26 May 2016
EMA/517040/2016
Committee for Medicinal Products for Human Use (CHMP)

Group of variations including an extension of indication assessment report

Invented name: Kyprolis

International non-proprietary name: carfilzomib

Procedure No. EMEA/H/C/003790/II/0001/G

Marketing authorisation holder (MAH): Amgen Europe B.V.

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR – adverse drug reaction
AE – adverse event
ALT – alanine aminotransferase
AMT – nonprotocol antimyeloma therapy
ANC – absolute neutrophil count
AST - aspartate aminotransferase
AUC – area under the curve
BSA – body surface area
CBR - clinical benefit rate
Cd – carfilzomib plus dexamethasone
CHMP – Committee for Human Medicinal Products
CI – confidence interval
Cmax - maximum serum concentration
COMP - Committee for Orphan Medicinal Products
CR – complete response
CrCL – creatinine clearance
CT-L - Cytotoxic T-Lymphocyte
DCR – disease control rate
DOR - duration of response
EC – European Commission
ECOG – eastern cooperative oncology group
EORTC – European organization for research and treatment of cancer
ERA – environmental risk assessment
ESRD – end-stage renal disease
FACT-GOG/Ntx – functional assessment of cancer therapy/gynecologic oncology group neurotoxicity
FISH – fluorescent *in-situ* hybridization
GCP – good clinical practice
HR – hazard ratio
IDMC – Independent Data Monitoring Committee
IgA - immunoglobulin A
IMiD – immunomodulatory drug
IMWG-URC – International Myeloma Working Group Uniform Response Criteria
IRC – independent review committee
ISS - International Staging System
ITT – intent-to-treat
IV – intravenous
LDH – lactate dehydrogenase
LVEF - left ventricular ejection fraction
MAA – marketing authorisation application
MAH - Marketing authorisation holder
MedDRA - medical dictionary for regulatory activities
MM – multiple myeloma
MR – minimal response
MRD – minimal residual disease
MRTinf – mean residence time extrapolated to infinity
MRU – medical resource utilization
MTD - maximum tolerated dose
NCI-CTCAE – National Cancer Institute – Common Toxicity Criteria for Adverse Events
NE – not estimable
OAT - organic anion transporter
OATP - organic anion-transporting polypeptide
OCT - organic cation transporter
ORCA – Onyx Response Computational Assessment
ORR - overall response rate
OS – overall survival
PBMC - peripheral blood mononuclear cell

PD – progressive disease
PDCO – Paediatric Committee
PDn – pharmacodynamics
PFS – progression-free survival
PI – product information
PIP – paediatric investigation plan
PK – pharmacokinetics
PN – peripheral neuropathy
PO - *per os* (orally)
PR – partial response
PRAC – Pharmacovigilance risk assessment committee
PSUR – periodic safety update report
QLQ-C30 – quality of life questionnaire core module
QLQ-MY20 – quality of life questionnaire for multiple myeloma
QoL – quality of life
RMP – risk management plan
RV - right ventricular
SAE – serious adverse event
SAG – scientific advisory group
SC – subcutaneous
sCR – stringent complete response
SD – stable disease
HR-QoL – Health-Related Quality of Life
SFLC - serum free light chain
SmPC - Summary of product characteristics
sNDA – supplemental new drug application
SPEP - serum protein electrophoresis
t1/2 – elimination half-life
TLS - tumour lysis syndrome
Tmax – time to maximum plasma concentration
TTP – time-to-progression
UPEP – urine protein electrophoresis
Vd - bortezomib (Velcade) plus dexamethasone
VGPR – very good partial response
Vss - volume of distribution at steady state

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Amgen Europe B.V. submitted to the European Medicines Agency on 4 December 2015 an application for a group of variations.

This application concerns the following medicinal product:

Centrally authorised Medicinal product(s): **For presentations: See Annex A**	**International non-proprietary name**
Kyprolis	CARFILZOMIB

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

The Marketing authorisation holder (MAH) applied for an extension of the indication for the treatment in combination with either lenalidomide and dexamethasone or dexamethasone alone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
Consequently, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated in accordance.
In addition, the MAH updated section 6.6 of the SmPC to include the option to administer Kyprolis in a 100 mL intravenous bag containing 5% glucose solution for injection in line with the extension of indication part of this variation.
Furthermore the MAH took the opportunity to include some editorial changes and harmonisations in the PI.

The requested group of variations proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Kyprolis, was designated as an orphan medicinal product EU/3/08/548 on 3 June 2008. Kyprolis was designated as an orphan medicinal product in the following indication: treatment of multiple myeloma.

