Regimen - Before and After Trimmed sIPTW Adjustment (1 to 3 Prior Line of Therapy Analysis Set)

	Unadjusted				Propensity Score Adjusted			
	A.R.R.O.W. + CHAMPION-1 20/70 mg/m^2 Kd QW (N = 344)	ENDEAVOR 20/56 mg/m^2 Kd BIW (N = 464)	Standardized Difference	p-value[a]	A.R.R.O.W. + CHAMPION-1 20/70 mg/m^2 Kd QW (N = 378.6)	ENDEAVOR 20/56 mg/m^2 Kd BIW (N = 464.2)	Standardized Difference	p-value[a]
Age group - n (%)								
< 65 years	138 (40.1)	223 (48.1)			179.2 (47.3)	206.0 (44.4)		
≥ 65 to < 75 years	131 (38.1)	164 (35.3)	0.06	0.11	124.8 (33.0)	172.7 (37.2)	-0.09	0.57
≥ 75 years	75 (21.8)	77 (16.6)	0.13	0.020	74.6 (19.7)	85.5 (18.4)	0.03	0.99
ECOG performance status – n (%)								
0	163 (47.4)	221 (47.6)			163.1 (43.1)	219.4 (47.3)		
1 to 2	181 (52.6)	243 (52.4)	< 0.01	0.94	215.5 (56.9)	244.8 (52.7)	0.08	0.56
Time from initial diagnosis to randomization (months)								
Mean (SD)	47.67 (32.89)	54.01 (38.93)	-0.18	0.016	64.39 (45.52)	54.79 (36.75)	0.23	0.18
ISS stage at baseline – n (%)								
Stage 1	131 (38.1)	212 (45.7)			175.6 (46.4)	205.7 (44.3)		
Stage 2 and 3	209 (60.8)	252 (54.3)	0.13	0.043	200.9 (53.1)	258.5 (55.7)	-0.05	0.75
Creatinine clearance – n (%)								
< 50 mL/min	77 (22.4)	85 (18.3)			80.7 (21.3)	94.2 (20.3)		
≥ 50 to 80 mL/min	132 (38.4)	186 (40.1)	-0.04	0.21	156.2 (41.3)	177.7 (38.3)	0.06	0.95
≥ 80 mL/min	135 (39.2)	193 (41.6)	-0.05	0.18	141.7 (37.4)	192.3 (41.4)	-0.08	0.70
Total number of prior regimens – n (%)								
1 to 2	201 (58.4)	389 (83.8)			296.7 (78.4)	361.5 (77.9)		
3	143 (41.6)	75 (16.2)	0.58	< 0.001	81.9 (21.6)	102.6 (22.1)	-0.01	0.92
Prior transplant - n (%)								
Yes	172 (50.0)	266 (57.3)			204.0 (53.9)	260.1 (56.0)		
No	172 (50.0)	198 (42.7)	0.15	0.039	174.6 (46.1)	204.1 (44.0)	0.04	0.77
Prior exposure to lenalidomide – n (%)								
Yes	263 (76.5)	177 (38.1)			209.1 (55.2)	260.0 (56.0)		

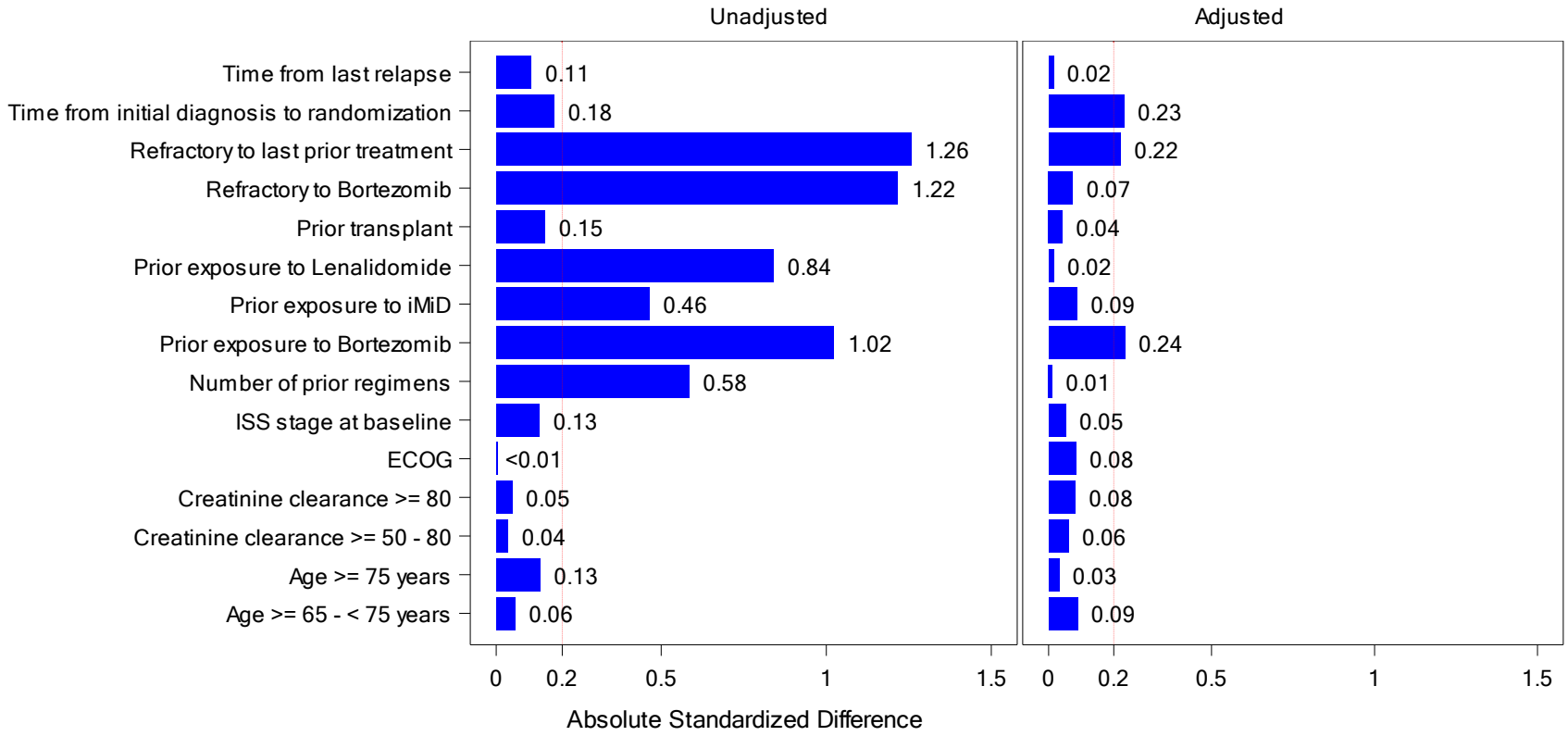
	Unadjusted				Propensity Score Adjusted			
	A.R.R.O.W. + CHAMPION-1 20/70 mg/m^2 Kd QW (N = 344)	ENDEAVOR 20/56 mg/m^2 Kd BIW (N = 464)	Standardized Difference	p-value[a]	A.R.R.O.W. + CHAMPION-1 20/70 mg/m^2 Kd QW (N = 378.6)	ENDEAVOR 20/56 mg/m^2 Kd BIW (N = 464.2)	Standardized Difference	p-value[a]
No	81 (23.5)	287 (61.9)	-0.84	< 0.001	169.5 (44.8)	204.2 (44.0)	0.02	0.92
Prior exposure to bortezomib – n (%)								
Yes	323 (93.9)	250 (53.9)			226.0 (59.7)	328.7 (70.8)		
No	21 (6.1)	214 (46.1)	-1.02	< 0.001	152.6 (40.3)	135.5 (29.2)	0.24	0.12
Refractory to any prior bortezomib-including regimen – n (%)								
Yes	168 (48.8)	15 (3.2)			77.7 (20.5)	109.6 (23.6)		
No	176 (51.2)	449 (96.8)	-1.22	< 0.001	300.9 (79.5)	354.5 (76.4)	0.07	0.61
Prior exposure to IMiD – n (%)								
Yes	304 (88.4)	325 (70.0)			316.2 (83.5)	371.9 (80.1)		
No	40 (11.6)	139 (30.0)	-0.46	< 0.001	62.4 (16.5)	92.2 (19.9)	-0.09	0.54
Refractory to last prior treatment– n (%)								
Yes	311 (90.4)	184 (39.7)			187.7 (49.6)	280.9 (60.5)		
No	33 (9.6)	280 (60.3)	-1.26	< 0.001	190.9 (50.4)	183.3 (39.5)	0.22	0.12
Time from last relapse (months)								
Mean (SD)	3.19 (6.22)	3.82 (5.61)	-0.11	0.14	4.15 (8.94)	4.27 (6.98)	-0.02	0.93

BIW = twice-weekly; ECOG = Eastern Cooperative Oncology Group; IMiD = immunomodulatory drug; ISS = International Staging System; Kd = carfilzomib plus dexamethasone; QW = once-weekly; sIPTW = stabilized inverse probability of treatment weighting

[a] p-value is not related to standardized difference, but based on a univariate regression model with each covariate as outcome, and treatment as predictor. For levels other than reference level (i.e., the first level) for categorical covariates, logistic regression model was used. For continuous covariate, linear regression was used with each covariate as outcome and only treatment as predictor in the model.

Source: A.R.R.O.W. ISE Table 14-2.2.1 and A.R.R.O.W. ISE Table 14-2.2.3

Figure 5. Bar Plot of Baseline Covariate Balance Before and After Adjustment (1 to 3 Prior Line of Therapy Analysis Set)



ECOG = Eastern Cooperative Oncology Group; IMiD = immunomodulatory drug; ISS = International Staging System.
Source: A.R.R.O.W. ISE Figure 14-2.2.1.400

Efficacy Analyses

Comparison of patient populations with similar baseline characteristics across studies demonstrated that Kd 20/70 mg/m^2 once-weekly has comparable efficacy to Kd 20/56 mg/m^2 twice-weekly.

In the unadjusted side-by-side comparison of study results, median PFS (95% CI) was lower for the Kd 20/70 mg/m^2 once-weekly group from A.R.R.O.W. (11.3 [8.6, 13.2] months) than the Kd 20/56 mg/m^2 twice-weekly group from ENDEAVOR (18.7 [15.6, not estimable] months) (Table 15). This result was unsurprising given the substantial differences in baseline characteristics between the 2 treatment groups (Baseline Characteristics). Indeed, the median PFS (95% CI) was comparable for the Kd 20/70 mg/m^2 once-weekly group from CHAMPION-1 (19.8 [14.3, 23.5] months) and the Kd 20/56 mg/m^2 twice-weekly group from ENDEAVOR (18.7 [15.6, not estimable] months); CHAMPION-1 and ENDEAVOR enrolled similar patient populations.

Likewise, the ORR (95% CI) was lower for the Kd 20/70 mg/m^2 once-weekly group from A.R.R.O.W. (63.8% [57.3%, 69.8%]) than the Kd 20/56 mg/m^2 twice-weekly group from ENDEAVOR (76.9% [72.8%, 80.7]); while the ORR (95% CI) was comparable for the Kd 20/70 mg/m^2 once-weekly group from CHAMPION-1 (74.0% [64.5%, 82.1%]) and the Kd 20/56 mg/m^2 twice-weekly group from ENDEAVOR (76.9% [72.8%, 80.7%]) (Table 15).

Because of the differences in baseline characteristics, the Kd 20/70 mg/m^2 once-weekly group from A.R.R.O.W. is more likely to have a poorer prognosis than the Kd 20/56 mg/m^2 twice-weekly group, who were in general treated less; thus, the unadjusted cross-study comparisons are likely to be biased in favor of the Kd 20/56 mg/m^2 twice-weekly group. For this reason, the propensity score analysis was prespecified as the primary cross-study comparison.

Of note, side-by-side comparison of PFS and ORR across studies for subjects who had 2 to 3 prior lines of therapy and were refractory to the last prior line demonstrated generally comparable efficacy for Kd 20/70 mg/m^2 once-weekly and Kd 20/56 mg/m^2 twice-weekly (Table 15).

Median follow-up times and their ranges are provided by group and study in Table 15. For the pooled Kd 20/70 mg/m^2 once-weekly group in A.R.R.O.W. plus CHAMPION-1, median (95% CI) follow-up time was 12.6 (11.4, 13.6) months, ranging for 0 to 38 months (Response to Information Request dated 23 August 2018 Table 1-1).

Table 15. Overview of Efficacy in the Cross-study Unadjusted Side-by-Side Analyses

	1 to 3 Prior Lines of Therapy				2 to 3 Prior Lines of Therapy and Refractory[a]			
	A.R.R.O.W.		CHAMPION-1	ENDEAVOR	A.R.R.O.W.		CHAMPION-1	ENDEAVOR
	20/27 mg/m^2 Kd BIW (N = 238)	20/70 mg/m^2 Kd QW (N = 240)	20/70 mg/m^2 Kd QW (N = 104)	20/56 mg/m^2 Kd BIW (N = 464)	20/27 mg/m^2 Kd BIW (N = 238)	20/70 mg/m^2 Kd QW (N = 240)	20/70 mg/m^2 Kd QW (N = 43)	20/56 mg/m^2 Kd BIW (N = 123)
PFS								
Number of subjects with a PFS event (n [%])	148 (62.2)	126 (52.5)	40 (38.5)	171 (36.9)	148 (62.2)	126 (52.5)	22 (51.2)	65 (52.8)
Median (95% CI) (months)	7.6 [5.7, 8.7)	11.3 [8.6, 13.2)	19.8 [14.3, 23.5)	18.7 [15.6, NE)	7.6 [5.7, 8.7)	11.3 [8.6, 13.2)	9.2 [4.6, 14.3)	8.5 [6.5, 14.9)
ORR								
Number of subjects with overall response (n [%])	98 (41.2)	153 (63.8)	77 (74.0)	357 (76.9)	98 (41.2)	153 (63.8)	26 (60.5)	73 (59.3)
ORR (95% CI)	41.2 (34.9, 47.7)	63.8 (57.3, 69.8)	74.0 (64.5, 82.1)	76.9 (72.8, 80.7)	41.2 (34.9, 47.7)	63.8 (57.3, 69.8)	60.5 (44.4, 75.0)	59.3 (50.1, 68.1)
Follow-up time (months)								
Median (95% CI)	12.0 [10.4, 12.6)	12.6 [11.7, 13.8)	11.5 [9.2, 15.9)	11.9 [11.2, 12.4)	12.0 [10.4, 12.6)	12.6 [11.7, 13.8)	11.1 [6.7, 22.0)	11.9 [10.2, 14.8)
Min, Max	0, 20	0, 19	0, 38	0, 26	0, 20	0, 19	0, 32	0, 25

BIW = twice-weekly, Kd = carfilzomib plus dexamethasone; ORR = overall response rate; PFS = progression-free survival; QW = once-weekly
Progression-free survival and ORR were assessed by an Independent Review Committee.
[a] Refractory to the last prior line of therapy
Source: Table 13, Table 17, Table 20, and Table 24 of A.R.R.O.W. Module 2.7.3, Summary of Clinical Efficacy; A.R.R.O.W. ISE Table 14-1.6.1, A.R.R.O.W. ISE Table 14-1.6.1.3

In the primary cross-study analysis (i.e., after propensity score adjustment) for subjects with 1 to 3 prior lines of therapy, median PFS (95% CI) was (21.0 [not estimable, not estimable] months) for the pooled Kd 20/70 mg/m^2 once-weekly group and (14.9 [13.1, not estimable] months) for the Kd 20/56 mg/m^2 twice-weekly group (HR [95% CI]: 0.64 (0.51, 0.81) (Table 16).

The ORR (95% CI) using the trimmed sIPTW adjustment for subjects with 1 to 3 prior lines of therapy was generally comparable for the pooled Kd 20/70 mg/m^2 once-weekly group (78.4% [74.2%, 82.5%]) and the Kd 20/56 mg/m^2 twice-weekly group (71.2% [67.0%, 75.3%]); odds ratio (95% CI): 1.468 (1.069, 2.014).

Table 16. Overview of Efficacy in the Cross-study Analyses With Propensity Score Adjustment (Trimmed sIPTW) (1-3 PLAS)

	A.R.R.O.W. + CHAMPION-1 20/70 mg/m^2 Kd QW (N = 378.6)	ENDEAVOR 20/56 mg/m^2 Kd BIW (N = 464.2)
PFS		
Number of subjects with a PFS event (n [%])	128.9 (34.0)	189.0 (40.7)
Median (95% CI) (months)	21.0 [NE, NE)	14.9 [13.1, NE)
Hazard ratio (QW/BIW) (95% CI)[a]	0.642 (0.512, 0.805)	
ORR		
Number of subjects with overall response	296.7	330.3
ORR (95% CI)	78.4 (74.2, 82.5)	71.2 (67.0, 75.3)
Odds ratio (QW/BIW) (95% CI)[a]	1.468 (1.069, 2.014)	

1-3 PLAS = 1 to 3 Prior Lines of Therapy Analysis Set (i.e., subjects with relapsed or refractory multiple myeloma after 1 to 3 prior lines of therapy from A.R.R.O.W., CHAMPION-1, and ENDEAVOR); BIW = twice-weekly; Kd = carfilzomib plus dexamethasone; NE = not estimable; ORR = overall response rate; PFS = progression-free survival; QW = once-weekly; sIPTW = stabilized inverse probability of treatment weighting
Progression-free survival and ORR were assessed by an Independent Review Committee.
sIPTW with the value of > 15 was trimmed to be the maximum value of sIPTW ≤ 15 in the analysis set.
The prognostic factors included in the primary analysis are listed in Table 12.
[a] Based on Cox regression
Source: A.R.R.O.W. ISE Table 14-3.1.2.3

As expected, median PFS and ORR after propensity score-adjustment differed from that of the unadjusted results, and is a consequence of the propensity score methodology, which balances the baseline characteristics in the 2 treatment groups to provide a less biased estimate of the treatment effect.

Because the primary analysis of propensity score adjustment using trimmed sIPTW resulted in treatment effect estimates in the opposite direction from the unadjusted method for subjects with 1 to 3 prior lines of therapy (Table 15 and Table 16), ad hoc analyses, including the traditional multiple regression analysis method and the propensity scores analysis method using stratification and matching approaches, were conducted for PFS and ORR as assessed by IRC to evaluate the robustness of the conclusions from the prespecified primary analysis. After

controlling for the imbalance of baseline characteristics between treatment groups using a variety of statistical methodologies, the consistent results across analyses, including the primary analysis (i.e., propensity score adjustment using trimmed sIPTW), demonstrate the robustness and reliability of the primary cross-study comparison results (Table 17).

Table 17. Summary of Cross-study Comparison Efficacy Analyses (1-3 PLAS)

Analysis	PFS Hazard Ratio (Kd 20/70 mg/m^2 QW/ Kd 20/56 mg/m^2 BIW) (95% CI)[a]	ORR Odds Ratio (Kd 20/70 mg/m^2 QW/ Kd 20/56 mg/m^2 BIW) (95% CI)
Unadjusted	1.471 (1.188, 1.822)	0.605 (0.443, 0.826)
Propensity score using trimmed sIPTW (primary analysis)	0.642 (0.512, 0.805)	1.468 (1.069, 2.014)
Multivariable Cox regression (full model)	0.748 (0.562, 0.994)	1.705 (1.076, 2.703)
Multivariable Cox regression (stepwise model selection)	0.778 (0.595, 1.016)	1.550 (1.025, 2.344)
Propensity score matching	0.604 (0.431, 0.846)	2.187 (1.211, 3.952)
Propensity score stratification	0.816 (0.614, 1.083)	1.611 (1.023, 2.536)

1-3 PLAS = 1 to 3 Prior Lines of Therapy Analysis Set (i.e., subjects with relapsed or refractory multiple myeloma after 1 to 3 prior lines of therapy from A.R.R.O.W., CHAMPION-1, and ENDEAVOR); BIW = twice-weekly; Kd = carfilzomib plus dexamethasone; ORR = overall response rate; PFS = progression-free survival; QW = once-weekly; sIPTW = stabilized inverse probability of treatment weighting
A hazard ratio < 1 indicates a treatment effect favoring Kd 20/70 mg/m^2 once-weekly. An odds ratio > 1 indicates a treatment effect favoring Kd 20/70 mg/m^2 once-weekly.
[a] Based on Cox regression
Source: Table 16 and Table 23 of A.R.R.O.W. Module 2.7.3, Summary of Clinical Efficacy

As of the data cutoff dates for the primary analyses of A.R.R.O.W. and ENDEAVOR, OS data were immature and the unadjusted median OS was not reached for either the Kd 20/70 mg/m^2 once-weekly group from A.R.R.O.W. or the Kd 20/56 mg/m^2 twice-weekly group from ENDEAVOR (Section 3.2.3 of A.R.R.O.W. Module 2.7.3, Summary of Clinical Efficacy); OS data were not collected in CHAMPION-1. Among subjects with 2 to 3 prior lines of therapy who were refractory to the last line of therapy, OS was generally comparable for the Kd 20/70 mg/m^2 once-weekly group from A.R.R.O.W. and the Kd 20/56 mg/m^2 twice-weekly group before and after propensity score adjustment (HR [95% CI]: 0.77 [0.51, 1.16] and 0.74 [0.49, 1.12], respectively).

The primary analysis of DOR and TTR using trimmed sIPTW adjustment also demonstrated similar results between the Kd 20/70 mg/m^2 once-weekly and Kd 20/56 mg/m^2 twice-weekly groups (Section 3.2.4 and Section 3.2.5 of A.R.R.O.W. Module 2.7.3, Summary of Clinical Efficacy).

