1. ABSTRACT

- **Title**

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

  Date: 13 January 2023

- **Keywords**

  Carfilzomib (K), carfilzomib in combination with dexamethasone (Kd), Kyprolis®, benefit-risk, pooled analysis, multiple myeloma

- **Rationale and Background**

  This study was conducted to fulfill a United States (US) Food and Drug Administration (FDA) postmarketing commitment (3022-2) to characterize the comparative safety and efficacy and to provide a comprehensive analysis of the clinical factors that may inform the choice of dose regimen of K or Kd 20/27 or 20/56 mg/m^2 twice-weekly. The aim of this post hoc pooled analysis was to characterize the safety and efficacy of K dosing regimens and to evaluate data from Amgen-sponsored clinical studies to determine a favorable or unfavorable association of clinical parameters associated with the efficacy and safety outcomes of subjects treated with 1 of 4 different dosing regimens (K27, Kd27, K56, Kd56).

- **Research Question and Objectives**

  To evaluate the favorable or unfavorable association of the clinical parameters with efficacy and safety outcomes for each K dosing regimen (20/27 mg/m^2 and 20/56 mg/m^2) with or without dexamethasone, which may inform the choice of K dose.

  Primary Objective:

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

  Secondary Objective:

  - To compare efficacy and safety outcomes for K dosing regimens with dexamethasone (Kd27 vs Kd56).

  Exploratory Objective:

  - To compare efficacy and safety outcomes for K27 dosing regimens without and with dexamethasone (K27 vs Kd27).

- **Study Design**

  This was a retrospective, post-hoc, pooled analysis of 13 Amgen-sponsored interventional carfilzomib studies using internal data from Onyx-owned databases and the Amgen RAVE database. For the primary objective, data from these clinical trials were pooled to evaluate efficacy (overall response rate [ORR] and progression-free survival [PFS]) and safety outcomes (prespecified events of interest [cardiac failure, acute renal failure, hypertension, ischemic heart disease, torsades des pointes] and fatal adverse events) for each K dosing regimens (K27, Kd27, K56, Kd56). In addition, a propensity score matching procedure was followed to create

Matched Analysis Sets, which were used to compare the efficacy and safety outcomes for Kd56 vs Kd27 and for K27 vs Kd27.

- **Setting**

  Eligible subjects were from Amgen sponsored clinical studies conducted between 2005 and 2019, with a data cutoff of 14 July 2019.

- **Subjects and Study Size**

  The 13 clinical studies included in this analysis included subjects with relapsed or refractory multiple myeloma who received consistent K dosing regimens of 27 or 56 mg/m^2 twice weekly for 3 of the 4-week cycles for all cycles of treatment.

  To avoid the anticipated variations in the sample sizes and data variables collected for these clinical trials, a primary analysis was preformed to prevent the introduction of extra variation to the pooled data and a subsequent sensitivity analysis.

  The primary data analysis set included clinical studies with at least 20 subjects in each of K dosing regimen and at least 80% completeness of data for each variable. The sample size was 564 subjects from 5 clinical studies for K monotherapy and 1199 subjects from 6 clinical studies for Kd. In the primary analysis data set, Kd group had the largest sample size that provided robust analysis of Kd27 (n = 583) and Kd56 (n = 616), to summarize potential clinical parameters that may impact the choice of K regimens.

  In the propensity score matched analysis sets, the sample size was 176 subjects for Kd56 and 176 subjects for Kd27, and 187 subjects for Kd27 and 187 subjects for K27.

  The sensitivity data analyses consist of all trials that meet the eligibility criteria without regard to sample size or completeness of data. The sample size for the sensitivity analysis was 604 subjects from 9 clinical studies for K monotherapy, and 1213 subjects from 9 clinical studies for Kd.

- **Variables**

  The clinical parameters for analysis for efficacy outcomes included PFS and ORR. Safety outcomes included incidence of grade 3 or higher, serious, and fatal adverse events of special interest as well as fatal adverse events. The adverse events of special interest include acute renal failure, hypertension, cardiac failure, ischemic heart disease, Torsades des pointes including QT prolongation, and fatal adverse events.

- **Data Source and Methods**

  For this study, internal data from 13 interventional clinical studies were pooled from Onyx-owned databases and the Amgen RAVE database.

  In the original studies included in this report, all subject data were recorded on case report forms (CRFs) unless transmitted to the sponsor electronically. The investigator verified the accurate data entries by signing the CRF. Clinical monitors performed source data verification to confirm that CRF data were accurate. The sponsor data management department performed the edit checks outlined in the data management plans. The sponsor validated the analysis datasets and variables of each individual clinical study in this pooled analysis. All data among sources were linked based on the unique identifier for each subject.

