1. ABSTRACT

- **Title**

Real-world Evidence of the Use of Carfilzomib Among Multiple Myeloma Patients in Europe Who Have Received at Least One Prior Therapy.

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- **Keywords**

Multiple Myeloma, Carfilzomib, Observational Study, Drug Utilisation, Europe

- **Rationale and Background**

At the time carfilzomib was approved in Europe as a treatment option for multiple myeloma (MM), few data were available on how the drug was being used outside of the clinical trial setting. This study therefore provides data to demonstrate the real-world utilisation of carfilzomib.

- **Research Question and Objectives**

  Primary Objective:

  - To describe carfilzomib utilisation in routine clinical practice, including dosage, administration schedule, regimen, duration of treatment, and reason for discontinuation.

  Secondary Objectives:

  - Describe the population treated with carfilzomib in terms of demographics, MM disease characteristics, treatment history, and comorbidities.
  - Describe the safety profile of carfilzomib in routine clinical practice.
  - Describe response to treatment as assessed by the physician and recorded in the medical file.
  - Describe healthcare resource utilisation of subjects treated with carfilzomib, in terms of unplanned hospitalisations.
  - Describe the reasons for choosing carfilzomib as the MM treatment of choice.
  - Describe specific concomitant therapy.
  - Describe a cardiovascular assessment at carfilzomib regimen initiation and at occurrence of cardiac adverse events, where available per routine care.

Exploratory Objectives:

- Describe treatment response as assessed by physician and per International Myeloma Working Group (IMWG) criteria, where recorded per routine practice: duration of response (DOR), time to response, time to best response.
- Describe time to progression.
- Describe primary and relevant secondary outcomes by patient frailty level as recorded by the physician at end of treatment (EOT).
- Describe primary and relevant secondary outcomes, stratified by enrolment in a patient support programme (PSP) while receiving carfilzomib treatment.

- **Study Design**

Observational cohort study in which data were collected through serial review of consenting subjects' medical charts.

- **Setting**

This study was conducted in cancer treatment centres (including academic, local, and, private offices) in selected countries in Europe (Austria, Belgium, Bulgaria, Czech Republic, France, Greece, Italy, the Netherlands, Norway, and Romania) and Israel.

- **Subjects and Study Size, Including Dropouts**

Adult patients with multiple myeloma who had received at least 1 prior therapy prior to receiving carfilzomib in routine clinical practice and who had received at least 1 administration of carfilzomib as prescribed by their physician were considered for enrolment into the study. Patients were considered for enrolment if they provided informed consent (where required), were receiving radiotherapy concurrently with carfilzomib. Patients were excluded if they were enrolled in a clinical trial (although participation in a separate observational study was not an exclusion criteria). A sample size of approximately 800 subjects had been selected for this observational study to permit individual countries (or regions, where applicable) to enrol between 100 and 200 subjects. A total of 705 subjects were enrolled in study, but 4 subjects were not included in study analyses due to post-enrolment non-compliance with study eligibility criteria.

- **Variables and Data Sources**

Data were collected via review of subjects' patient charts.

Baseline variables include: subject demographic characteristics, medical history, disease and treatment history.

Follow-up variables include: carfilzomib administration, response and safety outcomes; hospitalisations, planned subsequent treatment and use of concomitant medications.

- **Results**

A total of 701 subjects treated with carfilzomib were included in final analysis set. These subjects were enrolled across 113 sites in 11 countries (Austria, Belgium, Bulgaria, Czech Republic, France, Greece, Israel, Italy, Netherlands, Norway, and Romania) from March 2017 to 12 September 2019 and followed-up to study close on 17 March 2020 with over half of subjects (n = 383, 55%) initiated carfilzomib, lenalidomide and dexamethasone (KRd), and 39% (n = 271) initiated carfilzomib and dexamethasone alone (Kd). The remaining subjects (n = 47, 7%) received other carfilzomib-based regimens.

At carfilzomib initiation, KRd subjects were younger than Kd subjects with median age of 65 and 68 years, respectively, and comprised more male subjects, proportionally, than Kd subjects (61.6% and 50.9%, respectively). A large proportion of subjects presented with pre-existing cardiovascular conditions in both cohorts (49.3% for KRd, 61.6% for Kd subjects), mostly attributable to vascular hypertension (35.0% for KRd, 41.7% for Kd). Approximately one-third of KRd and one-fifth of Kd subjects had cytogenetic risk data documented at time of MM diagnosis, with 43.4% and 65.3% of these Kd and KRd subjects, respectively, having had high/unfavourable cytogenetic risk. One-third of subjects had calculated International Staging System (ISS) status available at carfilzomib initiation; of these, 23.3% KRd and 37.9% Kd subjects were ISS stage 3. Approximately 65% of all subjects had Eastern Cooperative Oncology Group (ECOG) performance assessed at carfilzomib initiation and also had a frailty score (per Palumbo criteria [Palumbo et al, 2015]) derived from available data. Of subjects with

available data, 84.8% of KRd and 80.2% of Kd subjects had an ECOG ≤1. Of those subjects with an available frailty score at carfilzomib initiation, 30.7% of KRd and 51.6% of Kd subjects were defined as frail. The median elapsed time since discontinuation of last prior treatment was 10.30 months for KRd subjects and 1.30 months for Kd subjects with KRd subjects having received a median of 1 prior line of therapy while Kd subjects received a median of 3 prior lines. Nearly all subjects (95.6% of KRd and 97.0% of Kd) had had prior exposure to bortezomib.