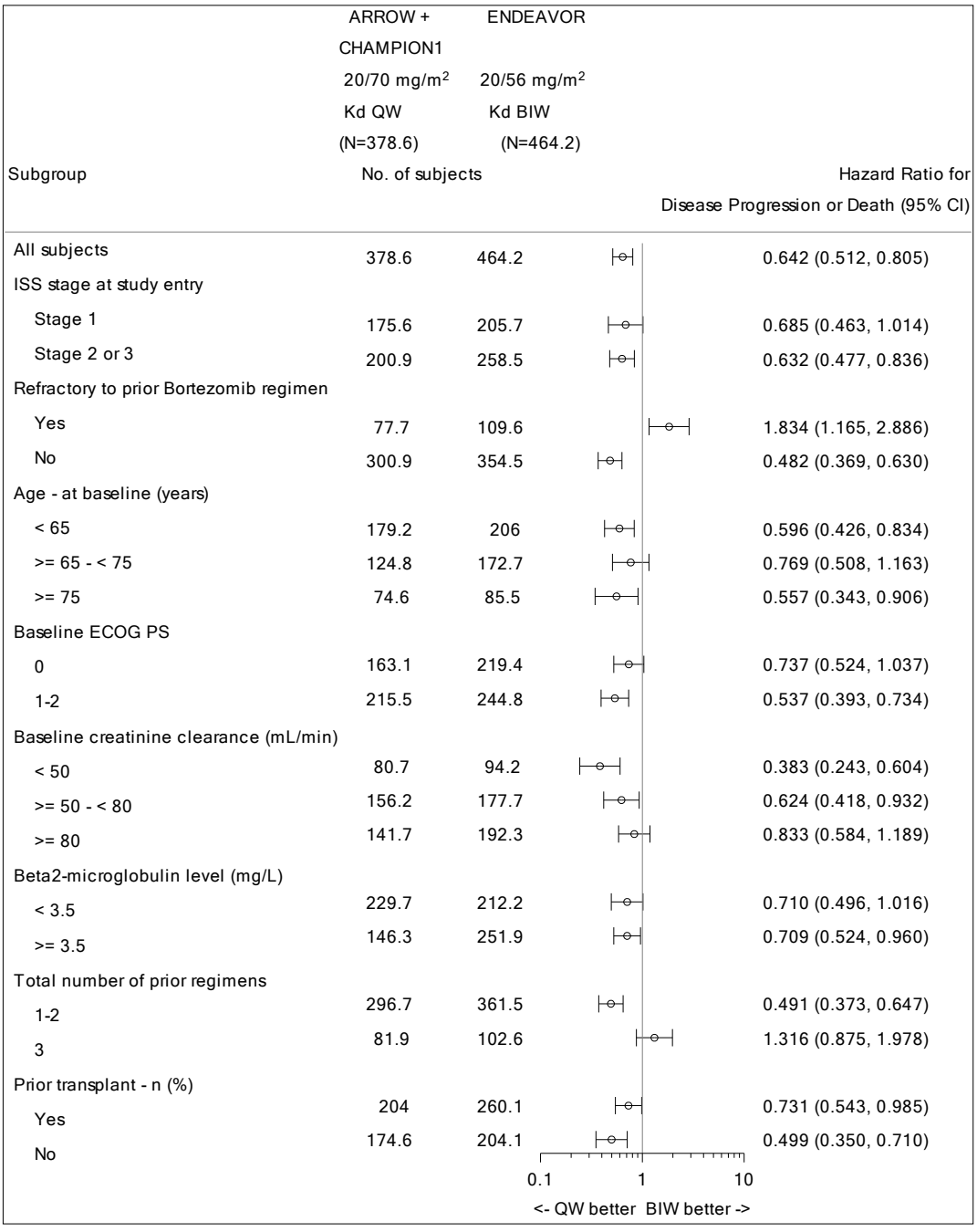
Secondary and Other Endpoints

All efficacy endpoints for the cross-study comparisons are described under Primary Endpoints as endpoints were not prespecified as primary or secondary.

Subpopulations

Based on the primary analysis of propensity score method using trimmed sIPTW adjustment for subjects with relapsed or refractory multiple myeloma who received 1 to 3 prior lines of therapy, results of PFS and ORR analyses comparing Kd 20/70 mg/m^2 once-weekly with Kd 20/56 mg/m^2 twice-weekly were generally consistent across prespecified subgroups (Figure 6 and
Figure 7).

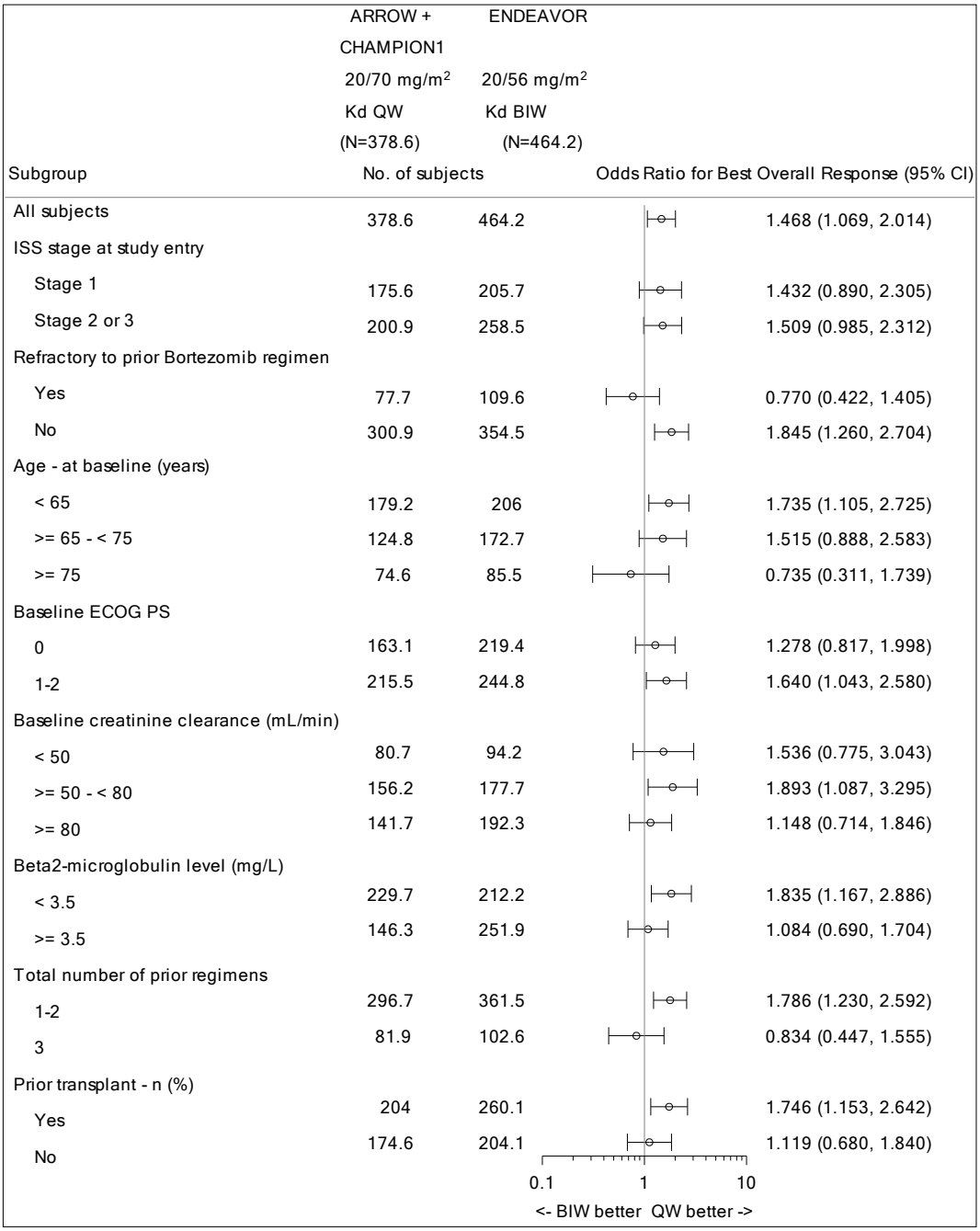
Figure 6. Forest Plot of Subgroup Analyses of Progression-free Survival as Assessed by Independent Review Committee (Trimmed sIPTW) (1-3 PLAS)



1-3 PLAS = 1 to 3 Prior Lines of Therapy Analysis Set (i.e., subjects with relapsed or refractory multiple myeloma after 1 to 3 prior lines of therapy); BIW = twice-weekly; ECOG PS = Eastern Cooperative Oncology Group performance status; ISS = International Staging System; Kd = carfilzomib plus dexamethasone; QW = once-weekly; sIPTW = stabilized inverse probability of treatment weighting
A hazard ratio < 1 favors Kd 20/70 mg/m^2 once-weekly over Kd 20/56 mg/m^2 twice-weekly.
sIPTW with the value of > 15 was trimmed to be the maximum value of sIPTW $\leq$ 15 in the analysis set.

Source: A.R.R.O.W. ISE Figure 14-3.4.4.3

Figure 7. Forest Plot of Subgroup Analyses of Overall Response Rate as Assessed by Independent Review Committee (Trimmed sIPTW) (1-3 PLAS)



1-3 PLAS = 1 to 3 Prior Lines of Therapy Analysis Set (i.e., subjects with relapsed or refractory multiple myeloma after 1 to 3 prior lines of therapy); BIW = twice-weekly; ECOG PS = Eastern Cooperative

Oncology Group performance status; ISS = International Staging System; Kd = carfilzomib plus dexamethasone; QW = once-weekly; sIPTW = stabilized inverse probability of treatment weighting
An odds ratio > 1 favors Kd 20/70 mg/m^2 once-weekly over Kd 20/56 mg/m^2 twice-weekly.
sIPTW with the value of > 15 was trimmed to be the maximum value of sIPTW ≤ 15 in the analysis set.
Source: A.R.R.O.W. ISE Figure 14-3.3.4.3

Additional Efficacy Considerations

No differences in efficacy are anticipated from those presented herein and the efficacy of Kd 20/70 mg/m^2 once-weekly in the postmarketing setting, even though the population evaluated in A.R.R.O.W. (i.e., subjects with relapsed and refractory multiple myeloma who have received 2 to 3 prior lines of therapy and were refractory to the last prior line) differs from the currently indicated population for Kd treatment (i.e., subjects with relapsed or refractory multiple myeloma who have received 1 to 3 lines of therapy). The cross-study analyses included data from CHAMPION-1, which evaluated Kd 20/70 mg/m^2 once-weekly in subjects with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy (i.e., the indicated population). Based on these analyses, differences in efficacy are not expected in the postmarketing experience. In addition, efficacy results were generally consistent across subgroups both within A.R.R.O.W. and the cross-study comparisons (Efficacy Results – Primary Endpoint (Including Sensitivity Analyses) and Efficacy Results – Secondary and other relevant endpoints in Section 7.1.2 and Subpopulations in Section 7.1.3), including the North America region which was evaluated in A.R.R.O.W.

Furthermore, potential differences are not expected between how the Kd 20/70 mg/m^2 once-weekly dose regimen was studied in A.R.R.O.W. versus how it will be used in the postmarketing setting, as dose administration, including dose modifications, is consistent with the current and proposed USPI.

The FDA's Assessment:
To further evaluate the efficacy results based on propensity score analysis, FDA requested additional information from the Applicant during the review cycle. Since the majority of the standardized mean differences are less than 0.25 (Rubin, 2001; Stuart, 2010) after trimmed sIPTW adjustment (shown on Table 14/Figure 4), the distribution of the potential prognostic factors (that can be observed) appears to be balanced between treatment groups based on the propensity score adjusted analysis. The Applicant also performed additional analyses based on the patient population who received 1 prior line of therapy. The results also appear to be consistent with those analyses for patients who received 1 to 3 prior lines of therapy. However, some imbalances of distribution of the prognostic factors are observed (e.g. mean time from initial diagnosis to randomization, prior exposure to lenalidomide and prior exposure to bortezomib) in the analyses after the trimmed sIPTW adjustment. It is not clear if this imbalance is due to the smaller sample size in the sub-population.

While the distribution of the potential prognostic factors appears to be balanced between treatment groups after propensity score adjusted analyses, the FDA has the following comments related to the between study comparisons:

1. These analyses are exploratory since they were not pre-specified prior to collection of the data. For example, there are no pre-specified sets of covariates included in the analyses; the trimming factors (i.e. 15 was chosen as the trim factor in the propensity score adjusted analyses for patients who received 1-3 prior lines of therapy) in the propensity score analyses using the sIPTW were not pre-specified.
2. The magnitude of the treatment effect cannot be adequately characterized. The hazard ratio estimates varied based on the different analysis methods (see Table 15) used. Therefore, while Kd 20/70 mg/m^2 once-weekly appears to demonstrate favorable results over the Kd 20/56 mg/m^2 twice-weekly regimen, the magnitude of the effect based on PFS is not clear.
3. The analysis does not have the ability to create a balance between treatment groups with respect to unmeasured and unknown covariates. If important unmeasured or unknown covariates are omitted, the propensity score method is known to yield biased estimates.
4. The timing of data collection in each of the trials was different.
5. The subgroup analysis results of whether subjects were refractory to prior bortezomib (Y/N) and total number of prior regimens (1-2 and 3) did not demonstrate internal consistency.

7.1.4. Integrated Assessment of Effectiveness

The Applicant's Position:

Efficacy data from the A.R.R.O.W. study demonstrated statistically significant and clinically meaningful improvements in PFS and ORR, a trend toward longer OS, and greater convenience with positive impacts on HRQoL and patient satisfaction for Kd 20/70 mg/m^2 once-weekly compared with Kd 20/27 mg/m^2 twice-weekly, an unlabeled dose regimen (Section 7.1.2).

While a direct clinical study comparing the efficacy of Kd 20/70 mg/m^2 once-weekly with the labeled Kd 20/56 mg/m^2 twice-weekly dose regimen would have been informative, a variety of rigorous, prespecified and ad hoc statistical analyses were performed, in different study populations, and in prespecified subgroups to provide a thorough understanding of the efficacy (i.e., PFS, ORR, OS, DOR, and TTR) of the targeted Kd 20/70 mg/m^2 once-weekly dose regimen with respect to that of the labeled Kd 20/56 mg/m^2 twice-weekly dose regimen. These cross-study comparisons included prespecified unadjusted and propensity score adjusted analyses, as well as ad hoc analyses.

- Unadjusted side-by-side comparisons of A.R.R.O.W., CHAMPION-1, and ENDEAVOR showed:
  - similar efficacy (PFS, ORR) of Kd 20/70 mg/m^2 once-weekly in CHAMPION-1 versus Kd

20/56 mg/m^2 twice-weekly in ENDEAVOR (i.e., in subjects with relapsed or refractory multiple myeloma after 1 to 3 prior lines of therapy) (Table 15)
    - differences in efficacy (PFS, ORR) for the full study populations of Kd 20/70 mg/m^2 once-weekly in A.R.R.O.W. versus Kd 20/56 mg/m^2 twice-weekly in ENDEAVOR, which are likely explained by differences in baseline characteristics between the populations (i.e., subjects in the Kd 20/70 mg/m^2 once-weekly group in A.R.R.O.W. received more prior lines of therapy, were more likely to have been exposed to prior lenalidomide and/or bortezomib, and were more likely to have refractory disease compared with subjects in the Kd 20/56 mg/m^2 twice-weekly group in ENDEAVOR) (Table 13 and Table 15)
    - generally comparable efficacy (PFS, ORR, OS) for Kd 20/70 mg/m^2 once-weekly in A.R.R.O.W. and CHAMPION-1, and for Kd 20/56 mg/m^2 twice-weekly in ENDEAVOR for subjects with relapsed and refractory multiple myeloma after 2 to 3 prior lines of therapy who were refractory to the last prior therapy (i.e., the A.R.R.O.W. population) (Table 15)
- Propensity score adjustment for subjects with 1 to 3 prior lines of therapy (as well as subjects with 2 to 3 prior lines of therapy who were refractory to the last prior therapy) also demonstrated efficacy (PFS, ORR, OS) that was generally comparable between Kd 20/70 mg/m^2 once-weekly and Kd 20/56 mg/m^2 twice-weekly dose regimen (Table 16). Duration of response and TTR were also similar across groups.
- Results were generally consistent across sensitivity analyses and prespecified subgroup analyses of PFS and ORR, confirming the robustness of the primary analysis results (Figure 6 and
- Figure 7).
- Results were largely consistent across ad hoc analyses of PFS and ORR using a variety of statistical methodologies to control for the imbalances between treatment groups and were consistent with the primary analysis using the propensity score adjustment, further supporting the robustness and reliability of the results (Table 17).

Taken together, comparison of patient populations with similar baseline characteristics across studies demonstrated that Kd 20/70 mg/m^2 once-weekly has comparable efficacy to Kd 20/56 mg/m^2 twice-weekly. The Kd 20/56 mg/m^2 twice-weekly dose regimen has previously demonstrated 9- and 8-month improvements in PFS and OS, respectively, versus treatment with Vd. Thus, Kd 20/70 mg/m^2 has clinically meaningful efficacy and has the added benefit of reducing the burden of treatment on patients and prescribers.

The FDA's Assessment:

The findings from the FDA's independent efficacy analyses of Kd 20/70 mg/m^2 once-weekly are consistent with the Applicant's. However, caution should be taken when interpreting the cross-study comparison analysis results due to the limitations of the propensity score analyses.

7.2. Review of Safety

The Applicant's Position:

The safety review of Kd 20/70 mg/m^2 once-weekly is primarily based on a within-study comparison for A.R.R.O.W. of Kd 20/70 mg/m^2 once-weekly versus Kd 20/27 mg/m^2 twice-weekly. Cross-study safety analyses were also conducted comparing Kd 20/70 mg/m^2 once-weekly with the on-label Kd 20/56 mg/m^2 twice-weekly dose regimen.

A within-study comparison demonstrated that the safety profiles of Kd 20/70 mg/m^2 once-weekly and Kd 20/27 mg/m^2 twice-weekly were comparable. The cross-study analyses demonstrated the safety profile for Kd 20/70 mg/m^2 once-weekly is consistent with that observed with Kd 20/56 mg/m^2 twice-weekly dosing. No new safety concerns were observed with the Kd 20/70 mg/m^2 once-weekly dose.

The FDA's Assessment:
The FDA agrees with the Applicant's approach. The FDA's analyses demonstrated that the safety profile of Kd 20/70 mg/m^2 once weekly is similar to Kd 20/27 m^2 twice weekly. There were no unexpected safety findings.

7.2.1. Safety Review Approach

The Applicant's Position:

The primary analysis of adverse events was a within-study comparison for A.R.R.O.W. of Kd 20/70 mg/m^2 once-weekly and Kd 20/27 mg/m^2 twice-weekly; laboratory parameters for Kd 20/70 mg/m^2 once-weekly were evaluated within A.R.R.O.W. only. The Kd 20/70 mg/m^2 once-weekly group from A.R.R.O.W. (data cutoff 15 June 2017) was compared side-by-side with the Kd 20/70 mg/m^2 once-weekly group from CHAMPION-1 (data cutoff 22 July 2016) and the Kd 20/56 mg/m^2 twice-weekly group from ENDEAVOR (data cutoff 03 January 2017). In addition, the Kd 20/70 mg/m^2 once-weekly groups from A.R.R.O.W. and CHAMPION-1 were combined for comparison with the Kd 20/27 mg/m^2 twice-weekly and Kd 20/56 mg/m^2 twice-weekly groups.

The Safety Analysis Set included all carfilzomib-treated subjects from A.R.R.O.W. and ENDEAVOR, and all subjects treated with Kd 20/70 mg/m^2 once-weekly from CHAMPION-1 who received at least 1 dose of any investigational product. The cross-study analyses of adverse events were performed on subjects in the Safety Analysis Set with relapsed or refractory multiple myeloma after 1 to 3 prior lines of therapy and after 2 to 3 prior lines of therapy. Data for subjects with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy are presented in Section 7.2.4; data for subjects with relapsed or refractory multiple myeloma who have received 2 to 3 prior lines of therapy are presented in Section 2 of A.R.R.O.W. Module 2.7.4, Summary of Clinical Safety.

In addition to the crude subject incidence of events, the exposure-adjusted incidence rate (per 100 subject-years) was calculated to account for the different exposure duration to investigational product across groups. Exposure-adjusted incidence rates are included in the cross-study analyses when the crude subject incidence was not comparable between treatment groups (i.e., a difference of ≥ 5% for any grade adverse events, ≥ 2% for grade ≥ 3 adverse events, or ≥ 1% for serious adverse events).

No formal hypothesis testing was performed; analyses of adverse events were descriptive.

The FDA's Assessment:
For this sNDA, the Applicant submitted safety data from the A.R.R.O.W study, a phase 3, open-label, randomized study comparing Kd 20/70 mg/m^2 to Kd 20/27 mg/m^2 in subjects with relapsed/refractory multiple myeloma who had received 2-3 prior lines of therapy. Data from two additional studies, CHAMPION-1 and ENDEAVOR were used to support the safety findings. CHAMPION-1 was a Phase 1/2, open-label, dose escalation and expansion study that evaluated once weekly dosing of Kd in subjects with relapsed/refractory multiple myeloma who had received 1-3 prior lines of therapy. ENDEAVOR was a phase 3, open-label, randomized study in which subjects with relapsed/refractory multiple myeloma who had received 1-3 prior lines of therapy, were randomized to receive either Kd 20/56 mg/m^2 twice weekly or bortezomib and dexamethasone. Data from the ENDEAVOR study was previously reviewed (see Clinical Review for NDA 202714, S-010 by Donna Przepiorka, MD, PhD dated 12/31/2015) and used to support the Kd 20/56 mg/m^2 twice weekly dosing regimen. The FDA's safety analyses for this application focused on data from the A.R.R.O.W. study, with supportive data from CHAMPION-1 and ENDEAVOR.

7.2.2. Review of the Safety Database

Overall Exposure

The Applicant's Position:

Safety data from 342 subjects treated with Kd 20/70 mg/m^2 once-weekly are provided, including 238 subjects from A.R.R.O.W. and 104 subjects from CHAMPION-1 (Table 18). In addition, safety data were also included from 235 subjects in the Kd 20/27 mg/m^2 twice-weekly group from A.R.R.O.W. and 463 subjects in the Kd 20/56 mg/m^2 twice-weekly group from ENDEAVOR. The sample size of the safety database was not specifically discussed with the FDA during protocol development or the prefiling meeting.