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol assistance

This study design was finalized according to feedback from EMA Protocol Assistance (15 December 2011) and from the FDA Type C meeting (25 January 2012). This advice has been followed, and no changes to the protocol occurred that would constitute a deviation from the guidance and recommendations provided by either the EMA or the FDA.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

CHMP Rapporteur: Arantxa Sancho-Lopez CHMP Co-Rapporteur: Pierre Demolis

PRAC Rapporteur: Marina Dimov Di Giusti

Timetable	Actual dates
Submission date	4 December 2015
Start of procedure	3 January 2016
CHMP Rapporteur's preliminary assessment report circulated on	7 March 2016
CHMP Rapporteur's updated assessment report circulated on	23 March 2016
Request for supplementary information and extension of timetable adopted by the CHMP on	1 April 2016
MAH's responses submitted to the CHMP on	26 April 2016
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	3 May 2016
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	13 May 2016
PRAC RMP advice and assessment overview adopted by PRAC	13 May 2016
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on:	20 May 2016
CHMP opinion	26 May 2016
The CHMP adopted a report on similarity of Kyprolis with Thalidomide Celgene, Revlimid, Imnovid, Farydak and Darzalex (Appendix 1) on:	26 May 2016

2. Scientific discussion

2.1. Introduction

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor that selectively and irreversibly binds to the N terminal threonine containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome, and displays little to no activity against other protease classes. Carfilzomib had antiproliferative and proapoptotic activities in preclinical models in haematologic tumours. In animals, carfilzomib inhibited proteasome activity in blood and tissue and delayed tumour growth in models of multiple myeloma. In vitro, carfilzomib was found to have minimal neurotoxicity and minimal reaction to non proteasomal proteases (SmPC section 5.1).

The current indication for Kyprolis is as follows:

Kyprolis in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy (see section 5.1).

The marketing authorisation holder (MAH) applied for the following indication:

Kyprolis in combination with *either* lenalidomide and dexamethasone *or dexamethasone alone* is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy (see section 5.1).

When combined with dexamethasone, Kyprolis is administered intravenously as a 30 minute infusion on two consecutive days, each week for three weeks (days 1, 2, 8, 9, 15, and 16) followed by a 12-day rest period (days 17 to 28). Each 28-day period is considered one treatment cycle.

Kyprolis is administered at a starting dose of 20 mg/m2 (maximum dose 44 mg) in cycle 1 on days 1 and 2. If tolerated, the dose should be increased on day 8 of cycle 1 to 56 mg/m2 (maximum dose 123 mg) (SmPC section 4.2).

2.2. Non-clinical aspects

2.2.1. Introduction

Kyprolis (carfilzomib) is currently approved for the treatment of patients with relapsed multiple myeloma in combination with lenalidomide and dexamethasone. In the approved SmPC, when combined with lenalidomide and dexamethasone Kyprolis is administered at a starting dose of 20 mg/m^2 (maximum dose is 44 mg) in cycle 1 on days 1 and 2. If tolerated, the dose should be increased on day 8 of cycle 1 to 27 mg/m^2 (maximum dose 60 mg). From cycle 13, the day 8 and 9 doses of Kyprolis are omitted.

The present Variation has been submitted to propose an update to the therapeutic indication in the SmPC for Kyprolis to account for efficacy data from the Phase 3 clinical study 2011-003 (also known as ENDEAVOR).

Based on the posology in the ENDEAVOR study, when combined with dexamethasone, Kyprolis is administered at a starting dose of 20 mg/m^2 (maximum dose is 44 mg) in cycle 1 on days 1 and 2. If tolerated, the dose should be increased on day 8 of cycle 1 to 56 mg/m^2 (maximum dose 123 mg).

As a result of the increased maximum dose, the applicant has submitted an updated Environmental Risk Assessment (ERA) with this submission.

2.2.2. Ecotoxicity / environmental risk assessment

The MAH has provided an updated Environmental Risk Assessment (ERA) in accordance with EMA recommendations, the *Guideline on the Environmental Risk Assessment of medicinal products for human use* (EMA/CHMP/SWP/4447/00, 2006) and the *Questions and Answers document on the Guideline* (EMA/CHMP/SWP/44609/2010).

Phase I ERA: Estimation of exposure

- ***Screening for Persistence, Bioaccumulation and Toxicity (PBT)***

As part of the screening for persistence, bioaccumulation and toxicity, the Applicant provided $log_{10}P_{OW}$ (4.6). The octanol-water partition coefficient (P_{OW}) has been estimated at pH 4, 7 and 9 and 20 ºC using "Shake Flask Method" according to the OECD 107.

Data from this study is provided in Table 1 below.