Of those subjects with a response assessment (per physician criteria), a high overall response rate (ORR; defined as proportion of assessed subjects with stringent complete response [sCR], complete response [CR], very good partial response [VGPR], or partial response [PR]) of 83.6% was seen in KRd subjects, with 31.7% achieving CR or better and 66.7% achieving a VGPR or better. An ORR of 68.8% was observed in Kd subjects, with 13.2% of subjects achieving CR or better and 43.6% achieving VGPR or better.

ORRs were generally higher for subjects with fewer lines or prior therapy. Among KRd subjects, ORRs ranged from low of 77.1% among those with 3 prior lines of therapy to a high of 85.3% among those with 1 prior line of therapy. Among Kd subjects, ORRs ranged from a low of 60.0% among those with 4+ prior lines of therapy to a high of 79.2% among those with 1 prior line of therapy.

90.6% of KRd and 77.5% of Kd subjects were planned to receive dosing per EU label (20/27 mg/m^2 and 20/56 mg/m^2, respectively). The mean carfilzomib dose received relative to EU label was 94.59% for KRd subjects and 77.64% for Kd subjects.

A total of 224 (58.5%) KRd and 206 (76.0%) Kd subjects discontinued carfilzomib during the study; 14 (3.7%) KRd and 23 (8.5%) of Kd subjects had died by the end of the study and a further 4 (1.0%) KRd and 2 (0.7%) Kd subjects were lost to follow-up. The estimated median (Kaplan-Meier) time to discontinuation was 14.6 months (95% confidence interval [CI]: 12.9, 16.4) for KRd and 7.7 months (95% CI: 6.5, 9.0) for Kd subjects during a median follow-up (estimated using reverse Kaplan-Meier method) of 17.7 months (95% CI: 17.3, 17.7) and 17.5 months (95% CI: 16.8, 17.9) for KRd and Kd subjects, respectively.

Common Terminology Criteria for Adverse Events (CTCAE) grade 3 and above treatment-emergent AEs (CTCAE 3+) were reported for 48.0% of KRd and 45.0% of Kd subjects, with 24.5% of KRd and 20.7% of Kd subjects experiencing events considered to be treatment related. Most frequently reported events (at MedDRA System Organ Class [SOC] level) were, for KRd subjects, blood disorders (19.8%), infections and infestations (14.4%), and vascular disorders (7.0%); among Kd subjects these were infections and infestations (17.0%), blood disorders (14.4%), and respiratory, thoracic and mediastinal disorders (8.1%). The most frequent (ie, affecting approximately 1% of all subjects [≥7 subjects]) treatment-emergent treatment-related CTCAE 3+ at preferred term (PT) level for all subjects were neutropenia (5.0%), thrombocytopenia (4.3%), anaemia (4.1%), hypertension (3.7%), and cardiac failure (1.1%). Fatal treatment-related CTCAE 3+ were reported for 0.5% (n = 2) of KRd and 0.7% (n = 2) of Kd subjects. Treatment-related serious CTCAE 3+ were observed in 12.0% (n = 46) of KRd and 14.0% (n = 38) of Kd subjects. Overall, 4.7% of KRd and 5.9% of Kd subjects experienced a treatment-related CTCAE 3+ which led to discontinuation of carfilzomib. Only 1 event (cardiac failure [0.9%, n =6]) at PT level affecting 3 or more subjects was observed that led to discontinuation of carfilzomib.

- **Discussion**

This medical record review study was conducted to assess the real-life utilisation of carfilzomib. Differences (eg, demographics, prior lines therapy) observed between KRd

and Kd subjects in real-world clinical practice were similar to those observed in the pivotal clinical trials. Response results are consistent with the known profile of carfilzomib and considering the differences in patient population with the clinical trial data. The impact of COVID-19 on the study was minimal as the study ended (as planned) at the beginning of the epidemic in Europe (March, 2020).

- **Marketing Authorization Holder(s)**
  - Amgen Europe B.V

2. LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AE	Adverse event
BSA	Body surface area
C1D1	Cycle 1 Day 1
CI	Confidence interval
CEE	Central and Eastern Europe
CR	Complete response
CRAB	Calcium elevation, Renal insufficiency, Anaemia, Lytic bone lesions
CRF	Case Report Form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
FSE	First subject enrolled
HSCT	Hematopoietic stem cell transplant
IEC	Independent Ethics Committee
ImiD	Immunomodulatory Drug
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
ISS	International Staging System
Kd	Carfilzomib, and dexamethasone
KRd	Carfilzomib, lenalidomide and dexamethasone
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
MR	Minimal response
MRI	Magnetic resonance imaging
NAP	Not applicable
NE	Not evaluated
NEE	Bulgaria, Czech Republic, Israel, Romania
ORR	Overall response rate
ORSR	Observational Research Study Report
PD	Progressive disease
PET-CT	Positron emission tomography–computed tomography
PI	