Table 18. Safety Population, Size, and Denominators

Safety Database for Kd 20/70 mg/m^2 Once-weekly Individuals exposed to the investigational product in this development program for the indication under review N = 342			
Clinical Trial Groups	Kd 20/70 mg/m^2 Once-weekly	Kd 20/27 mg/m^2 Twice-weekly	Kd 20/56 mg/m^2 Twice-weekly
A.R.R.O.W.	238	235	-
CHAMPION-1	104	-	-
ENDEAVOR	-	-	463
Safety Analysis Set 1 to 3 Prior Lines of Therapy	342	235	463
Safety Analysis Set 2 to 3 Prior Lines of Therapy	288	235	231

Kd = carfilzomib plus dexamethasone; - = not applicable

Treatment duration and the average dose of carfilzomib is provided by dose regimen and population in Table 19. Median relative dose intensity was similar across treatment groups and ranged from 91% to 98% (Section 1.4 of Module 2.7.4, Summary of Clinical Safety).

Table 19. Summary of Exposure to Carfilzomib

	Median Duration of Carfilzomib (weeks)			Mean Average Dose (mg)			Median Average Dose (mg)		
Population	Kd 20/70 mg/m^2 QW	Kd 20/27 mg/m^2 BIW	Kd 20/56 mg/m^2 BIW	Kd 20/70 mg/m^2 QW	Kd 20/27 mg/m^2 BIW	Kd 20/56 mg/m^2 BIW	Kd 20/70 mg/m^2 QW	Kd 20/27 mg/m^2 BIW	Kd 20/56 mg/m^2 BIW
A.R.R.O.W. Safety Analysis Set	38.00	29.14	-	114.89	47.89	-	116.90	48.40	-
CHAMPION-1 Safety Analysis Set	33.00	-	-	123.19	-	-	129.02	-	-
ENDEAVOR Safety Analysis Set	-	-	48.00	-	-	93.50	-	-	94.91
Safety Analysis Set 1 to 3 Prior Lines of Therapy	37.14	29.14	48.00	117.41	47.89	93.50	119.84	48.40	94.91
Safety Analysis Set 2 to 3 Prior Lines of Therapy	35.64	29.14	41.00	115.70	47.89	93.37	117.16	48.40	94.18

Kd = carfilzomib plus dexamethasone; - = not applicable
Source: A.R.R.O.W. ISS Table 1.1, A.R.R.O.W. ISS Table 1.3, A.R.R.O.W. ISS Table 1.4, A.R.R.O.W. ISS Table 14-1.2.2

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of exposure. A total of 342 subjects were treated with the 20/70 mg/m^2 once weekly in the A.R.R.O.W. and CHAMPION studies with a median duration of treatment of 37 weeks. FDA's assessment of the treatment exposure for A.R.R.O.W. is shown in the table below. The duration of treatment was slightly longer in the 20/70 mg/m^2 treatment group, and as expected, the average BSA adjusted dose was higher.

Table 20. A.R.R.O.W.: Summary of Treatment Exposure

	Once-weekly Kd 20/70 mg/m^2 (N = 238)	**Twice-weekly Kd 20/27 mg/m^2 (N = 235)**
Duration of Treatment (Week)		
Mean (SD)	35.8 (22.7)	31.5 (21)
Median (Min - Max)	38 (0.1 - 84.1)	29.1 (0.1 - 84.3)
Number of Cycles		
Mean (SD)	9.5 (5.6)	8.4 (5.2)
Median (Min - Max)	10 (1 - 22)	8 (1 - 22)
Total BSA Adjusted Doses Admin (mg/m^2)		
Mean (SD)	1767.1 (1127.6)	1237.3 (817)
Median (Min - Max)	1798.7 (19.7 - 4360)	1147.5 (19.6 - 3430.1)
Average BSA Adjusted Dose (mg/m^2)		
Mean (SD)	63.4 (8.4)	26 (1.4)
Median (Min - Max)	66.4 (16.6 - 71.5)	26.3 (19.6 - 28.6)
Average Dose per Administration(mg)		
Mean (SD)	114.9 (20.9)	47.9 (6.1)
Median (Min - Max)	116.9 (30.4 - 152.3)	48.4 (30.6 - 59.1)
Relative Dose Intensity (%)		
Mean (SD)	92.2 (11.2)	92.7 (10)
Median (Min - Max)	95.7 (26.1 - 104.7)	96.1 (47 - 106.1)
Actual Dose Intensity (mg/m^2/week)		
Mean (SD)	46.1 (6.7)	37.5 (4.1)
Median (Min - Max)	48.2 (13.3 - 53.7)	38.6 (19 - 47.4)
Intended Dose Intensity (mg/m^2/week)		
Mean (SD)	50.1 (4.1)	40.4 (1.1)
Median (Min - Max)	51.4 (20 - 52.3)	40.4 (37 - 47)
Source: ADaM dataset: adex.xpt		

Relevant characteristics of the safety population:

The Applicant's Position:

Demographic and baseline characteristics in A.R.R.O.W., ENDEAVOR, and CHAMPION-1 were generally representative of a relapsed and/or refractory multiple myeloma population (Table 10 and Table 13). However, the study populations had notable differences in baseline characteristics (see Baseline Characteristics).

The FDA's Assessment:
FDA agrees with the Applicant's assessments of the demographic and baseline characteristics across the three studies. The FDA conducted its own analyses for A.R.R.O.W. and CHAMPION-1. The safety population was representative of the multiple myeloma patient population. The baseline characteristics were well balanced between the treatment groups.

Adequacy of the safety database:

The Applicant's Position:

The safety database is considered to be adequate to assess the safety of Kd 20/70 mg/m^2 once-weekly. A total of 342 subjects have been treated with Kd 20/70 mg/m^2 once-weekly for a median duration of 37 weeks (Table 18 and Table 19).

Demographic and baseline characteristics of subjects treated with Kd 20/70 mg/m^2 once-weekly in A.R.R.O.W. and CHAMPION-1 were generally representative of a relapsed and/or refractory multiple myeloma population in the US. Treated subjects varied with regards to race, ethnicity, and age, and included those with renal or hepatic impairment. While subjects with certain pre-existing cardiac conditions were excluded from the safety database, this is consistent with the current and proposed USPI (Kyprolis USPI, 2018).

The FDA's Assessment:
The FDA agrees with the Applicant's assessment of the overall adequacy of the safety database.

7.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No issues were identified regarding data integrity or submission quality that had an effect on the safety review. The clinical sites for A.R.R.O.W., ENDEAVOR, and CHAMPION-1 were monitored by clinical research associates following study-specific monitoring plans for consistency. Data were queried per study-specific data management plans, including

automated database edit checks and internal data review by data management, clinical program management, and medical reviewers. Additionally, an external and independent Data Monitoring Committee periodically reviewed safety data for A.R.R.O.W. and ENDEAVOR.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment of data integrity and submission quality. The data submitted was of adequate quality and there were no issues identified regarding data or submission quality.

Categorization of Adverse Event

The Applicant's Position:

Standard methodologies were used to categorize adverse events. The analyses used the current version of MedDRA (version 20.0 for the cross-study comparisons) and adverse events were graded using the current version of National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 4.03 for the cross-study comparisons). Events of interest were evaluated based on standardized MedDRA queries, high-level group terms, or high-level terms, when possible, or predefined Amgen MedDRA queries.

The collection of adverse events in the clinical studies was also appropriate. The protocols defined adverse events and serious adverse events, as well as the reporting procedures (see A.R.R.O.W. Protocol Section 12 [Section 16.1.1 of Study 20140355]). Adverse events were collected at all clinical visits from screening until 30 days after the last dose of investigational product. All adverse events considered to be related to investigational product and all serious adverse events regardless of relationship were required to be followed to resolution or stabilization if improvement was not expected. Treatment-emergent adverse events were defined as any adverse event with an onset date between the date of first dose and 30 days after the date of last dose of any investigational product, which is consistent with that used in previous carfilzomib submissions.

The FDA's Assessment:
The FDA agrees with the Applicant's methodologies for collection and categorization of adverse events.

Routine Clinical Tests

The Applicant's Position:

In A.R.R.O.W., routine clinical tests included full hematology and serum chemistry panels, which were evaluated by the central laboratory at screening, before carfilzomib administration on days 1, 8, and 15 for the first 4 cycles and on days 1 and 15 thereafter, and at the end of

treatment visit (Table 4). In CHAMPION-1, hematology and serum chemistry were evaluated at screening, days 1, 8, and 15; and the end of treatment visit; abbreviated serum chemistry panels were evaluated on days 8 and 15 of each cycle. Laboratory values were graded using the current version of NCI-CTCAE (version 4.03 for A.R.R.O.W. and CHAMPION-1).

Vital signs were also assessed at screening, before each administration of carfilzomib, and at the end of treatment visit. Clinically significant abnormal vital signs were to be reported as adverse events.

The time points and analyses of clinical tests for the Kd 20/70 mg/m^2 once-weekly dose regimen were consistent with previous pivotal studies.

The FDA's Assessment:
The FDA agrees with the Applicant's collection of routine clinical tests in the A.R.R.O.W. and CHAMPION-1 studies.

7.2.4. Safety Results

Deaths

The Applicant's Position:

Fatal adverse events were reported for 9.2% of subjects in the Kd 20/70 mg/m^2 once-weekly group and 7.7% of subjects in the Kd 20/27 mg/m^2 twice-weekly group in A.R.R.O.W., 4.8% of subjects in the Kd 20/70 mg/m^2 once-weekly group in CHAMPION-1, and 6.9% of subjects in the Kd 20/56 mg/m^2 twice-weekly group in ENDEAVOR (Table 21).

Most fatal adverse events in all 3 studies occurred within the system organ class of infections and infestations, including the preferred terms sepsis and septic shock, or were events consistent with disease progression, including the preferred terms disease progression and plasma cell myeloma. No fatal adverse events occurred with a > 1% higher subject incidence in the pooled Kd 20/70 mg/m^2 once-weekly group than the Kd 20/56 mg/m^2 twice-weekly group.

Table 21. Summary of Fatal Adverse Events by System Organ Class (and Preferred Term Occurring in ≥ 2 Subjects in Any Group) (1 to 3 Prior Line of Therapy Safety Analysis Set)

System Organ Class Preferred Term	A.R.R.O.W. 20/27 mg/m^2 Kd BIW (N = 235)	A.R.R.O.W. 20/70 mg/m^2 Kd QW (N = 238)	CHAMPION-1 20/70 mg/m^2 Kd QW (N = 104)	A.R.R.O.W. + CHAMPION-1 20/70 mg/m^2 Kd QW (N = 342)	ENDEAVOR 20/56 mg/m^2 Kd BIW (N = 463)
Number of subjects with fatal adverse events	18 (7.7)	22 (9.2)	5 (4.8)	27 (7.9)	32 (6.9)
Infections and infestations	6 (2.6)	7 (2.9)	1 (1.0)	8 (2.3)	8 (1.7)
Infection	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.6)	0 (0.0)
Sepsis	2 (0.9)	2 (0.8)	1 (1.0)	3 (0.9)	1 (0.2)
Septic shock	1 (0.4)	2 (0.8)	0 (0.0)	2 (0.6)	3 (0.6)
Pneumonia	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	7 (3.0)	5 (2.1)	0 (0.0)	5 (1.5)	4 (0.9)
Plasma cell myeloma	7 (3.0)	4 (1.7)	0 (0.0)	4 (1.2)	3 (0.6)
Respiratory, thoracic and mediastinal disorders	1 (0.4)	2 (0.8)	1 (1.0)	3 (0.9)	3 (0.6)
Acute respiratory distress syndrome	0 (0.0)	1 (0.4)	1 (1.0)	2 (0.6)	1 (0.2)
Cardiac disorders	1 (0.4)	0 (0.0)	1 (1.0)	1 (0.3)	3 (0.6)
Cardiac arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)
General disorders and administration site conditions	3 (1.3)	3 (1.3)	1 (1.0)	4 (1.2)	9 (1.9)
Disease progression	1 (0.4)	2 (0.8)	1 (1.0)	3 (0.9)	4 (0.9)
Sudden death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)

BIW = twice-weekly; Kd = carfilzomib plus dexamethasone; QW = once-weekly
Treatment-emergent adverse events are defined as any adverse event with an onset date between the date of first dose and 30 days after the date of last dose of any investigational product. Adverse events were coded using Medical Dictionary for Regulatory Activities version 20.0.
Source: A.R.R.O.W. ISS Table 14-2.13.2 and A.R.R.O.W. ISS Table 14.4

The FDA's Assessment:

FDA's analyses are consistent with the Applicant's in regards to the number of patients that died within 30 days after the last dose of carfilzomib. In the A.R.R.O.W. study, 22 (9.2%) subjects in the 20/70 mg/m^2 group and 18 (7.7%) in the 20/27 mg/m^2 group experienced Grade 5 treatment-emergent adverse events. In the CHAMPION-1 study, 5 (4.8%) subjects who received the 20/70 mg/m^2 dosing experienced a fatal adverse event. In all studies, the majority of the fatal adverse events occurred within the system organ class of infections and infestations, including the preferred terms of sepsis and septic shock, or were events consistent with disease progression, including preferred terms disease progression and plasma cell myeloma. There were no fatal adverse events that occurred with greater than 1% higher subject incidence in the pooled Kd 20/70 mg/m^2 once-weekly group than the Kd 20/27 mg/m^2 twice-weekly group or the Kd 20/56 mg/m^2 twice-weekly treatment group. Overall, there were similar numbers of Grade 5 treatment-emergent adverse events across all treatment groups in the three studies with no meaningful differences between the groups.

Serious Adverse Events

The Applicant's Position:

Serious adverse events were reported for 43.3% of subjects in the Kd 20/70 mg/m^2 once-weekly group and 40.9% of subjects in the Kd 20/27 mg/m^2 twice-weekly group in A.R.R.O.W., 37.5% of subjects in the Kd 20/70 mg/m^2 once-weekly group in CHAMPION-1, and 58.7% of subjects in the Kd 20/56 mg/m^2 twice-weekly group in ENDEAVOR (Table 22).

In A.R.R.O.W., serious adverse events with a ≥ 1% higher subject incidence in the Kd 20/70 mg/m^2 once-weekly group than in the Kd 20/27 mg/m^2 twice-weekly group were pneumonia (8.4%, 7.2%), sepsis (2.5%, 1.3%), septic shock (2.1%, 0.4%), tumor lysis syndrome (1.7%, 0.4%), pulmonary embolism (1.7%, 0.0%), fatigue (1.3%, 0.0%), and lung infection (1.3%, 0.0%) (Section 2.1.3 of A.R.R.O.W. Module 2.7.4, Summary of Clinical Safety).

Serious adverse events with a ≥ 2% subject incidence in the Kd 20/70 mg/m^2 once-weekly groups in A.R.R.O.W. and CHAMPION-1, and the Kd 20/56 mg/m^2 twice-weekly group in ENDEAVOR were pneumonia and acute kidney injury (Table 22).

Serious adverse events with a ≥ 1% higher subject incidence in the pooled Kd 20/70 mg/m^2 once-weekly group than the Kd 20/56 mg/m^2 twice-weekly group for subjects with 1 to 3 prior lines of therapy were acute kidney injury (5.0%, 2.4%) and sepsis (3.5%, 1.5%). The exposure-adjusted risk estimates of serious adverse events remained higher in the pooled Kd 20/70 mg/m^2 once-weekly group than the Kd 20/56 mg/m^2 twice-weekly group for acute kidney injury (6.81, 2.01 per 100 subject years) and sepsis (4.81, 1.28 per 100 subject years) (A.R.R.O.W. ISS Table 15.2).

Table 22. Summary of Serious Adverse Events by System Organ Class (and Preferred Term Occurring in ≥ 2% of Subjects in Any Group) (1 to 3 Prior Line of Therapy Safety Analysis Set)

System Organ Class Preferred Term	A.R.R.O.W. 20/27 mg/m^2 Kd BIW (N = 235)	A.R.R.O.W. 20/70 mg/m^2 Kd QW (N = 238)	CHAMPION-1 20/70 mg/m^2 Kd QW (N = 104)	A.R.R.O.W. + CHAMPION-1 20/70 mg/m^2 Kd QW (N = 342)	ENDEAVOR 20/56 mg/m^2 Kd BIW (N = 463)
Number of subjects with serious adverse events	96 (40.9)	103 (43.3)	39 (37.5)	142 (41.5)	272 (58.7)
Infections and infestations	42 (17.9)	44 (18.5)	15 (14.4)	59 (17.3)	132 (28.5)
Pneumonia	**17 (7.2)**	**20 (8.4)**	**5 (4.8)**	**25 (7.3)**	**48 (10.4)**
Sepsis	3 (1.3)	**6 (2.5)**	**6 (5.8)**	**12 (3.5)**	7 (1.5)
Septic shock	1 (0.4)	**5 (2.1)**	1 (1.0)	6 (1.8)	4 (0.9)
Respiratory tract infection	1 (0.4)	2 (0.8)	0 (0.0)	2 (0.6)	**10 (2.2)**
Renal and urinary disorders	12 (5.1)	11 (4.6)	7 (6.7)	18 (5.3)	21 (4.5)
Acute kidney injury	**8 (3.4)**	**10 (4.2)**	**7 (6.7)**	**17 (5.0)**	**11 (2.4)**
Blood and lymphatic system disorders	11 (4.7)	10 (4.2)	3 (2.9)	13 (3.8)	15 (3.2)
Anaemia	**7 (3.0)**	4 (1.7)	1 (1.0)	5 (1.5)	4 (0.9)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	10 (4.3)	7 (2.9)	2 (1.9)	9 (2.6)	21 (4.5)
Plasma cell myeloma	**7 (3.0)**	4 (1.7)	0 (0.0)	4 (1.2)	5 (1.1)
Respiratory, thoracic and mediastinal disorders	5 (2.1)	13 (5.5)	10 (9.6)	23 (6.7)	51 (11.0)
Pulmonary embolism	0 (0.0)	4 (1.7)	0 (0.0)	4 (1.2)	**10 (2.2)**
Chronic obstructive pulmonary disease	0 (0.0)	0 (0.0)	**5 (4.8)**	5 (1.5)	2 (0.4)
Dyspnoea	1 (0.4)	0 (0.0)	1 (1.0)	1 (0.3)	**18 (3.9)**
General disorders and administration site conditions	12 (5.1)	13 (5.5)	4 (3.8)	17 (5.0)	43 (9.3)
Pyrexia	**5 (2.1)**	4 (1.7)	1 (1.0)	5 (1.5)	**19 (4.1)**

BIW = twice-weekly; Kd = carfilzomib plus dexamethasone; QW = once-weekly
Treatment-emergent adverse events are defined as any adverse event with an onset date between the date of first dose and 30 days after the date of last dose of any investigational product. Adverse events were coded using Medical Dictionary for Regulatory Activities version 20.0.
Bold text identifies preferred terms with ≥ 2% subject incidence.
Source: A.R.R.O.W. ISS Table 14-2.5.2 and A.R.R.O.W. ISS Table 15.2

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of serious adverse events presented in the table above. FDA's analyses of serious adverse events were consistent with the Applicant's. In the pooled analyses from the A.R.R.O.W. and CHAMPION-1 studies, more subjects who received Kd 20/70 mg/m^2 once weekly experienced the SAEs of acute kidney injury (5.0% vs 3.4%) and sepsis (3.5% vs. 1.3%) than in the 20/27 mg/m^2 once weekly group, but these differences were small. There were no other serious adverse events with a ≥2% higher subject incidence in the pooled Kd 20/70 mg/m^2 once-weekly group than the 20/27 mg/m^2 twice-weekly group or the Kd 20/56 mg/m^2 twice-weekly group. Overall, the incidence of serious adverse events was balanced between the treatment groups.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

Criteria for the permanent discontinuation of investigational product were prespecified in the protocols and are consistent with the USPI (see Section 7.1.1 and Kyprolis USPI, 2018).

In A.R.R.O.W., 12.6% of subjects in the Kd 20/70 mg/m^2 once-weekly group and 11.5% of subjects in the Kd 20/27 mg/m^2 twice-weekly group had at least 1 adverse event leading to the discontinuation of carfilzomib (Section 2.1.4.1 of A.R.R.O.W. Module 2.7.4, Summary of Clinical Safety). No adverse events leading to the discontinuation of carfilzomib occurred with a ≥ 1% higher subject incidence in either treatment group compared with the other.

The only adverse event leading to the discontinuation of carfilzomib that occurred with a ≥ 1% subject incidence in the Kd 20/70 mg/m^2 once-weekly groups in A.R.R.O.W. and CHAMPION-1, and the Kd 20/56 mg/m^2 twice-weekly group in ENDEAVOR was acute kidney injury.

Adverse events leading to the discontinuation of carfilzomib were reported for 13.5% of subjects in the pooled Kd 20/70 mg/m^2 once-weekly group and 25.1% of subjects in the Kd 20/56 mg/m^2 twice-weekly group for subjects with 1 to 3 prior lines of therapy. The most commonly reported (occurring in ≥ 1% of subjects in either group) adverse events that led to treatment discontinuation of carfilzomib (pooled Kd 20/70 mg/m^2 once-weekly, Kd 20/56 mg/m^2 twice-weekly) were acute kidney injury (1.7%, 1.7%), fatigue (1.0%, 0.4%), plasma cell myeloma (1.0%, 1.3%), cardiac failure (0.7%, 1.7%), decreased ejection fraction (0.7%, 1.7%), and dyspnea (0%, 1.3%). No adverse event leading to the discontinuation of carfilzomib occurred with a ≥ 1% higher subject incidence in the pooled Kd 20/70 mg/m^2 once-weekly group than the Kd 20/56 mg/m^2 twice-weekly group.

The FDA's Assessment:

The FDA's analyses of treatment discontinuations due to treatment-emergent adverse events are consistent with the Applicant's findings above. In the A.R.R.O.W. study, 30 (12.6%) of subjects in the Kd 20/70 mg/m^2 group and 27 (11.5%) in the Kd 20/27 mg/m^2 group discontinued treatment due to an adverse event. There were no adverse events leading to study drug discontinuation that occurred with a ≥ 1% higher subject incidence in the 20/70 mg/m^2 once weekly treatment group. Overall, the adverse events leading to treatment discontinuation were balanced between the treatment groups and within the expected incidence range.