Table 1. Data from OECD Study to Assess the Octanol / Water Partition Coefficient of carfilzomib

Buffer Solution	P_{ow}	$log_{10} P_{ow}$
pH4	3580	3.6
pH 7	40100	4.6
pH 9	29000	4.5

As the log_{10}Pow value is > 4.5 at pH 7, there is requirement to screen carfilzomib for persistence, bioaccumulation and toxicity (PBT).

According to the EU TGD (ECHA 2014), the PBT/vPvB assessment is required since the estimated log K_{OW} value is clearly above the cut-off of 4.5.

Based on the log10Pow (Log Kow) at pH 7 of 4.6 the applicant has initiated the first step of a PBT assessment in the form of an OECD 308 (Aerobic and Anaerobic Transformation in Aquatic Sediment Systems) study in two aerobic sediments.

A specific PBT assessment according to the REACH Annex III is ongoing. Therefore, the applicant was recommended to submit the missing data as soon as their results will be available and an update of the ERA accordingly. The applicant has agreed to submit the results of the OECD 308 (Aerobic and Anaerobic Transformation in Aquatic Sediment Systems) study and an updated ERA by April 2017.

- ***Calculation of the Predicted Environmental Concentration (PEC)***

The applicant calculated a refined $PEC_{surfacewater}$ in compliance with the guideline on the ERA for carfilzomib. As the action limit of 0.01 µg/L is not exceeded further risk assessment in Phase II of the procedure is not required.

2.2.3. Discussion on non-clinical aspects

An Environmental Risk Assessment has been undertaken for carfilzomib in accordance with EMA recommendations, the Guideline on the Environmental Risk Assessment of medicinal products for human

use (EMA/CHMP/SWP/4447/00, 2006) and the Questions and Answers document on the Guideline (EMA/CHMP/SWP/44609/2010).

The predicted environmental concentration (PEC), based on the refined Fpen, was calculated and is not expected to exceed 0.01 µg/L. Thus, no further Phase II environmental fate and effect analysis is deemed necessary.

The octanol-water partition coefficient (Kow) was estimated using a validated and recognized method "Shake Flask Method" according to the OECD 107. The log p_{ow} value (4.6) presented by the applicant for carfilzomib is above the PBT, vPvB criteria. Therefore, a PBT assessment is required. The applicant is performing a specific PBT assessment according to the criteria as laid down in REACH Annex III. The first step of a PBT assessment in the form of an OECD 308 in two aerobic sediments is ongoing.

The applicant has agreed to provide the results of OECD 308 and the updated ERA by April 2017. This is considered acceptable.

2.2.4. Conclusion on the non-clinical aspects

A specific PBT assessment according to the criteria as laid down in REACH Annex III is ongoing.

The CHMP recommended the submission of the results of OECD 308 and the updated ERA by April 2017.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID Centers	Study design Enrollment	Study and Control Drugs Dose, Route, Regimen, Treatment duration	Primary study Objective (s)	Inclusion in SCE	Diagnosis and Main Inclusion Criteria	Endpoints (Primary and Secondary)
2011-003 (ENDEAVOR) 198 centres in 27 countries located in Europe, North America, Asia Pacific, South America	Phase 3, randomised, open-label, active-controlled FPI: 20 June 2012 Data cut-off date for primary	Cd: Carfilzomib (IV 30 min): 20/56 mg/m in 28-day cycles, consisting of 20mg/m for Cycle 1, Days 1 and 2, then step up to 56mg/m on Days 8, 9, 15, and 16 and all doses thereafter until PD or intolerable side effects	Efficacy	Pivotal efficacy study in relapsed multiple myeloma	Relapsed multiple myeloma, 1-3 prior therapies	Primary: PFS Secondary: OS, ORR, DOR, neuropathy events, safety and tolerability

	efficacy analysis: 10 Nov 2014 N=929	DEX; 20mg on Days 1, 2, 8, 9, 15, 16, 22 and 23 <u>Vd:</u> Bortezomib (IV push or SC): 1.3 mg/ on Days 1, 4, 8 and 11 of each 21-day cycle until PD or intolerable side effects DEX: 20mg on Days 1, 2, 4, 5, 8, 9, 11 and 12 of each 21-day cycle				

2.3.2. Pharmacokinetics

An updated clinical pharmacology data package has been submitted to support the marketing application of the Phase 3 study 2011-003, studying carfilzomib (Kyprolis) plus dexamethasone [Kd] versus bortezomib (Velcade) plus dexamethasone [Vd]. In this trial, carfilzomib 20/56 mg/m^2 was administered as an IV infusion over 30 minutes in subjects with relapsed multiple myeloma.