- **Results**

K Dosing Regimens

- In the K27 group, median PFS (95% CI) was 6.6 (5.8, 8.3) months and the ORR was 28.1% (95% CI: 24.4, 32.1). In the K56 group, the median PFS (95% CI) was 7.0 (1.9, NE) months and the ORR was 45.8% (95% CI: 25.6, 67.2).
- In the K27 group, the median duration (range) of K administration was 18.29 weeks (0.3 to 160.4 weeks) and median cumulative dose (range) received was 741.00 mg/m^2(40.0 to 5791.0 mg/m^2). In the K56 group, the median duration (range) of K administration was 11.21 weeks (0.3 to 153.3 weeks) and median cumulative dose (range) received was 867.64 mg/m^2(36.4 to 11179.6 mg/m^2).
- The incidence of prespecified adverse event of interest and fatal adverse events in the K27 and K56 groups were consistent with the known safety profiles of these treatment regimens (as expected for this previously generated and reported clinical trials data).
- Overall, efficacy and safety results in K dosing regimens were consistent across clinically meaningful subgroups.

Kd Dosing Regimens

- In the Kd27 group, the median PFS (95% CI) was 6.9 (5.6, 7.6) months and the ORR was 31.0% (95% CI: 27.3, 35.0). In the Kd56 group, the median PFS (95% CI) was 16.6 months (14.9, 19.4), and the ORR was 78.6% (95% CI: 75.1, 81.7).
- In the Kd27 group, the median duration of carfilzomib administrations was 19.29 weeks (0.1 to 156.3 weeks) and median cumulative dose received was 765.27 mg/m^2(19.6 to 6049.8 mg/m^2). In the Kd56 group, the median duration of carfilzomib administrations was 46.14 weeks (0.3 to 261.3 weeks) and median cumulative dose received was 3281.27 mg/m^2(39.6 to 20093.2 mg/m^2).
- The incidence of prespecified adverse event of interest and fatal adverse events in the Kd27 and Kd56 groups were consistent with the known safety profiles of these treatment regimens (as expected for this previously generated and reported clinical trials data).
- Overall, efficacy and safety results in Kd dosing regimens were consistent across clinically meaningful subgroups.

Kd56 vs Kd27

- After propensity score matching, the median PFS (95% CI) was 6.9 (95% CI: 5.1, 8.3) months for the Kd27 group and 10.4 (95% CI: 8.3, 14.5) months for the Kd56 group. The HR of 0.588 [95% CI: 0.457, 0.757]) supports a clinically meaningful improvement in PFS for patients treated with Kd56. The ORR was 38.6% (95% CI: 31.4, 46.3) in the Kd27 group and 67.0% (95% CI: 59.6, 73.9) in the Kd56 (OR: 3.231 [95% CI: 2.088, 5.001]).
- After propensity score matching, the analysis of prespecified adverse events of interest and fatal adverse events did not demonstrate a clinically meaningful difference in the safety of Kd56 vs Kd27.

- Overall, in the Kd56 vs Kd27 matched analysis set, efficacy and safety results were consistent across clinically meaningful subgroups. No subgroup was identified for which outcomes are improved with Kd27 as compared to Kd56.

K27 vs Kd27

- After propensity score matching, the median PFS (95% CI) was 5.6 (95% CI: 4.3, 6.5) months in the K27 group and 7.4 (95% CI: 4.6, 10.4) months for the Kd27 group (HR [Kd27 vs K27]: 0.830 (95% CI: 0.606, 1.137). The ORR was 14.4% (95% CI: 9.7, 20.3) in the K27 group and 16.0% (95% CI: 11.1, 22.1) in the Kd27 group (OR [Kd27 vs K27]: 1.132 [95% CI]: 0.644, 1.992).
- After propensity score matching, the analysis of prespecified adverse events of interest and fatal adverse events did not demonstrate a clinically meaningful difference in the safety of K27 vs Kd27.
- Overall, in the K27 vs Kd27 matched analysis, efficacy and safety results were consistent across clinically meaningful subgroups. No subgroup was identified for which outcomes are improved with K27 as compared to Kd27.

- **Discussion**

The results of this study summarized the comparative safety and efficacy of K dosing regimens (K27, Kd27, K56, Kd56). Analyses after propensity matching showed Kd56 to have better efficacy and similar safety outcomes as Kd27. The median PFS and ORR were higher in the Kd56 group compared with the K27, Kd27, or K56 groups. In addition, the Kd56 group had a longer median duration of carfilzomib administration with higher cumulative dose received than in other K groups. Overall, matched analyses were consistent in both efficacy and safety outcomes across clinically important subgroups. The safety profile observed in the K and Kd dosing regimens were consistent with the known profile of the study treatments administered and no new safety signals were identified.

- **Conclusion**

Overall, the results of this post-hoc pooled analysis of interventional carfilzomib studies showed that the Kd56 group had better efficacy and similar safety outcomes compared with other K dosing regimens to treat patients with relapsed or refractory multiple myeloma. Additionally, these results were consistent across different clinically important subgroups. Results of sensitivity analyses confirmed the robustness of the primary analysis results. The safety profiles observed in the K and Kd dosing regimens were consistent with the known profiles of these study treatments.

- **Marketing Authorization Holder**

  Amgen Inc.

- **Names and Affiliations of Principal Investigators**

  Not applicable