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

Criteria for the interruption or reduction of treatment with investigational product were prespecified in the protocols and are consistent with the USPI (see Section 7.1.1 and Kyprolis USPI, 2018).

Dose Interruption
In A.R.R.O.W., 51.7% of subjects in the Kd 20/70 mg/m^2 once-weekly group and 49.4% of subjects in the Kd 20/27 mg/m^2 twice-weekly group had at least 1 adverse event leading to carfilzomib dose interruption (Section 2.1.4.2 of A.R.R.O.W. Module 2.7.4, Summary of Clinical Safety). The most commonly reported (occurring in ≥ 5% of subjects in either group) adverse events leading to carfilzomib dose interruption were (Kd 20/70 mg/m^2 once-weekly, Kd 20/27 mg/m^2 twice-weekly) pneumonia (8.8%, 6.0%), bronchitis (5.0%, 4.3%), pyrexia (5.0%, 3.8%), upper respiratory tract infection (5.0%, 5.5%), and respiratory tract infection (4.2%, 5.1%). Adverse events leading to carfilzomib dose interruption reported with ≥ 2% higher subject incidence in the Kd 20/70 mg/m^2 once-weekly group than the Kd 20/27 mg/m^2 twice-weekly group were pneumonia and fatigue.

Adverse events leading to carfilzomib dose interruption that occurred with a ≥ 2% subject incidence in the Kd 20/70 mg/m^2 once-weekly groups in A.R.R.O.W. and CHAMPION-1, and the Kd 20/56 mg/m^2 twice-weekly group in ENDEAVOR were pneumonia, pyrexia, and upper respiratory tract infection.

Adverse events leading to carfilzomib dose interruption were reported for 49.1% of subjects in the pooled Kd 20/70 mg/m^2 once-weekly group and 73.7% of subjects in the Kd 20/56 mg/m^2 twice-weekly group for subjects with 1 to 3 prior lines of therapy. No adverse events leading to carfilzomib dose interruption were reported with a ≥ 2% higher subject incidence in the pooled Kd 20/70 mg/m^2 once-weekly group than the Kd 20/56 mg/m^2 twice-weekly group.

Dose Reduction
In A.R.R.O.W., 10.5% of subjects in the Kd 20/70 mg/m^2 once-weekly group and 4.7% of subjects in the Kd 20/27 mg/m^2 twice-weekly group had at least 1 adverse event leading to carfilzomib dose reduction (Section 2.1.4.3 of A.R.R.O.W. Module 2.7.4, Summary of Clinical Safety). The most frequently reported adverse event leading to carfilzomib dose reduction was fatigue (2.1% Kd 20/70 mg/m^2 once-weekly, 0.9% Kd 20/27 mg/m^2 twice-weekly), which was also the only adverse event leading to carfilzomib dose reduction that occurred with a ≥ 1% higher subject incidence in the Kd 20/70 mg/m^2 once-weekly group than the Kd 20/27 mg/m^2 twice-weekly group.

No adverse events leading to carfilzomib dose reduction occurred with a ≥ 1% subject incidence in the Kd 20/70 mg/m^2 once-weekly groups in A.R.R.O.W. and CHAMPION-1, and the Kd 20/56 mg/m^2 twice-weekly group in ENDEAVOR.

Adverse events leading to carfilzomib dose reduction were reported for 12.6% of subjects in the pooled Kd 20/70 mg/m^2 once-weekly group and 29.4% of subjects in the Kd 20/56 mg/m^2 twice-weekly group for subjects with 1 to 3 prior lines of therapy. The most commonly reported adverse event leading to carfilzomib dose reduction (≥ 1% subject incidence) were fatigue, dyspnea, hypertension, acute kidney injury, asthenia, diarrhea, nausea, pyrexia, vomiting, increased alanine aminotransferase, anemia, cardiac failure, and chills. No adverse event leading to carfilzomib dose reduction occurred with a ≥ 1% higher subject incidence in the pooled Kd 20/70 mg/m^2 once-weekly group than the Kd 20/56 mg/m^2 twice-weekly group.

The FDA's Assessment:

The FDA agrees with the Applicant's analyses of dose interruptions and discontinuations due to adverse events. A summary of the FDA's analyses of dose modifications in the A.R.R.O.W. study is presented in the table below.

Table 23. A.R.R.O.W.: Summary of Dose Modifications

	Once-weekly Kd 20/70 mg/m^2 (N = 238)	**Twice-weekly Kd 20/27 mg/m^2 (N = 235)**
Treatment discontinuation due to TEAEs	30 (12.6%)	27 (11.5%)
Dose Modification (Interruption and/or Reduction) due to TEAEs	135 (56.7%)	119 (50.6%)
Dose Interruption due to TEAEs	123 (51.7%)	116 (49.4%)
Dose Reduction due to TEAEs	25 (10.5%)	11 (4.7%)
Source dataset: adae.xpt		

Significant Adverse Events

The Applicant's Position:

Grade ≥ 3 adverse events (NCI-CTCAE version 4.03) with a ≥ 2% higher subject incidence in the Kd 20/70 mg/m^2 once-weekly group than in the Kd 20/27 mg/m^2 twice-weekly group in A.R.R.O.W. were pneumonia (10.1%, 6.8%), fatigue (4.6%, 2.1%), tumor lysis syndrome (2.9%, 0.9%), and decreased neutrophil count (2.9%, 0.4%) (Section 2.1.1.1 of A.R.R.O.W. Module 2.7.4, Summary of Clinical Safety).

The grade ≥ 3 adverse events with a ≥ 5% subject incidence in the Kd 20/70 mg/m^2 once-weekly groups in A.R.R.O.W. and CHAMPION-1, and the Kd 20/56 mg/m^2 twice-weekly group in ENDEAVOR were anemia, thrombocytopenia, pneumonia, and hypertension (Table 24).

Grade ≥ 3 adverse events with a ≥ 2% higher subject incidence in the pooled Kd 20/70 mg/m^2 once-weekly group than the Kd 20/56 mg/m^2 twice-weekly group for subjects with 1 to 3 prior lines of therapy were neutropenia (5.3%, 2.4%) and sepsis (3.8%, 1.5%). The exposure-adjusted risk estimates of grade ≥ 3 adverse events remained higher in the pooled Kd 20/70 mg/m^2 once-weekly group than the Kd 20/56 mg/m^2 twice-weekly group for neutropenia (7.34, 2.04 per 100 subject years) and sepsis (5.21, 1.28 per 100 subject years).

Table 24. Summary of Grade ≥ 3 Adverse Events by System Organ Class (and Preferred Term Occurring in ≥ 5% of Subjects in Any Group) (1 to 3 Prior Line of Therapy Safety Analysis Set)

System Organ Class Preferred Term	A.R.R.O.W. 20/27 mg/m^2 Kd BIW (N = 235)	A.R.R.O.W. 20/70 mg/m^2 Kd QW (N = 238)	CHAMPION-1 20/70 mg/m^2 Kd QW (N = 104)	A.R.R.O.W. + CHAMPION-1 20/70 mg/m^2 Kd QW (N = 342)	ENDEAVOR 20/56 mg/m^2 Kd BIW (N = 463)
Number of subjects with grade ≥ 3 adverse events	145 (61.7)	161 (67.6)	69 (66.3)	230 (67.3)	376 (81.2)
Blood and lymphatic system disorders	58 (24.7)	62 (26.1)	17 (16.3)	79 (23.1)	127 (27.4)
Anaemia	**42 (17.9)**	**42 (17.6)**	**8 (7.7)**	**50 (14.6)**	**76 (16.4)**
Thrombocytopenia	**16 (6.8)**	**17 (7.1)**	**7 (6.7)**	**24 (7.0)**	**41 (8.9)**
Neutropenia	**16 (6.8)**	**14 (5.9)**	4 (3.8)	**18 (5.3)**	11 (2.4)
Infections and infestations	46 (19.6)	54 (22.7)	19 (18.3)	73 (21.3)	145 (31.3)
Pneumonia	**16 (6.8)**	**24 (10.1)**	**7 (6.7)**	**31 (9.1)**	**52 (11.2)**
Sepsis	3 (1.3)	6 (2.5)	**7 (6.7)**	13 (3.8)	7 (1.5)
Vascular disorders	15 (6.4)	16 (6.7)	13 (12.5)	29 (8.5)	85 (18.4)
Hypertension	**12 (5.1)**	**13 (5.5)**	**11 (10.6)**	**24 (7.0)**	**67 (14.5)**
Investigations	26 (11.1)	35 (14.7)	10 (9.6)	45 (13.2)	84 (18.1)
Platelet count decreased	**12 (5.1)**	10 (4.2)	2 (1.9)	12 (3.5)	18 (3.9)
Lymphocyte count decreased	1 (0.4)	2 (0.8)	0 (0.0)	2 (0.6)	**29 (6.3)**
General disorders and administration site conditions	22 (9.4)	20 (8.4)	16 (15.4)	36 (10.5)	95 (20.5)
Fatigue	5 (2.1)	11 (4.6)	**12 (11.5)**	**23 (6.7)**	**31 (6.7)**
Renal and urinary disorders	13 (5.5)	11 (4.6)	10 (9.6)	21 (6.1)	37 (8.0)
Acute kidney injury	8 (3.4)	8 (3.4)	**7 (6.7)**	15 (4.4)	12 (2.6)
Respiratory, thoracic and mediastinal disorders	7 (3.0)	18 (7.6)	17 (16.3)	35 (10.2)	59 (12.7)
Dyspnoea	2 (0.9)	1 (0.4)	5 (4.8)	6 (1.8)	**29 (6.3)**

BIW = twice-weekly; Kd = carfilzomib plus dexamethasone; QW = once-weekly
Treatment-emergent adverse events are defined as any adverse event with an onset date between the date of first dose and 30 days after the date of last dose of any investigational product. Adverse events were coded using Medical Dictionary for Regulatory Activities version 20.0 and graded using National Cancer Institute – Common Terminology Criteria for Adverse Events version 4.03.
Bold text identifies preferred terms with ≥ 5% subject incidence.
Source: A.R.R.O.W. ISS Table 14-2.4.2 and A.R.R.O.W. ISS Table 12.2

The FDA's Assessment:

The FDA agrees with the Applicant's analyses of significant adverse events. In the A.R.R.O.W. study, Grade ≥3 adverse events that occurred more frequently in the 20/70 mg/m^2 once-weekly treatment group compared to the 20/27 mg/m^2 twice-weekly treatment group included pneumonia (10.1% vs. 6.8%) and fatigue (4.6% vs 2.1%). The remainder of Grade ≥3 adverse events were well balanced between the two treatment groups.

Treatment Emergent Adverse Events and Adverse Reactions

The Applicant's Position:

Common Adverse Events

In A.R.R.O.W., adverse events of pyrexia occurred more frequently (≥ 5% higher subject incidence) in the Kd 20/70 mg/m^2 once-weekly group than the Kd 20/27 mg/m^2 twice-weekly group (Table 25). Adverse events of anemia and insomnia occurred more frequently (≥ 5% higher subject incidence) in the Kd 20/27 mg/m^2 twice-weekly group than the Kd 20/70 mg/m^2 once-weekly group.

Adverse events that occurred with a ≥ 10% subject incidence in the Kd 20/70 mg/m^2 once-weekly groups in A.R.R.O.W. and CHAMPION-1, and the Kd 20/56 mg/m^2 twice-weekly group in ENDEAVOR were anemia, thrombocytopenia, pyrexia, fatigue, asthenia, hypertension, diarrhea, nausea, insomnia, cough, headache, upper respiratory tract infection, and back pain.

Among the adverse events in ≥ 10% of subjects in any treatment group, no adverse events occurred with a higher subject incidence in the pooled Kd 20/70 mg/m^2 once-weekly group than the Kd 20/56 mg/m^2 twice-weekly group for subjects with 1 to 3 prior therapies.

Table 25. Summary of Adverse Events by System Organ Class (and Preferred Term Occurring in ≥ 10% of Subjects in Any Group) (1 to 3 Prior Lines of Therapy Safety Analysis Set)

System Organ Class Preferred Term	A.R.R.O.W. 20/27 mg/m^2 Kd BIW (N = 235)	A.R.R.O.W. 20/70 mg/m^2 Kd QW (N = 238)	CHAMPION-1 20/70 mg/m^2 Kd QW (N = 104)	A.R.R.O.W. + CHAMPION-1 20/70 mg/m^2 Kd QW (N = 342)	ENDEAVOR 20/56 mg/m^2 Kd BIW (N = 463)
Number of subjects with adverse events	229 (97.4)	227 (95.4)	104 (100.0)	331 (96.8)	457 (98.7)
Blood and lymphatic system disorders	92 (39.1)	89 (37.4)	44 (42.3)	133 (38.9)	254 (54.9)
Anaemia	**75 (31.9)**	**63 (26.5)**	**30 (28.8)**	**93 (27.2)**	**197 (42.5)**
Thrombocytopenia	21 (8.9)	**31 (13.0)**	**25 (24.0)**	**56 (16.4)**	**100 (21.6)**
General disorders and administration site conditions	122 (51.9)	132 (55.5)	83 (79.8)	215 (62.9)	360 (77.8)
Pyrexia	**38 (16.2)**	**55 (23.1)**	**30 (28.8)**	**85 (24.9)**	**150 (32.4)**
Fatigue	**47 (20.0)**	**48 (20.2)**	**56 (53.8)**	**104 (30.4)**	**149 (32.2)**
Asthenia	**25 (10.6)**	**24 (10.1)**	**14 (13.5)**	**29 (10.1)**	**107 (23.1)**
Oedema peripheral	**25 (10.6)**	18 (7.6)	**24 (23.1)**	26 (9.0)	**98 (21.2)**
Vascular disorders	71 (30.2)	61 (25.6)	31 (29.8)	92 (26.9)	235 (50.8)
Hypertension	**48 (20.4)**	**51 (21.4)**	**18 (17.3)**	**69 (20.2)**	**149 (32.2)**
Gastrointestinal disorders	90 (38.3)	92 (38.7)	72 (69.2)	164 (48.0)	291 (62.9)
Diarrhoea	**47 (20.0)**	**44 (18.5)**	**35 (33.7)**	**79 (23.1)**	**168 (36.3)**
Nausea	**26 (11.1)**	**34 (14.3)**	**43 (41.3)**	**77 (22.5)**	**109 (23.5)**
Constipation	22 (9.4)	19 (8.0)	**17 (16.3)**	**36 (10.5)**	**75 (16.2)**
Vomiting	12 (5.1)	19 (8.0)	**17 (16.3)**	**36 (10.5)**	**77 (16.6)**
Psychiatric disorders	70 (29.8)	53 (22.3)	54 (51.9)	107 (31.3)	184 (39.7)
Insomnia	**47 (20.0)**	**35 (14.7)**	**34 (32.7)**	**69 (20.2)**	**125 (27.0)**
Anxiety	4 (1.7)	4 (1.7)	**12 (11.5)**	16 (4.7)	19 (4.1)
Respiratory, thoracic and mediastinal disorders	72 (30.6)	83 (34.9)	72 (69.2)	155 (45.3)	288 (62.2)
Cough	**30 (12.8)**	**35 (14.7)**	**30 (28.8)**	**65 (19.0)**	**128 (27.6)**
Dyspnoea	23 (9.8)	23 (9.7)	**30 (28.8)**	**53 (15.5)**	**149 (32.2)**
Nervous system disorders	58 (24.7)	61 (25.6)	61 (58.7)	122 (35.7)	246 (53.1)
Headache	23 (9.8)	**25 (10.5)**	**32 (30.8)**	**57 (16.7)**	**95 (20.5)**
Neuropathy peripheral	10 (4.3)	7 (2.9)	10 (9.6)	17 (5.0)	**49 (10.6)**
Dizziness	10 (4.3)	5 (2.1)	**19 (18.3)**	24 (7.0)	42 (9.1)
Infections and infestations	147 (62.6)	152 (63.9)	73 (70.2)	225 (65.8)	367 (79.3)
Upper respiratory tract infection	**29 (12.3)**	**31 (13.0)**	**37 (35.6)**	**68 (19.9)**	**119 (25.7)**
Pneumonia	20 (8.5)	**28 (11.8)**	10 (9.6)	**38 (11.1)**	**68 (14.7)**
Bronchitis	**25 (10.6)**	**27 (11.3)**	8 (7.7)	**35 (10.2)**	**108 (23.3)**
Viral upper respiratory tract infection	**30 (12.8)**	**24 (10.1)**	9 (8.7)	33 (9.6)	**76 (16.4)**
Respiratory tract infection	21 (8.9)	17 (7.1)	1 (1.0)	18 (5.3)	**51 (11.0)**
Urinary tract infection	9 (3.8)	10 (4.2)	**12 (11.5)**	22 (6.4)	39 (8.4)

System Organ Class Preferred Term	A.R.R.O.W. 20/27 mg/m^2 Kd BIW (N = 235)	A.R.R.O.W. 20/70 mg/m^2 Kd QW (N = 238)	CHAMPION-1 20/70 mg/m^2 Kd QW (N = 104)	A.R.R.O.W. + CHAMPION-1 20/70 mg/m^2 Kd QW (N = 342)	ENDEAVOR 20/56 mg/m^2 Kd BIW (N = 463)
Musculoskeletal and connective tissue disorders	100 (42.6)	96 (40.3)	74 (71.2)	170 (49.7)	281 (60.7)
Back pain	**28 (11.9)**	**28 (11.8)**	**23 (22.1)**	**51 (14.9)**	**107 (23.1)**
Muscle spasms	20 (8.5)	21 (8.8)	**16 (15.4)**	**37 (10.8)**	**92 (19.9)**
Bone pain	15 (6.4)	20 (8.4)	3 (2.9)	23 (6.7)	**50 (10.8)**
Arthralgia	13 (5.5)	15 (6.3)	**20 (19.2)**	**35 (10.2)**	**60 (13.0)**
Pain in extremity	18 (7.7)	15 (6.3)	**18 (17.3)**	33 (9.6)	**55 (11.9)**
Muscular weakness	6 (2.6)	7 (2.9)	**17 (16.3)**	24 (7.0)	44 (9.5)
Musculoskeletal chest pain	10 (4.3)	7 (2.9)	**12 (11.5)**	19 (5.6)	39 (8.4)
Investigations	75 (31.9)	70 (29.4)	43 (41.3)	113 (33.0)	216 (46.7)
Platelet count decreased	21 (8.9)	**24 (10.1)**	7 (6.7)	31 (9.1)	**58 (12.5)**
Blood creatinine increased	7 (3.0)	14 (5.9)	**14 (13.5)**	28 (8.2)	**53 (11.4)**
Metabolism and nutrition disorders	60 (25.5)	79 (33.2)	50 (48.1)	129 (37.7)	227 (49.0)
Hypokalaemia	10 (4.3)	19 (8.0)	**11 (10.6)**	30 (8.8)	**60 (13.0)**
Decreased appetite	12 (5.1)	13 (5.5)	**15 (14.4)**	28 (8.2)	**50 (10.8)**
Hyperglycaemia	7 (3.0)	10 (4.2)	10 (9.6)	20 (5.8)	**54 (11.7)**
Skin and subcutaneous tissue disorders	42 (17.9)	36 (15.1)	49 (47.1)	85 (24.9)	149 (32.2)
Rash	12 (5.1)	7 (2.9)	**16 (15.4)**	23 (6.7)	41 (8.9)

BIW = twice-weekly; Kd = carfilzomib plus dexamethasone; QW = once-weekly
Treatment-emergent adverse events are defined as any adverse event with an onset date between the date of first dose and 30 days after the date of last dose of any investigational product. Adverse events were coded using Medical Dictionary for Regulatory Activities version 20.0.
Bold text identifies preferred terms with ≥ 10% subject incidence.
Source: A.R.R.O.W. ISS Table 14-2.2.1 and A.R.R.O.W. ISS Table 10.2

Adverse Events of Interest

Adverse events of interest were prespecified medical concepts identified based on their association with subjects with advanced myeloma, proteasome inhibition, or potential or identified association with carfilzomib. Adverse events of interest are provided for subjects with 1 to 3 prior lines of therapy in Table 26 and discussed in detail in Section 2.1.4.4 of A.R.R.O.W. Module 2.7.4, Summary of Clinical Safety. Overall, the subject incidence of adverse events of interest was similar for the pooled Kd 20/70 mg/m^2 once-weekly and Kd 20/56 mg/m^2 twice-weekly groups.