This updated clinical pharmacology data package:

- Provides results from sparse PK sampling from the Phase 3 study 2011-003
- Reiterates preliminary PK data to inform dosing recommendations in subjects with baseline hepatic impairment as well as subjects with baseline renal impairment from ongoing studies CFZ001(TR-1160-171) and CFZ002 (TR-1161-171) (inclusive of most of the planned PK samples) evaluating PK of carfilzomib at 27 and 56 mg/m2
- Summarizes potential effects of additional covariates (relative to the original population PK analysis), in particular, the effect of race, country of origin (Japan versus others), baseline renal/hepatic impairment, and baseline albumin on the PK of carfilzomib. This updated population PK analysis includes data from the above-mentioned studies, CFZ001, CFZ002, and 2011-003
- Provides Pharmacodynamics (PDn) results at 20/56 mg/m2 IV infusion over 30 minutes from PX-171-007 (DD-0176R-00). In addition, a summary of key PK and PDn data will be presented from PX-171-007, which will be cross-referenced to the previously submitted PK report (TR-0479-171) and PDn report (TR-0478-171)
- Provides an updated exposure-response analysis with data from 2011-003 (Amgen Pharmacometrics Report 121604, see Section 1.3.1; TR-1162-171)

Absorption

<u>Impact of Infusion Length on Pharmacokinetics of Carfilzomib</u>

Pharmacokinetic and PDn effects following a 30-minute IV infusion appear to be similar to those following a 2- to 10-minute IV infusion; an exception is a reduced Cmax as a result of the 30-minute IV infusion.

The PK profile of carfilzomib administered as a 30-minute IV infusion was characterized in PX-171-007 (intensive PK sampling) and 2011-003 (sparse PK sampling). The data at multiple dose levels in PX-171-007 indicated that a longer infusion of 30 minutes resulted in a similar half-life, CL, and AUC, but the Cmax level is approximately a 2- to 3-fold reduction relative to a 2- to 10-minute IV infusion. For example, the geometric mean (geometric %CV) of AUC0-inf following 30-minute IV administration of the 20 mg/m^2 dose was 292 (54.5%) ng•hr/mL (see table 2 below), within range of the AUC following the 2- to 10-minute IV infusion of the same dose of drug (geometric %CV = 223 [104%] ng•hr/mL.

Table 2. PX-171-007: Summary of Carfilzomib Pharmacokinetic Parameters Following 30-Minute IV Infusion on Day 1 of Cycle 1 in Subjects With Multiple Myeloma and Subjects With Solid Tumors (Overall)

PK Parameters	Multiple Myeloma 20 mg/m^2 (N = 30)	Multiple Myeloma and Solid Tumors Combined 20 mg/m^2 (N = 51)
$AUC_{0\text{-last}}$ (ng·hr/mL)	269 (54.3)	299 (56.8)
$AUC_{0\text{-inf}}$ (ng·hr/mL)	273 (55.3)[a]	292 (54.5)[c]
C_{max} (ng/mL)	722 (62.1)	796 (61.4)
T_{max} (hr)	0.250 (0.0833–0.750)	0.300 (0.0833–0.750)
$t_{1/2}$ (hr)	0.888 (0.411–1.57)[a]	0.888 (0.368–2.33)[c]
CL (L/hr)	164 (89.6)[a]	154 (82.6)[c]
MRT_{inf} (hr)	0.117 (0.0799)[b]	0.161 (0.124)[d]
V_{ss} (L)	21.8 (24.6)[b]	25.4 (23.8)[d]
CL/WT (L/hr/kg)	1.99 (1.14)[a]	1.82 (0.981)[c]
V_{ss}/WT (L/kg)	0.260 (0.336)[b]	0.308 (0.307)[d]

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%CV = percent coefficient of variation; $AUC_{0\text{-inf}}$ = area under the curve extrapolated to infinity; $AUC_{0\text{-last}}$ = area under the curve to the last measurable concentration; CL = clearance; C_{max} = maximum drug concentration in plasma (observed); IV = intravenous; MRT_{inf} = mean residence time extrapolated to infinity; PK = pharmacokinetic(s); StD = standard deviation; $t_{1/2}$ = terminal elimination half-life;
T_{max} = time to maximum plasma concentration; V_{ss} = volume of distribution at steady state; WT = body weight.
Note: For $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}, geometric mean (%CV) is presented; T_{max} and $t_{1/2}$ median (minimum–maximum) are presented; arithmetic mean ± StD is presented for all other parameters unless otherwise stated.
[a] n = 28.
[b] n = 27.
[c] n = 46.
[d] n = 45.