Table 26. Selected Adverse Events of Interest (1 to 3 Prior Lines of Therapy Safety Analysis Set)

Adverse Event of Interest Grouping Events of Interest Preferred Term	A.R.R.O.W. 20/27 mg/m^2 Kd BIW (N = 235)	A.R.R.O.W. 20/70 mg/m^2 Kd QW (N = 238)	CHAMPION-1 20/70 mg/m^2 Kd QW (N = 104)	A.R.R.O.W. + CHAMPION-1 20/70 mg/m^2 Kd QW (N = 342)	ENDEAVOR 20/56 mg/m^2 Kd BIW (N = 463)
Cardiac Adverse Events					
Cardiac arrhythmias (SMQN)	10 (4.3)	7 (2.9)	6 (5.8)	13 (3.8)	34 (7.3)
Cardiac failure (SMQN)	12 (5.1)	9 (3.8)	4 (3.8)	13 (3.8)	50 (10.8)
Ischaemic heart disease (SMQN)	3 (1.3)	4 (1.7)	4 (3.8)	8 (2.3)	18 (3.9)
Hematology Adverse Events					
Haematopoietic leukopenia (SMQN)	38 (16.2)	32 (13.4)	15 (14.4)	47 (13.7)	102 (22.0)
Haematopoietic thrombocytopenia (SMQN)	41 (17.4)	53 (22.3)	31 (29.8)	84 (24.6)	147 (31.7)
Haematopoietic erythropenia (SMQB)	77 (32.8)	64 (26.9)	31 (29.8)	95 (27.8)	201 (43.4)
Hemorrhage Adverse Events					
Haemorrhage terms (excl laboratory terms) (SMQN)	23 (9.8)	21 (8.8)	24 (23.1)	45 (13.2)	105 (22.7)
Hepatic Adverse Events					
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQN)	3 (1.3)	3 (1.3)	0 (0.0)	3 (0.9)	12 (2.6)
Liver related investigations, signs and symptoms (SMQN)	12 (5.1)	19 (8.0)	5 (4.8)	24 (7.0)	58 (12.5)
Infection Adverse Events					
Herpes viral infections (HLT)	4 (1.7)	5 (2.1)	1 (1.0)	6 (1.8)	17 (3.7)
Respiratory tract infections (HLGT)	123 (52.3)	137 (57.6)	59 (56.7)	196 (57.3)	334 (72.1)
Infusion Reaction Adverse Events					
Infusion reaction (AMQN) (Within One Day of Any Carfilzomib Dosing)	53 (22.6)	54 (22.7)	30 (28.8)	84 (24.6)	187 (40.4)
Infusion reaction (AMQN) (Within One Day of First Carfilzomib Dosing)	4 (1.7)	2 (0.8)	2 (1.9)	4 (1.2)	6 (1.3)
Reversible Posterior Leukoencephalopathy Events					
Reversible posterior leukoencephalopathy syndrome (AMQN)	22 (9.4)	21 (8.8)	18 (17.3)	39 (11.4)	80 (17.3)
Pulmonary Adverse Events					
Dyspnoeas (HLT)	26 (11.1)	28 (11.8)	33 (31.7)	61 (17.8)	163 (35.2)
Interstitial lung disease (SMQN)	0 (0.0)	2 (0.8)	2 (1.9)	4 (1.2)	7 (1.5)
Respiratory failure (SMQN)	4 (1.7)	2 (0.8)	6 (5.8)	8 (2.3)	14 (3.0)
Renal Adverse Events					
Acute renal failure (SMQN)	16 (6.8)	17 (7.1)	12 (11.5)	29 (8.5)	48 (10.4)
Thromboembolic Adverse Events					
Embolic and thrombotic events, venous (SMQN)	10 (4.3)	10 (4.2)	5 (4.8)	15 (4.4)	58 (12.5)
Tumor Lysis Syndrome Adverse Events					
Tumour lysis syndrome (SMQN)	2 (0.9)	7 (2.9)	0 (0.0)	7 (2.0)	3 (0.6)

Adverse Event of Interest Grouping Events of Interest Preferred Term	A.R.R.O.W. 20/27 mg/m^2 Kd BIW (N = 235)	A.R.R.O.W. 20/70 mg/m^2 Kd QW (N = 238)	CHAMPION-1 20/70 mg/m^2 Kd QW (N = 104)	A.R.R.O.W. + CHAMPION-1 20/70 mg/m^2 Kd QW (N = 342)	ENDEAVOR 20/56 mg/m^2 Kd BIW (N = 463)
Vascular Adverse Events					
Hypertension (SMQN)	50 (21.3)	52 (21.8)	18 (17.3)	70 (20.5)	156 (33.7)
Pulmonary hypertension (SMQN)	3 (1.3)	4 (1.7)	1 (1.0)	5 (1.5)	8 (1.7)
Vascular hypotensive disorders (HLT)	8 (3.4)	2 (0.8)	6 (5.8)	8 (2.3)	33 (7.1)

AMQN = Amgen MedDRA query, narrow scope; BIW = twice-weekly; HLGT = high-level group term; HLT = high-level term; Kd = carfilzomib plus dexamethasone; MedDRA = Medical Dictionary for Regulatory Activities; QW = once-weekly; SMQB = standardized MedDRA query, broad scope; SMQN = standardized MedDRA query, narrow scope

Treatment-emergent adverse events are defined as any adverse event with an onset date between the date of first dose and 30 days after the date of last dose of any investigational product. Adverse events were coded using MedDRA version 20.0.

Source: A.R.R.O.W. ISS Table 14-2.14.1, A.R.R.O.W. ISS Table 6.2, and A.R.R.O.W. ISS Table 30.2

Adverse Drug Reactions

Potential new adverse drug reactions (ADRs) were determined using the A.R.R.O.W. primary analysis, the pooled Kd 20/70 mg/m^2 once-weekly group for subjects who had received 1 to 3 prior lines of therapy, and the pooled Kd 20/70 mg/m^2 once-weekly group for subjects who had received 2 to 3 prior lines of therapy. New ADRs were identified using the following criteria: adverse events were designated ADRs if their incidence in the Kd 20/70 mg/m^2 once-weekly group was ≥ 5% (any grade), ≥ 2% (grade ≥ 3), or ≥ 1% (serious), or if they occurred at lower subject incidence but were either 1) considered biologically plausible or 2) were considered clinically relevant.

Septic shock was consistently identified across comparison groups (Table 27) and, therefore, is proposed as a new ADR. The full ADR table is provided in Appendix 3 of A.R.R.O.W. Module 2.7.4, Summary of Clinical Safety.

Table 27. New Adverse Drug Reactions Identified for Kd 20/70 mg/m^2 Once-weekly by Comparison Group

Comparison Group	Grade ≥ 3 Events in ≥ 2% of Subjects	Serious Adverse Events in ≥ 1% of Subjects
Kd 20/70 mg/m^2 once-weekly group within A.R.R.O.W.	septic shock infection	septic shock infection pathological fracture
Pooled Kd 20/70 mg/m^2 once-weekly group 1 to 3 prior lines of therapy	-	septic shock chronic obstructive pulmonary disease
Pooled Kd 20/70 mg/m^2 once-weekly group 2 to 3 prior lines of therapy	-	septic shock pathological fracture spinal cord compression

Kd = carfilzomib plus dexamethasone; - = not applicable
No new adverse drug reactions were identified based on the review of any grade adverse events or events that occurred at lower subject incidence than the thresholds above and were considered biologically plausible or clinically relevant.
Source: Section 2.1.5 of A.R.R.O.W. Module 2.7.4, Summary of Clinical Safety

The FDA's Assessment:

The FDA agrees with the Applicant's analyses above. The FDA conducted independent analyses of the safety data from the A.R.R.O.W. and CHAMPION-1 studies and the findings were consistent with those described by the Applicant above.

In the A.R.R.O.W. study, the majority of subjects in both treatment groups experienced at least one treatment-emergent adverse event (95.4% in the 20/70 mg/m^2 once weekly group, 97.4% in the 20/27 mg/m^2 twice weekly group). The most common adverse events in both groups were anemia, hypertension, pyrexia and fatigue. The majority of these were Grade 1 and 2 in severity. Overall, the incidence of adverse events was balanced between the treatment groups, with only pyrexia occurring more frequently in the 20/70 mg/m^2 once weekly group (23.1% vs. 16.2%). Anemia and insomnia occurred more frequently in the 20/27 mg/m^2 twice weekly group (31.9% vs. 26.5% and 20% vs. 14.7%, respectively). There were no other clinically meaningful differences in the common treatment-emergent adverse events between the two treatment groups.

The FDA conducted independent analyses of specified adverse events of special interest including cardiac events, renal and hepatic impairment, allergic and anaphylactic reactions, thrombotic/embolic events, hemorrhagic events, neurologic events and myelosuppression.

Cardiac Adverse Events

The table below depicts the cardiac events that occurred in the A.R.R.O.W. study. Overall, there was a trend towards fewer cardiac failure adverse events in the 20/70 mg/m^2 once weekly treatment group, though the numbers were small in both treatment groups. The incidence of cardiac arrhythmias was similar in the two treatment groups. A summary of the FDA's analysis of the cardiac adverse events by preferred term from the A.R.R.O.W. study is provided in the

table below.

Table 28. A.R.R.O.W.: Cardiac Adverse Events

	Once-weekly Kd 20/70 mg/m^2 (N = 238)		Twice-weekly Kd 20/27 mg/m^2 (N = 235)	
	All Grades	**Grade 3-5**	**All Grades**	**Grade 3-5**
Cardiac failure	**31 (13%)**	**8 (3.4%)**	**43 (18.3%)**	**12 (5.1%)**
Cardiac failure	3 (1.3%)	3 (1.3%)	5 (2.1%)	3 (1.3%)
Cardiac failure acute	3 (1.3%)	2 (0.8%)	2 (0.9%)	2 (0.9%)
Cardiac failure congestive	1 (0.4%)	1 (0.4%)	4 (1.7%)	3 (1.3%)
Edema	3 (1.3%)	0 (0%)	4 (1.7%)	0 (0%)
Edema peripheral	18 (7.6%)	0 (0%)	25 (10.6%)	2 (0.9%)
Peripheral swelling	2 (0.8%)	0 (0%)	4 (1.7%)	0 (0%)
Cardiac arrhythmias	**21 (8.8%)**	**8 (3.4%)**	**23 (9.8%)**	**4 (1.7%)**
Atrial fibrillation	3 (1.3%)	2 (0.8%)	4 (1.7%)	3 (1.3%)
Palpitations	5 (2.1%)	0 (0%)	4 (1.7%)	0 (0%)
Sinus tachycardia	1 (0.4%)	0 (0%)	4 (1.7%)	0 (0%)
Syncope	5 (2.1%)	5 (2.1%)	3 (1.3%)	1 (0.4%)
Tachycardia	6 (2.5%)	0 (0%)	6 (2.6%)	0 (0%)
Ischemic heart disease	**4 (1.7%)**	**2 (0.8%)**	**3 (1.3%)**	**2 (0.9%)**
Myocardial infarction	**1 (0.4%)**	**1 (0.4%)**	**2 (0.9%)**	**1 (0.4%)**

Hepatic adverse events

The FDA's analysis was consistent with the Applicant's analysis above. In the A.R.R.O.W. study, more subjects in the 20/70 mg/m^2 treatment group experienced liver related investigations, signs and symptoms (10.1% vs. 6.0%). However, the incidence of hepatic failure, fibrosis, cirrhosis and other liver damage-related conditions were similar between the two treatment groups. A summary of the FDA's analysis of hepatic adverse events from the A.R.R.O.W. study is provided in the table below.

Table 29. A.R.R.O.W.: Hepatic Adverse Events

	Once-weekly Kd 20/70 mg/m^2 (N = 238)		Twice-weekly Kd 20/27 mg/m^2 (N = 235)	
	All Grades	**Grade 3-5**	**All Grades**	**Grade 3-5**
Liver related investigations, signs and symptoms	**24 (10.1%)**	**11 (4.6%)**	**14 (6.0%)**	**4 (1.7%)**
ALT increased	3 (1.3%)	1 (0.4%)	4 (1.7%)	1 (0.4%)
AST increased	3 (1.3%)	1 (0.4%)	2 (0.9%)	0 (0%)
Alk Phos increased	3 (1.3%)	0 (0%)	2 (0.9%)	0 (0%)
Bilirubin increased	3 (1.3%)	0 (0%)	2 (0.9%)	0 (0%)
GGT increased	8 (3.4%)	5 (2.1%)	1 (0.4%)	1 (0.4%)
Hepatic function abnormal	5 (2.1%)	1 (0.4%)	1 (0.4%)	0 (0%)
Hypoalbuminemia	4 (1.7%)	1 (0.4%)	1 (0.4%)	1 (0.4%)
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions	**3 (1.3%)**	**1 (0.4%)**	**3 (1.3%)**	**2 (0.9%)**

The FDA's analyses of additional adverse events of special interest including allergic and anaphylactic reactions, thrombotic/embolic events, hemorrhagic events, neurologic events and myelosuppression were consistent with the findings the Applicant presented above. Overall, these adverse events of special interest were balanced between the treatment groups and there were no meaningful differences between the occurrence of these adverse events in subjects who received the 20/70 mg/m^2 once weekly dose and those who received the 20/27 mg/m^2 twice weekly dose.

Laboratory Findings

The Applicant's Position:

No notable trends were observed after treatment with Kd 20/70 mg/m^2 once-weekly in laboratory evaluations and the results were consistent with the known safety profile of carfilzomib (see also Section 12.7 of Study 20140355 and Section 12.7 of Study 2012-002).

The FDA's Assessment:

The FDA agrees with the Applicants assessment that there were no notable trends or

differences in laboratory evaluations between the two treatment groups.

Vital Signs

The Applicant's Position:

In A.R.R.O.W., no notable differences were observed between the Kd 20/70 mg/m^2 once-weekly and Kd 20/27 mg/m^2 twice-weekly groups for vital signs (Section 12.8 of Study 20140355). Outlier values that were reported as adverse events and adverse events in vital sign parameters, including hypotension, hypertension, and clinically significant changes in heart rate are presented under their respective adverse event section, including adverse events of interest (Table 25 and Table 26).

The FDA's Assessment:

The FDA agrees with the Applicant's assessment that there were no notable differences in vital signs between the two treatment groups, except as mentioned previously under adverse events of special interest.

Electrocardiograms (ECGs)

The Applicant's Position:

Electrocardiograms (ECGs) were evaluated at baseline and the end of treatment in A.R.R.O.W. No notable differences were observed between the Kd 20/70 mg/m^2 once-weekly and Kd 20/27 mg/m^2 twice-weekly groups for ECGs (Table 14-8.5 and Table 14-8.6 of Study 20140355).

The FDA's Assessment:

The FDA agrees with the Applicant's analysis and the conclusion that there were no differences observed between the Kd 20/70 mg/m^2 once-weekly and Kd 20/27 mg/m^2 twice-weekly treatment groups.

QT

The Applicant's Position:

No new thorough QT clinical trial information is provided in the current submission. However, a pharmacokinetic/pharmacodynamic analysis was performed using data from all subjects that had paired carfilzomib pharmacokinetic and ECG data after administration of Kd 20/70 mg/m^2 once-weekly or Kd 20/56 mg/m^2 twice-weekly. The objective of the analysis was to explore the relationships between the change from baseline in corrected QT interval by Fredericia criteria (ΔQTcF) and carfilzomib C_{max}. Carfilzomib C_{max} concentrations were simulated using the updated population pharmacokinetic model due to sparse data in these studies (see Section 5.2.1).

The ΔQTcF-exposure analysis revealed no clear signals of any carfilzomib concentration-related

effects (Report 150781).

The FDA's Assessment:
Refer to the original NDA review for an analysis of QT information.

Immunogenicity

The Applicant's Position:

Not applicable.

The FDA's Assessment:
Not applicable.

7.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:

No new potential safety issues were identified as a result of the safety review of Kd 20/70 mg/m^2 once-weekly. However, a new ADR of septic shock was identified; of note, sepsis is already an ADR of carfilzomib (see Treatment Emergent Adverse Events and Adverse Reactions). Prespecified adverse events of interest, consistent with the current and proposed USPI, are presented in Table 26.

The FDA's Assessment:
The FDA agrees with the Applicant's conclusion that no new safety issues were identified with the 20/70 mg/m^2 once weekly dosing.

7.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

No new information is provided in the current submission. Patient-reported outcomes in A.R.R.O.W. are discussed in Section 7.1.2.

The FDA's Assessment:
Refer to the table in Section 1.4

7.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

The subject incidence of adverse events and serious adverse events was evaluated by age (< 65 years versus ≥ 65 years and < 75 years versus ≥ 75 years) for the Kd 20/70 mg/m^2 once-weekly group and Kd 20/27 mg/m^2 twice-weekly group in A.R.R.O.W. and across studies; no meaningful differences were identified (Section 5.1 of A.R.R.O.W. Module 2.7.4, Summary of Clinical Safety).

The FDA's Assessment:
The FDA did not conduct separate safety analyses by demographic subgroups.

7.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

Not applicable as no studies were conducted to evaluate a specific safety concern.

The FDA's Assessment:
Not applicable.

7.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:
Carcinogenicity studies were not conducted or required to support this sNDA.

Human Reproduction and Pregnancy

The Applicant's Position:

As of 19 January 2018, 5 pregnancies were reported in which exposure to carfilzomib occurred during pregnancy through paternal exposure; no maternal exposure cases were reported (Section 16.3.4.3 of the Periodic Benefit-Risk Evaluation Report [PBRER], number 5, dated 14 March 2018). The birth outcomes were: lost to follow-up for 1 case, normal live birth for 1 case, and unknown for 3 cases (no pregnancy-related adverse events have been reported to date). In addition, 1 case was reported of an infant receiving breast milk from a mother with accidental exposure (spill on the skin) to carfilzomib. The outcome of the event was not reported; however, no adverse events were reported for the breast-fed child.

The FDA's Assessment:
The FDA agrees with the information the Applicant provided. As included in the Prescribing Information, based on findings from animal studies, carfilzomib can cause fetal harm. There are no adequate and well-controlled studies in pregnant women. Females of reproductive potential should be advised to avoid becoming pregnant while being treated with carfilzomib.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:
Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

No changes have been identified from the current carfilzomib product profile with respect to overdose, drug abuse, or withdrawal and rebound (Section 5.5, Section 5.6, and Section 5.7 of A.R.R.O.W. Module 2.7.4, Summary of Clinical Safety).

The FDA's Assessment:
FDA agrees with the Applicant's position.

7.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

The ADRs of hemolytic uremic syndrome, gastrointestinal perforation, and pericarditis were identified through postmarketing experience (Section 4 of PBRER, number 1, dated 11 March 2016) and were previously added to the USPI (Kyprolis USPI, 2018).

No new information is provided in the current submission.

The FDA's Assessment:
FDA receives periodic adverse event reports for NDA 202714 and has reviews these on an ongoing basis. Several adverse reactions (hemolytic uremic syndrome, gastrointestinal perforation and pericarditis) have been identified through postmarketing experience and have been added to Prescribing Information.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Not applicable as there is substantial postmarketing experience with carfilzomib.

The FDA's Assessment:
The FDA agrees with the Applicant's statement.

7.2.11. Integrated Assessment of Safety

The Applicant's Position:

The key risks with carfilzomib are cardiac failure, acute renal failure, and hypertension. Although these are underlying comorbidities of multiple myeloma (Kistler et al, 2014; Christiansen et al, 2011; Knauf et al, 2009), these risks were identified as key risks with carfilzomib treatment groups versus the comparators in the randomized clinical studies. Within A.R.R.O.W. (Kd 20/70 mg/m^2 once-weekly, Kd 20/27 mg/m^2 twice-weekly), the risk of hypertension (SMQN) (21.8%, 21.3%) and acute renal failure (SMQN) (7.1%, 6.8%) was consistent between treatment groups; whereas, the incidence of cardiac failure (SMQN) (3.8%, 5.1%) was lower in the Kd 20/70 mg/m^2 once-weekly group than in the Kd 20/27 mg/m^2 twice-weekly group (Table 26). The pooled Kd 20/70 mg/m^2 once-weekly group and the Kd 20/56 mg/m^2 twice-weekly group were consistent with respect to the risk of acute renal failure (SMQN) (8.5%, 10.4%), while lower subject incidences were reported for the pooled Kd 20/70 mg/m^2 once-weekly group compared with the Kd 20/56 mg/m^2 twice-weekly group for hypertension (SMQN) (20.5%, 33.7%) and cardiac failure (SMQN) (3.8%, 10.8%).

Overall, in A.R.R.O.W., the safety profiles of the Kd 20/70 mg/m^2 once-weekly and Kd 20/27 mg/m^2 twice-weekly groups were comparable (Section 7.2.4).

In the cross-study analyses, the overall safety profile observed in the pooled Kd 20/70 mg/m^2 once-weekly group from A.R.R.O.W. and CHAMPION-1 was consistent with the safety profile observed in the Kd 20/56 mg/m^2 twice-weekly group from ENDEAVOR. The subject incidence was lower in the pooled Kd 20/70 mg/m^2 once-weekly group (A.R.R.O.W. + CHAMPION-1) than in the Kd 20/56 mg/m^2 twice-weekly group for grade ≥ 3 adverse events (67.3%, 81.2%), serious adverse events (41.5%, 58.7%), and adverse events that led to the discontinuation of any investigational product (14.9%, 28.7%), but higher for fatal adverse events (7.9%, 6.9%). No preferred term for a fatal adverse event occurred with a > 1% higher subject incidence in the pooled Kd 20/70 mg/m^2 once-weekly group than the Kd 20/56 mg/m^2 twice-weekly group.

Routine risk minimization activities (i.e., risk communications through prescribing information, labeling, or packaging) are considered sufficient to manage the key risks associated with the use of carfilzomib).

The FDA's Assessment:
The FDA agrees with the Applicant's integrated assessment of safety. Overall, the safety profile of Kd 20/70 mg/m^2 once weekly was comparable to that of Kd 20/27 mg/m^2 twice weekly and Kd 20/56 mg/m^2 twice weekly. There were no new safety findings with the new dosing regimen.

SUMMARY AND CONCLUSIONS

7.3. Statistical Issues

The FDA's Assessment:

For the A.R.R.O.W. Study, the majority of subjects were from Europe (82.6%) and Asia (10.3%). The percentage of US subjects was only 0.6%. There are no other major statistical issues that could impact the interpretation of the PFS and ORR results.

For the cross-study comparison, the interpretation should consider the following limitations:

- The analysis does not have the ability to create a balance between treatment groups with respect to all covariates including unobserved covariates.
- The magnitude of the treatment effect cannot be adequately characterized based on the cross-study comparison.
- The timing of data collection in each of the trials was different.
- These analyses are exploratory since they were not pre-specified prior to collection of the data.
- The subgroup analysis results of whether subjects were refractory to prior bortezomib (Y/N) and total number of prior regimens (1-2 and 3) did not demonstrate internal consistency.

7.4. Conclusions and Recommendations

The FDA's Assessment:

Based on the favorable risk-benefit profile, the clinical and statistical reviewers recommend approval of:

Carfilzomib 20/70 mg/m^2 once weekly with dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.

Qing Xu, PhD
Primary Statistical Reviewer

Yuan-Li Shen, DrPh
Statistical Team Leader

Rachel Ershler, MD
Primary Clinical Reviewer

Vishal Bhatnagar, MD
Clinical Team Leader

8 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

The FDA did not hold an advisory committee meeting for this sNDA and no outside advice was required.

9 Pediatrics

The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:
Not applicable.

10 Labeling Recommendations

10.1. Prescription Drug Labeling

The Applicant's Position:

The high-level changes proposed to the current Kyprolis USPI are summarized in Table 30. All proposed changes are provided in the draft A.R.R.O.W. USPI.

The FDA's Assessment:
The FDA revisions and rationale were described in Column 3 of Table 30.

Table 30. Summary of Significant Labeling Changes

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's Proposed Labeling**
Highlights – Dosage and Administration, Clinical Studies	Addition of once-weekly dose and supporting studies.	Accepted proposed edits.
2 DOSAGE AND ADMINISTRATION	Addition of once-weekly dose under the Kyprolis in Combination with Dexamethasone heading.	Revised heading of Table 7 to "Dose Level Reductions for Kyprolis Toxicity"
5 WARNINGS AND PRECAUTIONS	Modified rates as necessary to reflect safety experience with once-weekly dose.	Recommended abbreviation of Warning 5.1 to provide a summary rate (for all dosage regimens) in the warning and provide details of rates for individual trials in Section 6. Section 5.16 Embryo-fetal toxicity; FDA updated to include an animal to human dose comparison and to add recommendations for duration of contraception use during treatment and cessation of therapy based upon draft guidance "Reproductive Toxicity Testing and Labeling Recommendations Guidance for Industry".
6 ADVERSE REACTIONS	Addition of safety experience with once-weekly dose for Kyprolis in Combination with Dexamethasone.	FDA recommended avoiding use of MedDRA terms "Preferred Term"; suggested "Adverse Reaction". Revised "adverse events" to "adverse reactions" per the Adverse Reactions Section of Labeling Guidance. Removed (b) (4) s they do not

		meet the definition for adverse reactions.
8 USE IN SPECIFIC POPULATIONS	Addition of safety and efficacy experience in geriatric use for once-weekly dose	Revised sections 8.1 through 8.3 to reflect DHP's current approach to PLLR labeling. Section 8.5, Geriatric Use: FDA recommends abbreviation of this section by pooling age data from all indications/trials and summarizing any differences between younger and older subjects.
12 CLINICAL PHARMACOLOGY	Modified section to include pharmacokinetic experience with once-weekly dose	FDA reformatted section 12.3 Pharmacokinetics according to the Clinical Pharmacology Labeling guidance.
14 CLINICAL STUDIES	Addition of 2 clinical studies to support once-weekly dose.	FDA suggested adding NCT #s and Trial Names in order to ease the identification of trials that are described in product labeling by clinicians. FDA recommended describing PFS by ORCA, rather than IRC since ORCA was primary endpoint analysis for trial. (b) (4) [redacted]

11 Risk Evaluation and Mitigation Strategies (REMS)

The Applicant's Position:

A risk evaluation and mitigation strategy has never been required for carfilzomib. Considering that no new safety concerns were identified with this submission, no additional risk minimization measures beyond product labeling is needed.

The FDA's Assessment:
No REMS is required.

12 Postmarketing Requirements and Commitment

The FDA's Assessment:
Not applicable. No PMRs will be issued as a result of this supplement.

13 Division Director (OCP)

Nam Atiqur Rahman, PhD
Division Director

14 Division Director (OB)

Thomas Gwise, PhD
Deputy Division Director

15 Division Director (Clinical)

On August 24, 2018, Onyx Pharmaceuticals, a wholly-owned subsidiary of Amgen Inc., submitted a supplemental NDA for the use of carfilzomib 20/70 mg/m^2 once weekly in combination with dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy. The supplemental application was reviewed using the Real-Time Oncology Review and Assessment Aid pilots. The application was primarily support by the results of the pivotal trial, A.R.R.O.W., a phase 3, open-label, randomized trial comparing carfilzomib 20/70 mg/m^2 once weekly with dexamethasone and carfilzomib 20/27 mg/m^2 twice weekly with dexamethasone in patients with relapsed or refractory multiple myeloma who had received 2-3 prior lines of treatment. The primary endpoint was progression-free survival assessed by Onyx Response Computational Assessment (ORCA). The median PFS in the carfilzomib 20/70 mg/m^2 once weekly treatment arm was 11.2 months compared to 7.6 months in the carfilzomib 20/27 mg/m^2 twice weekly treatment arm (HR=0.693, 95% CI: 0.544-0.883). The application was supported by data from a propensity score analysis, with pooled datasets from the A.R.R.O.W., CHAMPION-1, and ENDEAVOR trials. This was included in the application to allow for a comparison to the carfilzomib 20/56 mg/m^2 dose (the approved dose for carfilzomib in combination with dexamethasone) and to evaluate the use in patients who had received 1-3 prior line of therapy (as the A.R.R.O.W. trial was limited to patients who had received 2-3 prior lines of therapy). The propensity analysis provides supportive efficacy and results for the proposed indication. The safety analysis from the A.R.R.O.W. trial demonstrated comparable safety between the carfilzomib 20/70 mg/m^2 once weekly dose and the 20/27 mg/m^2 twice weekly dose. There were no new safety findings. I agree with the recommendation of the review team for regular approval of carfilzomib 20/70 mg/m^2 once weekly in combination with dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.

Nicole Gormley, MD
Deputy Division Director, DHP (acting)

16 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

Nicole Gormley, MD
Deputy Division Director, DHP (acting)

17 Appendices

17.1. References

The Applicant's References:

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17.2. Financial Disclosure

The Applicant's Position:

As described in Financial Disclosure and the tables below, 2 investigators in A.R.R.O.W. and 7 investigators in CHAMPION-1 received significant payments; steps were taken to minimize potential bias in both studies.

The FDA's Assessment:

Covered Clinical Study (Name and/or Number): A.R.R.O.W. (Study 20140355)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 814		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the Applicant, and confirmed/edited by the FDA.

Covered Clinical Study (Name and/or Number): CHAMPION-1 (Study 2012-002)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 748		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 7		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 6 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the Applicant, and confirmed/edited by the FDA.

17.3. OCP Appendices (Technical documents supporting OCP recommendations)

Applicant's Population PK Analysis:

Table 31 outlines the time course and amount of PK sampling data for each respective study that was included in the population PK analysis.

Table 31. Summary of Pharmacokinetic Data Included in the Population PK Analysis.

Study (Phase)	Description	No. of Subjects	Carfilzomib Dosing and Schedule	PK Sampling
Combination Studies				
PX-171-006 (1b)	Phase 1b dose-escalation study of carfilzomib, lenalidomide, and low-dose dexamethasone in subjects with relapsed or progressive multiple myeloma	39	2–10 min IV infusion 28-day treatment cycles: 3 weeks ON/1 week OFF Cycles 1–12: Days 1, 2, 8, 9, 15, and 16 Cycles 13+: Days 1, 2, 15, and 16 Cohorts 1–3: 15 mg/m2 Cohorts 4–5: 20 mg/m2 Cohort 6: 27 mg/m2	Cycle 1 Days 1 and 8; Cycle 2 Day 15 (predose, ~15 min postdose and 15 min to 3 h postdose)
PX-171-009 (3)	Phase 3, multicenter randomized study comparing carfilzomib, lenalidomide, and dexamethasone (CRd) versus lenalidomide and dexamethasone (Rd) in subjects with relapsed multiple myeloma	106	2–10 min IV infusion 28-day treatment cycles, up to 18 cycles 20/27 mg/m2: 20 mg/m2 on Days 1 and 2 of Cycle 1; 27 mg/m2 on Days 8, 9, 15, and 16 of Cycle 1 and continuing on Days 1, 2, 8, 9, 15, and 16 of Cycle 2–12. Cycles 13-18: 27 mg/m2 on Days 1, 2, 15, and 16	Cycle 1 Days 1 and 8 (predose, ~15 min postdose and between 15 min and 3 h postdose) Cycle 2 Day 15 (~15 min postdose and between 15 min and 3 h postdose)
2011-003 (3)	Phase 3, multicenter randomized study comparing carfilzomib, lenalidomide, and dexamethasone (CRd) versus lenalidomide and dexamethasone (Rd) in subjects with relapsed multiple myeloma	133	30 min IV infusion 28-day treatment cycles Cycle 1: 20 mg/m2 IV on Days 1 and 2, followed by escalation to 56 mg/m2 on Days 8, 9, 15, and 16 Cycles 2+: 56 mg/m2 Dexamethasone 20 mg on Days 1, 2, 8, 9, 15, 16, 22, and 23	Cycle 1: Day 1 (EOI, 10 min post-infusion) Day 2 (predose, 20 min postdose) Day 8 (EOI, 10, 60–75, and 80–95 min post-infusion)

Study (Phase)	Description	No. of Subjects	Carfilzomib Dosing and Schedule	PK Sampling
Single-Agent Carfilzomib Studies				
PX-171-007 (1b/2)	Phase 1b/2, multicenter open-label study of the safety and activity of carfilzomib in subjects with advanced solid tumors	29 for 2–10 min Infusion 73 for 30-min infusion	2–10 min or 30-min IV infusion 28-day treatment cycles, up to 12 cycles Three treatment cohorts: 20 mg/m2: All days 20/27 mg/m2: 20 mg/m2 Days 1 and 2 of Cycle 1, 27 mg/m2 thereafter 20/36 mg/m2: 20 mg/m2 Days 1 and 2 of Cycle 1, 36 mg/m2 thereafter	Cycle 1 Days 1 and 16; Cycle 3 Days 1 and 16; Cycle 5 Days 1 and 16 (predose, EOI, 5, 15 and 30 min, 1, 2, and 4 h postdose)
PX-171-003-Part 2(A1) (2)	Phase 2, open-label single-arm study of single-agent carfilzomib in subjects with relapsed and refractory multiple myeloma	102	2–10 min IV infusion 28-day treatment cycles, up to 12 cycles Dose escalation following Cycle 1 for A1 study: 20 mg/m2: Cycle 1, Days 1, 2, 8, 9, 15 and 16 27 mg/m2: Cycles 2+, Days 1, 2, 8, 9, 15, and 16	Cycle 1 Day 1 (predose, ~15 min postdose); Cycle 1 Day 8 (~30 min postdose); Cycle 2 Day 15 (30–60 min postdose)
PX-171-004 (2)	Phase 2, open-label, single-arm study of single-agent carfilzomib in subjects with relapsed and/or refractory multiple myeloma who are bortezomib-naïve and who have been previously treated with bortezomib	51	2–10 min IV infusion 28-day treatment cycles, up to 12 cycles All bortezomib-exposed subjects and one cohort of bortezomib-naïve subjects received 20 mg/m2 on Days 1, 2, 8, 9, 15, and 16 in all Cycles The remaining bortezomib-naïve subjects escalated from a starting dose of 20 mg/m2 to a target dose of 27 mg/m2 after Cycle 1.	Cycle 1 Day 1 (predose, ~15 min postdose); Cycle 1 Day 8 (~30 min postdose) Cycle 2 Day 15 (30-60 min postdose)
PX-171-005 (2)	Carfilzomib in multiple myeloma subjects with renal impairment: pharmacokinetics and safety	43	2–10 min IV infusion 28-day treatment cycles, up to 12 cycles Days 1, 2, 8, 9, 15, and 16 Cycle 1: 15 mg/m2 Cycle 2: Escalation to 20 mg/m2 Cycle 3+: 27 mg/m2	Cycle 1 Days 1 and 15; Cycle 2 Day 15 (predose, EOI, 5, 15 and 30 min, 1.0, 1.5, 2, 4, 6, and 24 h postdose) 24 h samples to be drawn prior to next scheduled dose
CFZ001 (1)	Phase 1, open-label, single-arm study of the pharmacokinetics and safety of carfilzomib in subjects with relapsed multiple myeloma and end-stage renal disease	21	30 min IV infusion 28-day treatment cycles Cycle 1: 20 mg/m2 IV on Days 1 and 2, followed by escalation to 27 mg/m2 on Days 8, 9, 15, and 16 Cycles 2+: 56 mg/m2 on Days 1, 2, 8, 9, 15, and 16	Cycle 1 Day 16 and Cycle 2 Day 1 (predose, 15 min after start of infusion, EOI, 5, 15, and 30 min, and 1, 2, 4, and 24 h after end of infusion)
CFZ002 (1)	Phase 1, open-label, single-arm study of the pharmacokinetics and safety of carfilzomib in subjects with advanced malignancies and varying degrees of hepatic impairment	30	30 min IV infusion 28-day treatment cycles Cycle 1: 20 mg/m2 IV on Days 1 and 2, followed by escalation to 27 mg/m2 on Days 8, 9, 15, and 16 Cycles 2+: 56 mg/m2 on Days 1, 2, 8, 9, 15 and 16	Cycle 1 Day 16 and Cycle 2 Day 1 (predose, 15 min a start of infusion, EOI, 5, 15, and 30 min, and 1, 2, 4 h, and 24 h after end of infusion)

Study (Phase)	Description	No. of Subjects	Carfilzomib Dosing and Schedule	PK Sampling
20140355 (3)	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	460	30 min IV infusion 28-day treatment cycles Arm A: Once-weekly • Carfilzomib 20 mg/m2 o Study Day 1 (Cycle 1) • Carfilzomib 70 mg/m2 o Study Days 8 and 15 (Cycle 1) • Carfilzomib 70 mg/m2 o Study Days 1, 8, and 15 (Cycles 2+) Arm B: Twice-weekly • Carfilzomib 20 mg/m2 o Study Days 1 and 2 (Cycle 1) • Carfilzomib 27 mg/m2 o Study Days 8, 9, 15, and 16 (Cycle 1) • Carfilzomib 27 mg/m2 o Study Days 1, 2, 8, 9, 15, and 16 (Cycles 2+)	Cycle 1 Day 15
2012-002 (1/2)	A Phase 1/2 Study of Weekly Carfilzomib in Combination with Dexamethasone for Progressive Multiple Myeloma	123	30 min IV infusion 28-day treatment cycles Cycle 1: 20 mg/m2 IV on Days 1. All subsequent carfilzomib doses (45, 56, 70, or 88 mg/m2) will be administered according to the dose assignment for each cohort	Cycle 1 Day 1 and Cycle 2 Day 15 (predose, 5, 15 min after start of infusion, EOI, 5, 15, and 30 min, and 1, 2, and 4h after end of infusion)

CRd = carfilzomib, lenalidomide, and dexamethasone; EOI = end of infusion; IV – intravenous; min = minutes; Rd = lenalidomide and dexamethasone

(Source: Applicant's Population PK Report 150597, Table 1)

Baseline Characteristics of the data are outlined in Table 32.

Table 32. Summary Statistics of Age, Body Weight, BSA, BMI, and Gender, Race by Clinical Study. Results Presented as Mean (SD).

Study	n	Age	Weight
1	16	64.1 (9.45) [49-78]	73.3 (11.8) [54.8-94.1]
2	22	63.1 (9.97) [37-78]	80 (20.1) [51.5-122]
2011	97	65.8 (10.9) [36-89]	71.7 (16.4) [37-116]
2012	27	62.9 (10.3) [43-83]	79.5 (18.6) [51.8-126]
2014	82	64.1 (9.5) [40-85]	75.5 (17.5) [45-130]
3	100	61.8 (10.3) [37.8-87.6]	78 (18.4) [41.7-144]
4	51	65.4 (10.4) [40.4-86]	84.3 (18.9) [50-128]
5	43	65.1 (8.79) [45.3-86]	81.6 (19.6) [45.8-127]
6	39	61.7 (8.79) [43.9-81.4]	85.4 (17.5) [58.9-123]
7	102	62.6 (9.92) [35-87.2]	84.4 (21.6) [46.2-165]
9	100	64.5 (9.56) [40-87]	78.6 (17.5) [48-148]
Total	679	63.8 (9.97) [35-89]	79 (18.8) [37-165]

Study	n	BSA	BMI
1	16	1.82 (0.149) [1.53-2.08]	26.3 (5.08) [17.1-36.3]
2	22	1.9 (0.28) [1.36-2.41]	27 (5.66) [17.9-40.4]
2011	97	1.77 (0.237) [1.2-2.24]	26.4 (4.74) [17-45.4]
2012	27	1.93 (0.251) [1.57-2.54]	31.4 (26.5) [17.9-161]
2014	82	1.86 (0.256) [1.34-2.63]	27.3 (4.46) [17.6-37.5]
3	100	1.87 (0.239) [1.37-2.52]	27.7 (5.64) [16.8-47.9]
4	51	1.96 (0.268) [1.44-2.51]	28.7 (4.69) [20.4-39]
5	43	1.91 (0.257) [1.4-2.41]	28.4 (5.93) [19.7-47.2]
6	39	1.95 (0.224) [1.53-2.36]	30 (5.91) [22.5-50.2]
7	102	1.96 (0.256) [1.41-2.82]	28.7 (6.88) [18.7-49.2]
9	100	1.9 (0.242) [1.41-2.7]	27.8 (4.81) [19.7-46.7]
Total	679	1.89 (0.252) [1.2-2.82]	28 (7.49) [16.8-161]

	Gender		Race				
Study	**0**	**1**	**1**	**2**	**3**	**4**	**5**
1	6	10	13	2	1	0	0
2	6	16	21	1	0	0	0
3	44	56	73	20	2	5	0
4	21	30	41	9	0	1	0
5	20	23	29	11	3	0	0
6	17	22	29	6	1	3	0
7	40	62	75	11	2	14	0
9	37	63	93	7	0	0	0
2011	39	58	68	1	28	0	0
2012	9	18	24	1	0	0	2
2014	37	45	80	2	0	0	0
Total	276	403	546	71	37	23	2
%	(40.6%)	(59.4%)	(80.4%)	(10.5%)	(5.45%)	(3.39%)	(0.295%)

(Source: Applicant's Population PK Report 150597, Table 3)

Base Model Development:

A schematic of this model structure is depicted in Figure 1.

"In initial two-compartment PK model, IIV were estimated in all PK parameters. However, large shrinkage was observed on IIV of V1 and the estimated IIV of V1 was close to 0 indicating current data may not contain sufficient information to characterize all IIV of PK parameters. Moreover, removing IIV on V1 resulted in minimum and non-statistically significant change in MVOF (ΔMVOF = 0.024 points). Thus, IIV of V1 was fixed to a value of 0.

Additionally, as compared to one proportional residual error model, a separate proportional error model between intense and sparse sampling studies resulted in a statistically significant improvement in model fit (ΔMVOF = - 87.7 points). Therefore, a separate error model was used in the base structural PK model. Graphical exploration of random effects revealed high correlation between IIVs on V2 and Q (r2=0.113, p<0.001). Estimation of covariance between IIV on V2 and Q resulted in another statistically significant change in MVOF (ΔMVOF = -16.130 points). Thus, covariance between IIV on V2 and Q was included in the base model. Models incorporating M3 method to evaluate BLQ data was also tested and compared to models

without M3. The difference between parameter estimates were less than 20%. Thus, M3 method for BLQ data was not included in the base model.

Collectively, the two-compartment model with IIVs estimated for CL, V2, Q, and covariance estimated between IIVs on V2 and Q was deemed appropriate as the base structural population PK model. All PK parameters were estimated with good precision (RSE% < 20%). The shrinkage on CL, V2, and Q were 32.4%, 52.2%, and 43.5%, respectively."

Final Model Development:

"Following the development of the base model, the effects of subject specific covariates on the random effects in the base structural model were explored graphically on key PK parameters. Trends were apparent in the relationships between PK parameters and a few of the covariates examined. The CL estimates appeared statistically significantly higher in male subjects with solid tumor, renal function category 1, or concomitant dexamethasone administration than female, subjects without solid tumor, other renal function category or without dexamethasone administration, respectively. The CL appeared highly correlated with age, weight, BSA, height and BMI. It was apparent that V2 was higher in subjects with renal function category 1, concomitant dexamethasone administration than subjects with other renal function category, and without dexamethasone administration, respectively. V2 appeared highly correlated with height, BSA and creatinine clearance. Q appeared statistically significantly higher in subjects with solid tumor, or without concomitant lenalidomide administration than subjects without solid tumor, or with concomitant lenalidomide administration, respectively. Upon forward inclusion and backward elimination, BSA was identified as the only significant predictors of CL. In other words, inclusion of BSA in the model corrected for many of the trends observed in the parameter versus covariate relationships. Thus, BSA was included in the final model.

Accordingly, the two-compartment model with IIVs estimated for CL, V2, Q2, and covariate effect of BSA on CL deemed appropriate as the final structural population PK model. All PK parameters were estimated with good precision (RSE% < 20%). The shrinkage on CL, V2, and Q were 35.2%, 50.9%, and 42.6%, respectively."

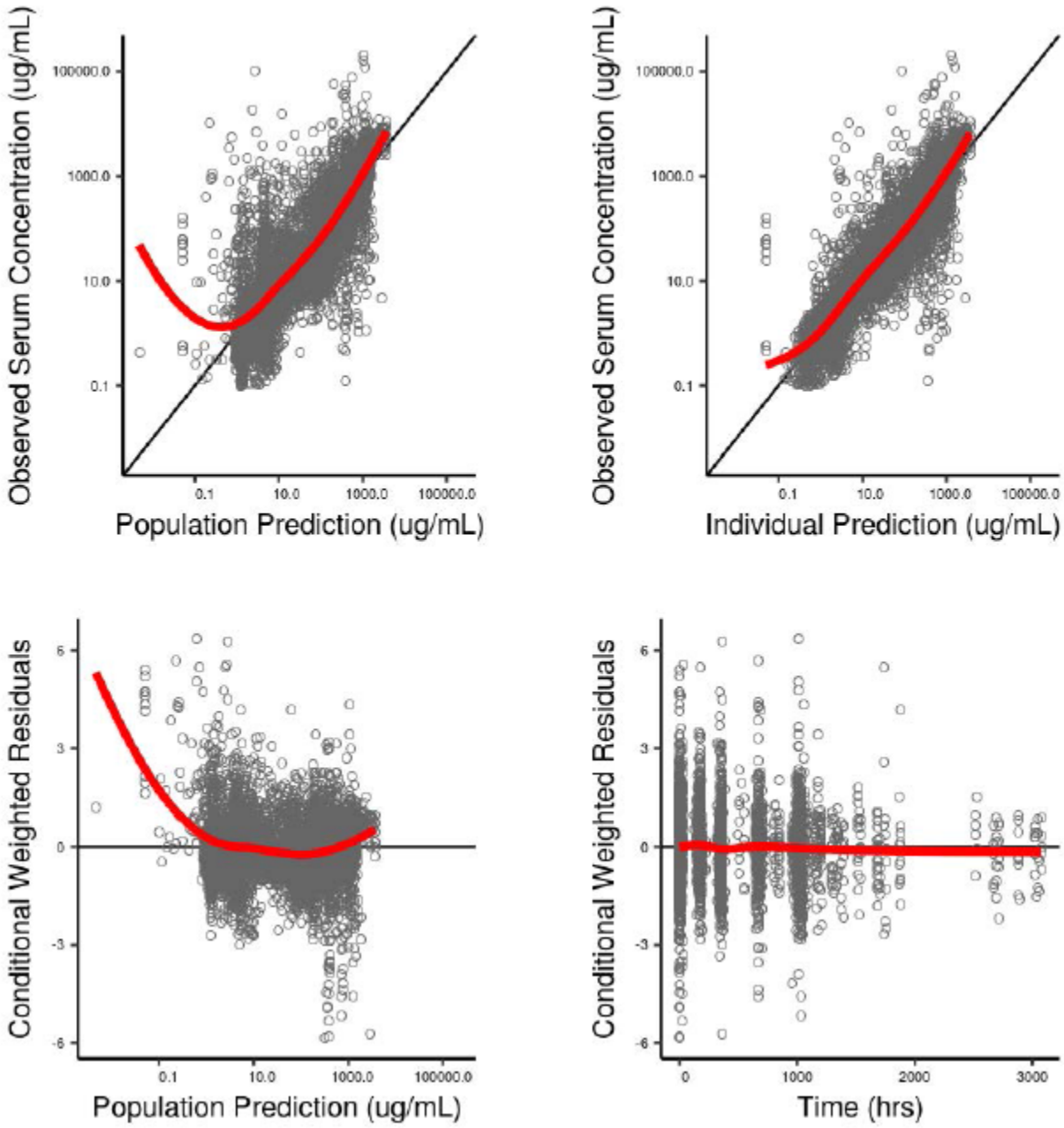
Figure 8 shows the goodness-of-fit plots for the final structural model.

Table 33. Parameter Estimates and Relative Standard Errors for the Base and Final Models.

Parameter	Base Model	Final Model
MVOF	9793.387	9751.316
CL (L/h)	110.2 (4)	109.6 (4)
V_1 (L)	17.6 (4)	17.5 (4)
V_2 (L)	4626.3 (15)	4694.9 (14)
Q (L/h)	76.7 (7)	77.2 (6)
Power for BSA on CL		1.2 (15)
ωCL (%)	44.1 (11)	40.7 (12)
ωV_2 (%)	121.8 (17)	120 (16)
ωQ (%)	58.2 (19)	56.7 (17)
Cor V_2-Q	0.50 (33)	0.42 (34)
$\sigma_{prop\ (sparse\ sampling\ studies)}$ (%)	149 (0.8)	150 (0.8)
$\sigma_{prop\ (intense\ sampling\ studies)}$ (%)	112 (0.6)	110 (0.6)

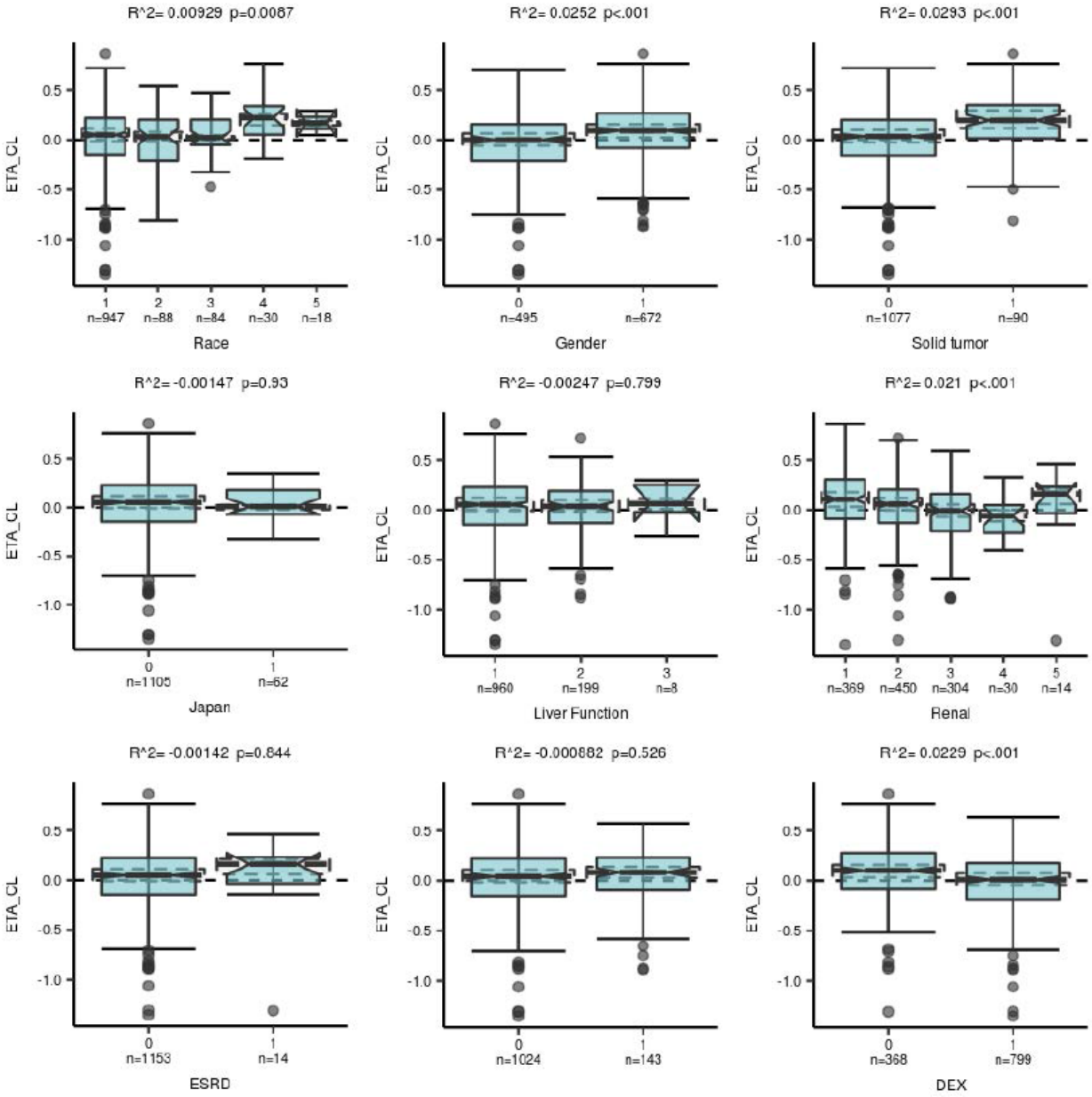
(Source: Applicant's Population PK Report, Table 5)

Figure 8. Goodness of fit plots for the Final Model. Red lines depicted are loess smooth lines.



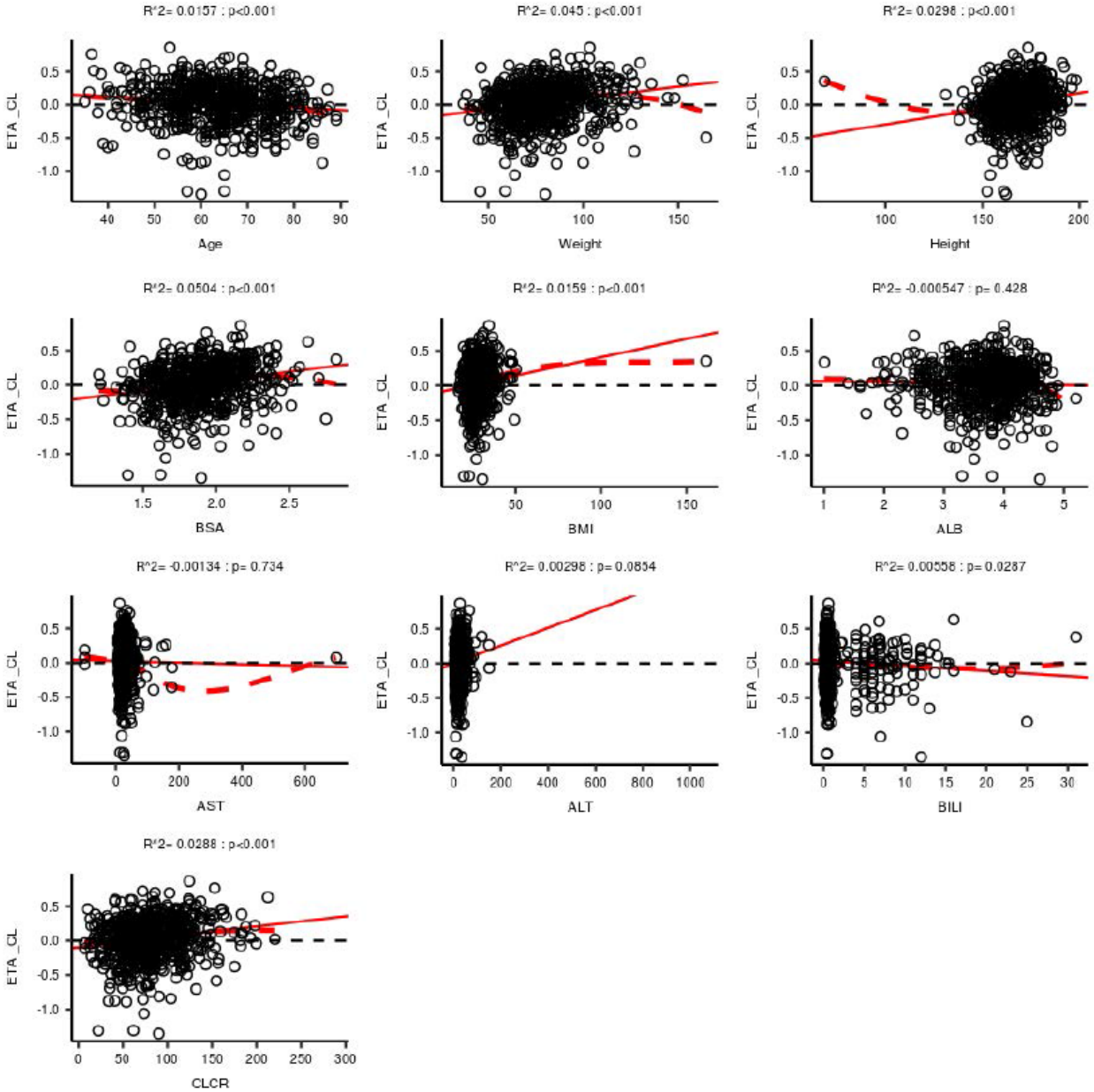
(Source: Applicant's Population PK Model, Figure 22)

Figure 9. Relationship between the Interindividual Random Effect for CL and Covariates (Race, Gender, Solid Tumor, Japanese, Liver Function, Renal Impairment, ESRD, Lenalidomide, Dexamethasone DDI) for the Base Model



(Source: Applicant's Population PK Report, Figure 16)

Figure 10. Relationship between the Interindividual Rand Effect for Systemic Clearance and Covariates



(Source: Applicant's Population PK Report, Figure 19)

Applicant's Conclusions:

"1. A two-compartment pharmacokinetic model with a linear elimination process from the central compartment was deemed appropriate to describe the pharmacokinetics of carfilzomib after single and/or multiple intravenous administrations in target patients.

2. Within the dose range of 15 to 88 mg/m2, there was no evidence of dose- or time-dependent pharmacokinetics.

3. Within the range of values evaluated, only BSA had a significant impact on carfilzomib pharmacokinetic parameter CL. As carfilzomib dose was already given based on BSA in all the studies, adjustment of carfilzomib dosing on the basis of these covariates was deemed unwarranted.

4. Inter- and intra-individual variability in carfilzomib distribution and elimination were relatively moderate to high (40~120%). This is not unexpected given the observed variability in the pharmacokinetic profiles in the target population."

Reviewer's Comments:

The Applicant's population PK model appears to capture the central tendency of the data. Combined with the low relative standard errors for the parameter estimates the model is acceptable for generating exposure metrics for the exposure-response analysis and describing carfilzomib PK in the label. The reviewer's assessment is consistent with the Applicant's that age, gender, race, dexamethasone DDI, mild liver impairment (as indicated from AST and BILI), and renal impairment are not significant covariates of carfilzomib clearance. Additionally, eta values for CL did not appear to correlate for these covariates in the base model (see Figure 9 and Figure 10).

Applicant's Exposure Response Analysis:

The Applicant conducted an exposure response for efficacy and safety with the following objectives: "

1. Examine the carfilzomib exposure-response relationships for efficacy in a randomized phase 3 Study 20140355 (A.R.R.O.W.) assessing carfilzomib at 20/70 mg/m2 plus dexamethasone (n = 53) once-weekly and 20/27 mg/m2 twice-weekly (n = 36).
2. Examine the carfilzomib exposure-response relationships for efficacy randomized phase 2 Study 2012-002 (CHAMPION-1) assessing carfilzomib at 20/70 mg/m2 plus dexamethasone (n = 21) and at 20/88 mg/m2 plus dexamethasone (n = 6) twice-weekly.
3. Summarize the results of a previously done carfilzomib exposure-response analysis (Study 121604) for efficacy in a randomized phase 3 Study 2011-003 (ENDEAVOR) assessing carfilzomib at 20/56 mg/m2 plus dexamethasone (n = 133) twice-weekly.
4. Conduct pooled analysis of the carfilzomib exposure-response relationships for efficacy and safety endpoints on pooling study 20140355 (A.R.R.O.W.) with the phase 1/2 study, Study 2012-002 (CHAMPION 1) and the phase 3 study, 2011- 003 (ENDEAVOR)."

The exposure-response analysis dataset consisted of subjects who had intensive or sparse PK samples from A.R.R.O.W., CHAMPION-1, and ENDEAVOR. Dosing data from each of the three studies were combined with post hoc subject-level PK parameter estimates obtained from the population PK model as described in the population PK report (Study 150597). The combined

individual dosing and PK parameters were used to estimate Cmax and AUC exposures for each dose. Exposure Response was evaluated for the following efficacy and safety endpoints:

Efficacy:

- Overall response rate (stringent complete response, complete response, very good partial response, or partial response)
- Clinical Benefit Rate
- Progression Free Survival
- Duration of Response

Safety:

- Overall AEs
- Any Grade Treatment Emergent AEs
- Grade 3 or Higher AEs
- Any grade: Cardiac Failure, Ischemic Heart Disease, Hepatic AE, Transaminase Elevation, Dyspnea, Pulmonary Hypertension, Interstitial Lung Disease, Acute Renal Failure (≥ Grade 3), ≥ Grade 3 Hypertension, ALT/AST Elevation

The following exposure metrics were computed based on the final population PK model (Study 150597). Each exposure metric was calculated using the individual subjects' parameters from the population PK model and dosing history.

The exposure metrics Cmax.C1D1, AUC.C1D1, Cmax.peak, and AUC.C1avg were used for the efficacy analysis. AUC.C1D1, Cmax.[ae], AUC.C1avg, and AUC.[ae] were used in the safety analysis. Cmax.[ae] and AUC.[ae] were computed for each safety endpoint for which an adverse event occurred. When a subject had no adverse event in a safety category, Cmax.peak was used for the Cmax.[ae] value and AUC0-lastdose was used for the AUC.[ae] value. Cmax and AUC were included in the model as continuous variables.

- AUC (ng•h/mL) and C_{max} (ng/mL) on cycle 1 day 1 ($AUC_{.C1D1}$ and $C_{max.C1D1}$) were calculated as follows:

  $AUC_{.C1D1}$ = dose in cycle 1 day 1 [mcg] / CL [L/h]

  $C_{max.C1D1} = C(T_{Inf}) = \frac{dose}{T_{Inf}}\left(\frac{A}{\alpha}(1-e^{-\alpha T_{Inf}}) + \frac{B}{\beta}(1-e^{-\beta T_{Inf}})\right)$, using dose (mcg) in cycle 1 day 1
- Average daily AUC (ng•h/mL) (based on average dose in cycle 1 ($AUC_{.C1avg}$) was calculated as follows:

  $AUC_{.C1avg}$ = (Total $dose_i$ in cycle 1 [mcg] / 28 days in cycle 1) / CL [L/h]
- C_{max} (ng/mL) at the highest dose in cycle 1 ($C_{max.peak}$)

  $C_{max.peak} = C(T_{Inf}) = \frac{dose}{T_{Inf}}\left(\frac{A}{\alpha}(1-e^{-\alpha T_{Inf}}) + \frac{B}{\beta}(1-e^{-\beta T_{Inf}})\right)$, using highest dose (mcg) in cycle 1
- For all the safety endpoints, additional PK parameter, C_{max} for the dose administered immediately before the adverse event ($C_{max.[ae]}$) was also estimated.

  $C_{max.[ae]}$ (ng/mL) $= C(T_{Inf}) = \frac{dose}{T_{Inf}}\left(\frac{A}{\alpha}(1-e^{-\alpha T_{Inf}}) + \frac{B}{\beta}(1-e^{-\beta T_{Inf}})\right)$, using the highest dose (mcg) immediately before the event
- For all safety endpoints, an additional PK parameter, AUC until the instance of an adverse event ($AUC_{.[ae]}$) was assessed using the differential PK equations. For subjects not showing the particular AE, the AUC until 24 hours after the last dose ($AUC_{0\text{-lastdose}}$) was calculated using the differential PK equations.

Model Development and Validation:

"In the current exploratory analysis, the association between each of the efficacy and safety endpoints and each of the exposure metrics was investigated. The efficacy endpoint, DOR was analyzed for studies 2011-003, 2012-002 and 20140355 data separately using log-rank test on the exposure quartiles. The efficacy analysis of ORR, CBR and PFS was performed on all three studies, 2011-003, 2012-002 and 20140355 separately, and as a pooled analysis of these three studies. The efficacy endpoints, ORR and CBR, and all of the aforementioned safety endpoints were analyzed using logistic regression models. DOR and PFS were analyzed using log-rank test on the exposure quartiles. Model parameters were estimated for each endpoint using the exposure metrics Cmax and AUC on day 1 in cycle 1 and peak Cmax and average AUC in cycle 1, as described in Section 6.3.1.3. For the safety endpoints, Cmax in cycle 1 was replaced with Cmax.[ae] from the dose preceding the adverse event. AUC.[ae] was also evaluated as an additional metric. The estimate of slope (for logistic models) and associated p-value (from

likelihood ratio test) were used to determine if an exposure metric was statistically significantly correlated to an increase in response or adverse event rate.

Statistically significant covariate effects were identified in the multiple logistic regression analysis by the use of an automated search procedure. Subjects with missing covariates were initially dropped from the dataset. Then, a stepwise forward/backward elimination algorithm was utilized that adds covariates to the model in stages, where at each stage the covariate that results in the greatest drop in the Akaike Information Criterion (AIC) for the model is incorporated in the model. When no unincorporated covariate improves AIC, the algorithm attempts to prune the model, in stages, by removing at each stage a covariate if doing so will further decrease AIC. The process was complete when no further removal of covariates decreased the AIC. A backward elimination only algorithm was also employed, where only the pruning process was conducted on the model that included all possible covariates.

The better of the 2 resulting models by AIC (stepwise or backward) was further refined. First, the dataset was expanded to include all subjects who had non-missing values for the covariates or responses identified by the stepwise model. This allowed for increase in sample size when covariates with a large proportion of missing values ended up excluded by the covariate selection process. Then the models were further reduced by removing covariates that were not statistically significant according to the likelihood ratio test (statistical significance level α = 0.05). This methodology made use of all possible data while avoiding biases that could arise from data imputation."

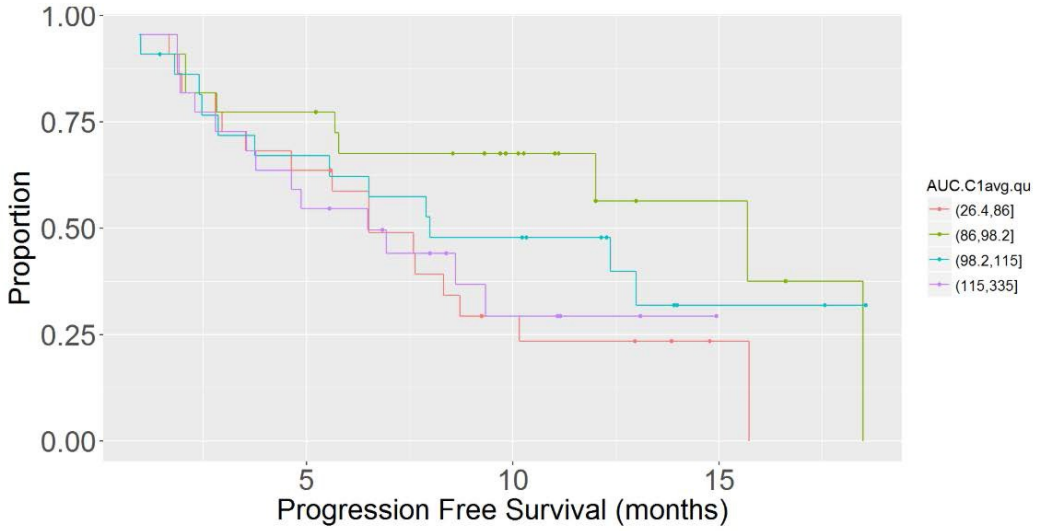
Results for E-R efficacy:

Individual Study Assessment for A.R.R.O.W. (Study 2014-0355)

The time-to-event analysis for PFS and DOR was performed in subjects based on quartiles of carfilzomib exposure (AUC or Cmax). Kaplan-Meier curves of PFS based on quartile of carfilzomib average AUC in cycle 1 are shown in Figure 11.

"The exposure-response analysis of efficacy endpoints in subjects from Study 20140355 alone, in which all subjects received either a 20/27 mg/m2 dose or a 20/70 mg/m2, did not show any statistically significant relationship between AUC.C1avg and Cmax.peak and the primary efficacy endpoints, PFS, DOR, ORR and CBR. PFS shows a statistically significant relationship with AUC.C1D1 within Study 20140355. However, this relationship is more likely to be an artefact of BSV since all subjects received the same dose on day 1 and the Kaplan Meier plot for PFS vs AUC.C1D1 shows mostly overlapping curves with no apparent trend (Figure 11)."

Figure 11. Kaplan-Meier Curves of PFS for Carfilzomib in Study 20140355 (A.R.R.O.W.) Based on Quartile of Cycle 1 Average AUC



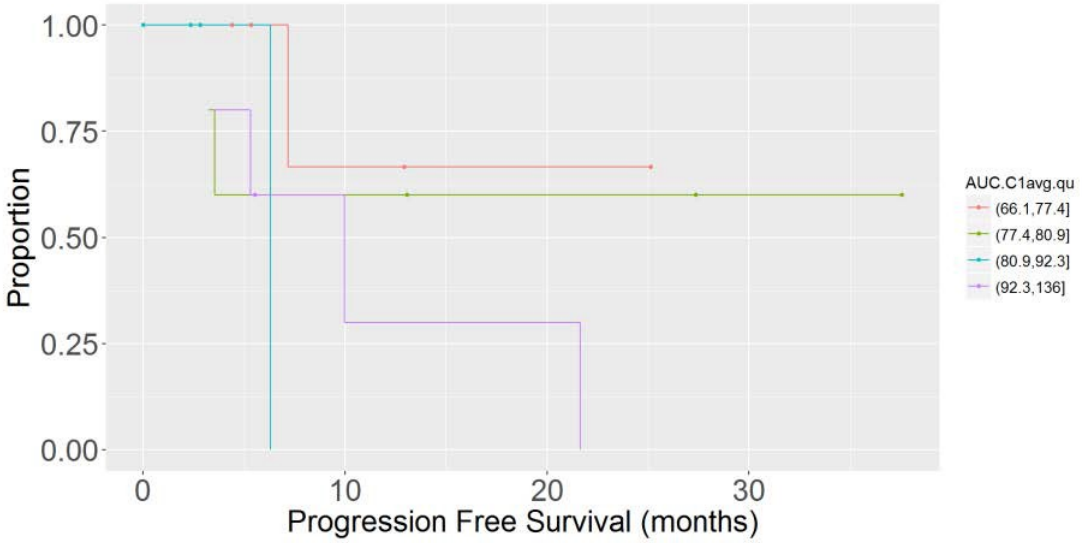
AUC = area under the concentration-time curve; AUC.C1avg.qu (ng•h/mL) = quartiles of average daily AUC in cycle 1;

(Source: Applicant's Pharmacometric Report 125697, Figure 1)

Individual Study Assessment for CHAMPION 1 (Study 2012-002):

"The time-to-event analysis for PFS and DOR was performed in subjects based on quartiles of carfilzomib exposure (AUC or Cmax). The exposure-response analysis of efficacy endpoints in subjects from Study 2012-002 alone, in which all subjects received either a 20/70 mg/m2 dose or a 20/88 mg/m2, did not show any statistically significant relationship between the exposure metrics and the efficacy endpoints, PFS, DOR, ORR and CBR except the one between Cmax.peak and CBR. However, this inference is not reliable as data from only 19 subjects was available for conducting the exposure-efficacy relationship with CBR and the model did not converge appropriately." Kaplan-Meier curves of PFS based on quartile of carfilzomib average AUC in cycle 1 are shown in

Figure 12. Kaplan-Meier Curves of PFS for Carfilzomib in Study 2012-002 (CHAMPION-1) Based on Quartile of Cycle 1 Average AUC



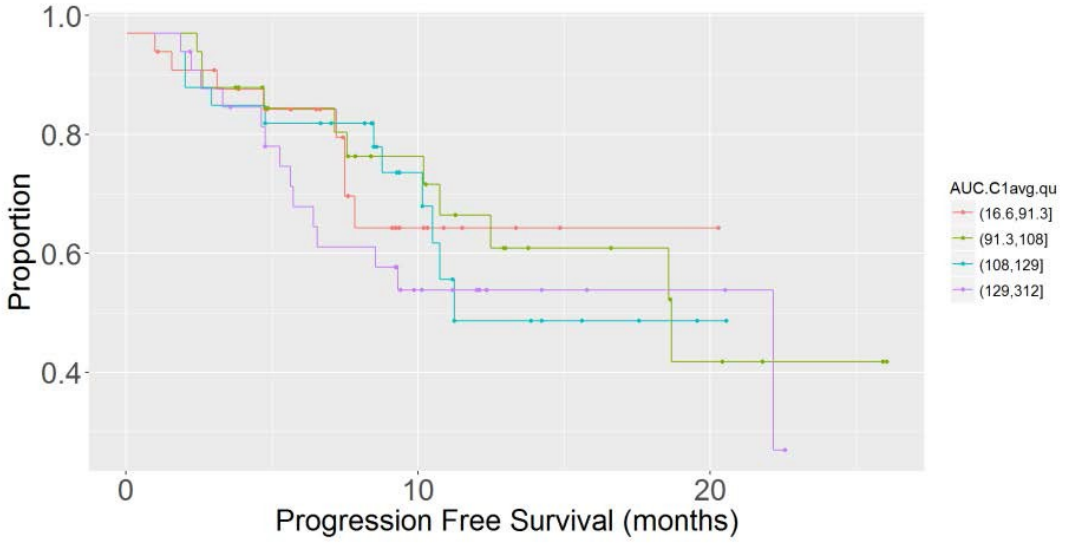
AUC = area under the concentration-time curve; AUC.C1avg.qu (ng•h/mL) = quartiles of average daily AUC in cycle 1;

(Source: Applicant's Pharmacometric Report 125697, Figure 1)

Individual Study Assessment for ENDEAVOR (Study 121604):

"The time-to-event analysis for PFS and DOR was previously performed in subjects based on quartiles of carfilzomib exposure (AUC or Cmax). Kaplan-Meier curves of PFS based on quartile of carfilzomib average AUC in cycle 1 are shown in Figure 13 (Study 121604). The Kaplan-Meier curves did not show any apparent relationships between any of the exposure measures (neither AUC nor Cmax) to PFS, the primary endpoint of this study (Figure 3), or DOR. The differences between PFS among exposure quartiles were not significant by log-rank test. The exploratory analysis of efficacy endpoints in Study 2011-003 showed no statistically significant relationships between carfilzomib exposure (AUC or Cmax) and either ORR or CBR (Study 121604)."

Figure 13. Kaplan-Meier Curves of PFS for Carfilzomib in Study 2011-003 (ENDEAVOR) Based on Quartile of Cycle 1 Average AUC (121604)



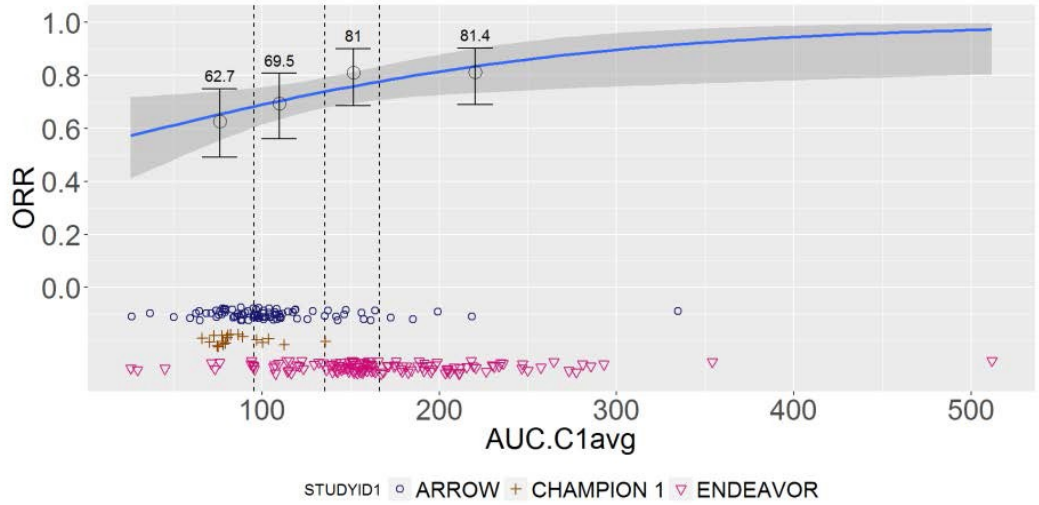
AUC = area under the concentration-time curve; AUC.C1avg.qu (ng•h/mL) = quartiles of average daily AUC in cycle 1;

(Source: Applicant's Pharmacometric Report, Figure 3)

Pooled Analysis of A.R.R.O.W., CHAMPION 1, and ENDEAVOR Clinical Trials:

"When combining data from all the studies in a pooled exposure response analysis of efficacy endpoints, the results of the exploratory efficacy analysis indicated a relationship between carfilzomib AUC.C1avg and response category ORR as determined by logistic regression (N = 235, 2-sided $p < 0.001$), with AUC.C1avg associated with increases in ORR over a dose range of the three studies (Figure 14). The mean ORR in the first and fourth quartile of average AUC (76.11 to 220.34 ng•h/mL) in cycle 1 were 62.7% and 81.4%, respectively. However, after adjusting for baseline characteristics and prognostic factors, AUC.C1avg was no longer associated with an increase in ORR. This analysis resulted in the conclusion that the ORR is no longer significant with AUC.C1avg when a covariate (PRI1 - no. of prior regimens = 1) is considered. However, it is important to note that in the pooled studies, this covariate is confounded by the exposures. Only subjects in 2011-003 and 2012-002, the two studies with the higher total cycle 1 doses, had subjects with 1 prior line of therapy. Therefore, PRI1 could potentially be a "surrogate" for the exposure itself."

Figure 14. Logistic Regression of the Probability of Overall Response Versus AUC (Pooled Analysis)



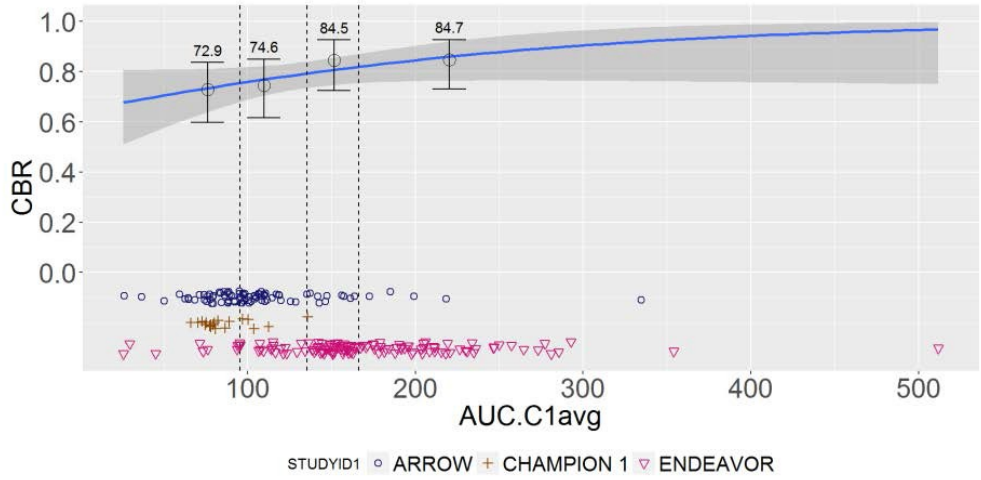
AUC = area under the concentration-time curve; $AUC_{.C1avg}$ = average AUC in cycle 1; ORR = overall response rate

Blue line indicates predicted probability of response. Gray ribbon indicates 95% confidence interval of predicted response. Black circles, vertical error bars and numbers indicated the observed response rate (mean and 95% confidence interval) within each quartile of exposure. Quartiles of exposure are separated by dashed lines. Individual exposure values from each study are shown as colored points.

(Source: Applicant's Pharmacometric Report, Figure 5)

"No statistically significant relationships were seen between AUC.C1avg and CBR or PFS (Figure 15, Figure 16). However, positive trends in the data suggest that higher exposures tend to result in longer PFS, consistent with the therapeutic benefit of carfilzomib."

Figure 15. Logistic Regression of the Probability of Clinical Benefit Versus AUC (Pooled Analysis)

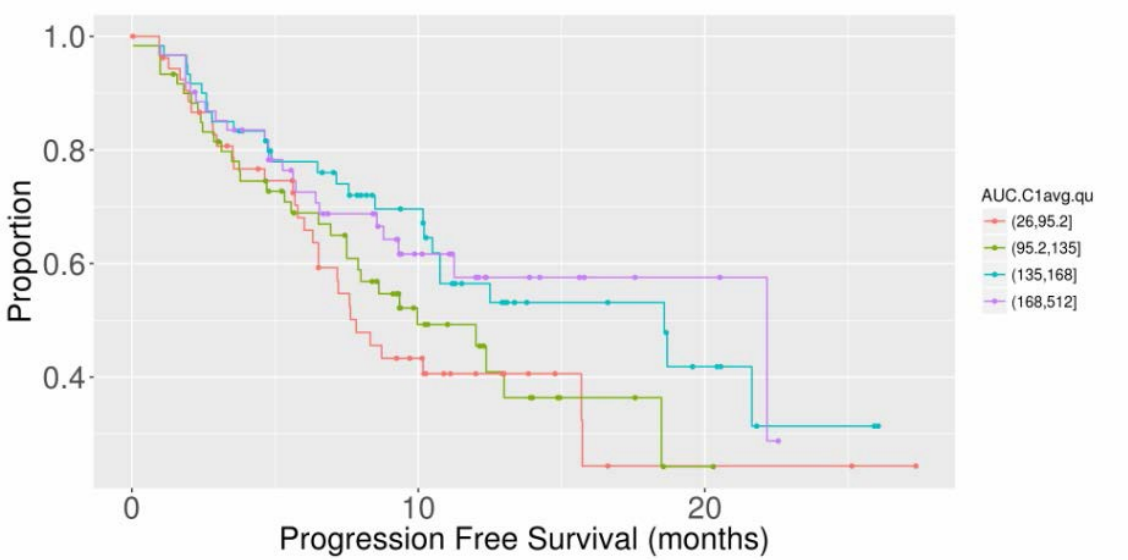


AUC = area under the concentration-time curve; $AUC_{.C1avg}$ = average AUC in cycle 1; CBR = clinical benefit rate

Blue line indicates predicted probability of response. Gray ribbon indicates 95% confidence interval of predicted response. Black circles, vertical error bars and numbers indicated the observed response rate (mean and 95% confidence interval) within each quartile of exposure. Quartiles of exposure are separated by dashed lines. Individual exposure values from each study are shown as colored points.

(Source: Applicant's Pharmacometric Report, Figure 6)

Figure 16. Kaplan-Meier Curves of PFS for Carfilzomib Based on Quartile of Cycle 1 Average AUC (Pooled Analysis)



AUC = area under the concentration-time curve; AUC.C1avg.qu (ng•h/mL) = quartiles of average daily AUC in cycle 1

(Source: Applicant's Pharmacometric Report, Figure 17)

Results for E-R safety:

"After inclusion of different populations (relapsed or relapsed/refractory) and different doses (from 20/27 mg/m2 to 20/70 mg/m2) in the pooled dataset, the results from the pooled analysis of safety endpoints indicated that acute renal failure (broad, grade 3+) showed a statistically significant relationship to AUC.C1D1. However, the incidence of this AE is very low (<5%) and it is related to a short-term exposure metric which is supported by studies that have found that carfilzomib causes some kidney injury on initial administration which is reversible and is not seen after administration of subsequent doses.

No positive statistically significant relationships between any of exposure parameters and the proportion of subjects with any grade dyspnea, any grade cardiac failure (SMQN), any grade ischemic heart disease, any grade hepatic failure, pulmonary hypertension, any grade interstitial lung disease, any grade chronic kidney disease, any acute renal failure (SMQN or ≥ grade 3) or any chronic kidney disease (SMQN or ≥ grade 3) was identified."

Reviewer's Comments:

The Applicant's exposure-response analysis is reasonable. As PK data was only collected in a subset (<30%) of patients from study A.R.R.O.W., CHAMPION-1, and ENDEAVOR. The reviewer conducted exploratory analysis to check whether patients in E-R dataset are representative of the overall population. As shown in Figure 17 *for study A.R.R.O.W., the PFS in the E-R analysis set (n=53) overlaps with the full analysis set (n=238) for the 20/70 mg/m^2 arm. Whereas for the 20/27 mg/m^2 arm, the PFS appears to be shorter in the E-R analysis set. For ENDEAVOR* Figure 18*, the subjects in the ER analysis set (n=105) had longer PFS compared with the full analysis set (n=356). As such, there is some concern that the trends in ER could be a result of the ER analysis set not representing the full analysis set for ENDEAVOR. Multivariate analysis should account for this difference however if all the inherent risk factors have been identified. In this case only the number of prior therapies was identified as a significant risk factor and exposure no longer had significance after accounting for the risk factors.*

Figure 17. Survival Probability Curves for Progression Free Survival in the A.R.R.O.W. Study

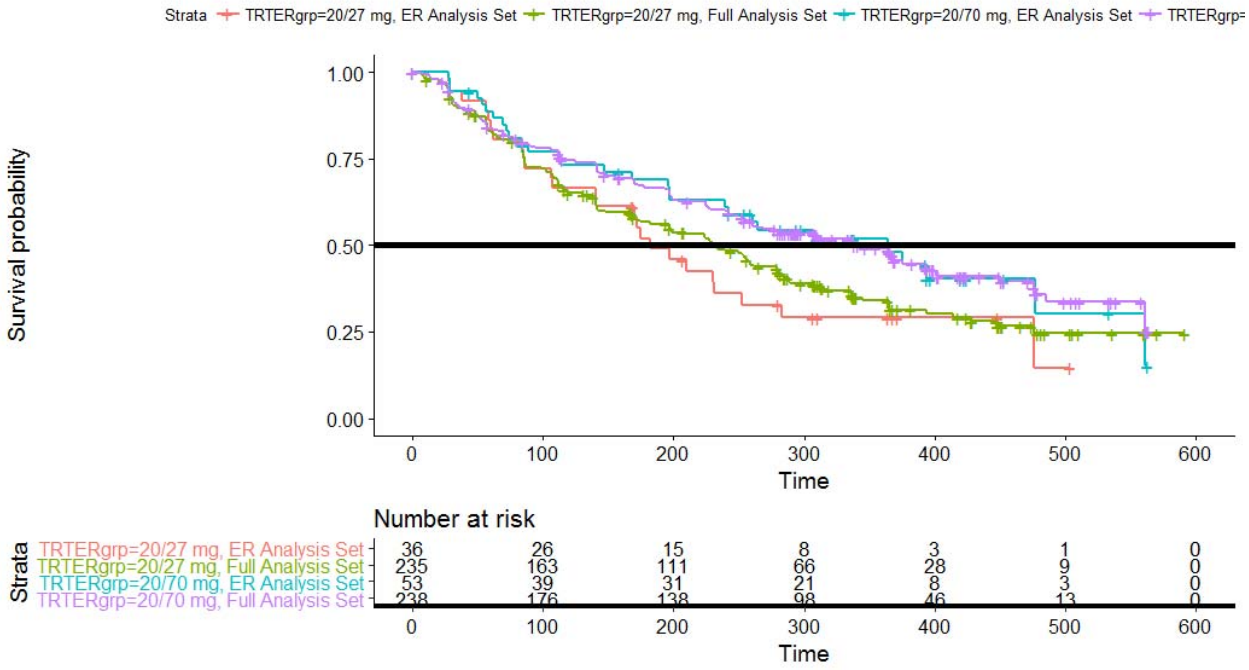
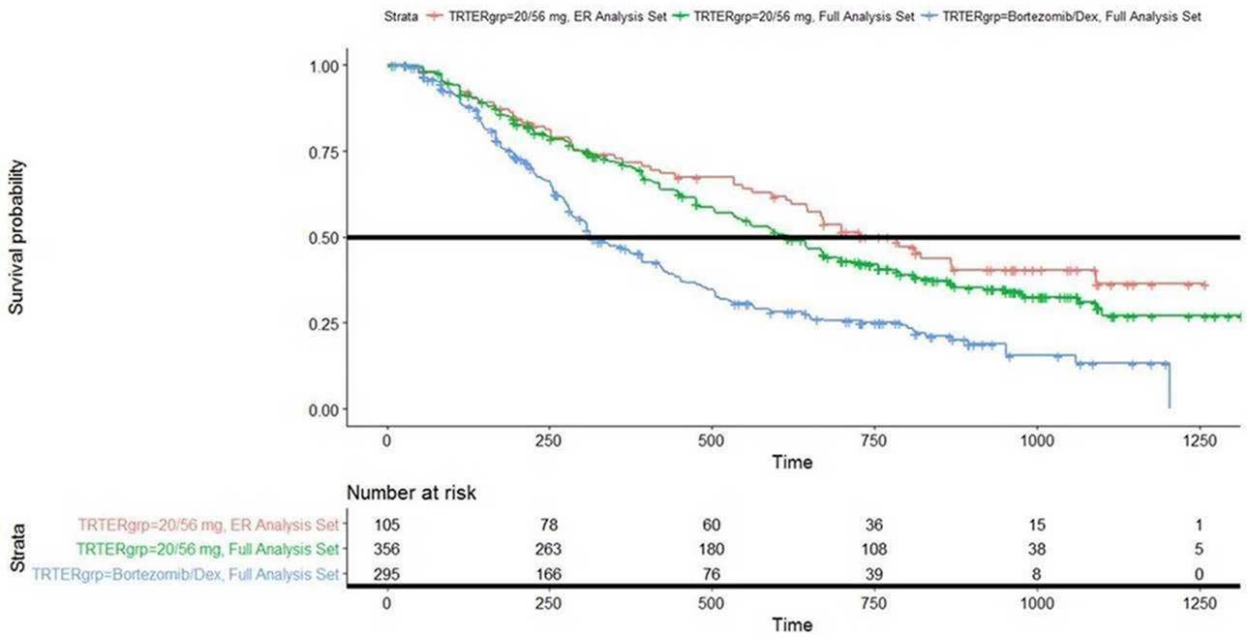


Figure 18. Survival Probability Curves for Progression Free Survival in the ENDEAVOR Study



17.4. Additional Safety Analyses Conducted by FDA

Not Applicable

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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09/27/2018

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QING XU
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YUAN L SHEN
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