The mean Cmax at the 20 mg/m^2 dose (796 ng/mL) was approximately 3-fold lower following the 30-minute infusion compared to the mean Cmax observed following the 2- to 10-minute IV infusion at 20 mg/m^2 (geometric %CV = 2390 [104%] ng/mL).

Time to maximum concentration occurred at the end of infusion following both 2- to 10-minute and 30-minute infusions. Comparable AUC, but lower Cmax, values were also seen with the 30-minute and the 2- to 10-minute IV infusions for the 36 mg/m^2 dose. The geometric %CV of AUC0-inf and Cmax values following the 30-minute infusions at 36 mg/m^2 were 426 (70.1) ng·hr/mL and 1061 (50.7) ng/mL, respectively compared to 663 (51.4) ng·hr/mL and 5718 (46.5) ng/mL following the 2- to 10-minute infusions. Sparse PK data at 56 mg/m^2 over the 30-minute infusion from Study 2011-003 were combined with data from other clinical studies in the population PK analysis. Despite a higher dose, a 56 mg/m^2 dose over a 30-minute infusion resulted in a reduced Cmax (2079 ng/mL) compared with a 27 mg/m^2 dose over a 2- to 10-minute infusion (4232 ng/mL); however, the corresponding AUC was double (948 ng·hr/mL versus 379 ng·hr/mL.

Distribution

Similar to those reported following a 2- to 10-minute IV infusion, the mean volume of distribution at steady state (Vss) after a 20 mg/m^2 dose of a 30-minute IV infusion of carfilzomib was 21.8 L in subjects with multiple myeloma (Study PX-171-007). In an *in vitro* study, binding of carfilzomib to human plasma proteins averaged 97% over the concentration range of 0.4 to 4 µM, and this extent of binding was not concentration dependent. *Ex vivo* assessment using plasma from subjects with multiple myeloma indicated that plasma protein binding of carfilzomib in subjects with mild to severe renal dysfunction was similar to those of normal renal function, and ranged from 97.6% to 98.3% (TR-0452-171).

Metabolism

Upon administration, carfilzomib was rapidly and extensively metabolized in subjects with multiple myeloma and solid tumours. The predominant metabolites measured in human plasma and urine and generated *in vitro* by human hepatocytes were peptide fragments (PR-389/M14, PR-413/M15) and the diol of carfilzomib (PR-519/M16), suggesting that peptidase cleavage and epoxide hydrolysis were the principal pathways of metabolism.

Cytochrome P450-mediated mechanisms appear to play a minor role in the overall metabolism of carfilzomib. Each of the metabolites (PR-389/M14, PR-413/M15, and PR-519/M16) lacks an epoxyketone pharmacophore and has no known biologic activity. In addition, the metabolites in humans are formed in preclinical species, and there are no unique or disproportionate metabolites in humans.

Excretion

Renal and biliary elimination of unlabelled carfilzomib was evaluated in subjects with multiple myeloma or solid tumours in lieu of a radiolabelled mass balance study in healthy volunteers. The excretion profile of carfilzomib and predominant metabolites was assessed by a 24-hour collection of urine and faecal samples in PX-171-008 and urine sample collection in PX-171-005. The metabolites of carfilzomib are primarily recovered in urine. Within 24 hours following IV administration of a single 27 mg/m^2 dose of carfilzomib to subjects with multiple myeloma or solid tumours, approximately 30% of the administered dose of carfilzomib was excreted in urine as metabolites PR-389/M14 (~24% to 31%) and PR-413/M15 (~2%). Urinary excretion of parent compound was negligible (0.3% of the total dose). A small amount of metabolite PR-389/M14 (0.2%) was recovered in faeces with no detection of carfilzomib and metabolites (PR-413/M15 and PR-519/M16) in faecal samples.

The relatively low recovery observed in urine and faecal samples could be due to the collection time limited to 24 hours post-dose and measurements not accounting for minor metabolites. In addition, carfilzomib is peptidic in nature and irreversibly binds to its target; thus, drug recovery might be limited by target binding in cells that are slow to turn over proteasomes and amino acids (leucine and phenylalanine) that may be incorporated into normal biosynthetic pathways.

Dose proportionality

Based on the data collected from PX-171-005 and PX-171-007, the exposure (AUC and C_{max}) increased in a dose-dependent manner from 15 to 56 mg/m^2 when looking at similar infusion durations. Dose-proportionality was assessed but was limited by the high variability in PK parameters and small sample size.

Special populations

The objectives of the carfilzomib population pharmacokinetic analysis are the following:

- To update the existing population PK model to include additional data from three studies: 2011-003, CFZ001, and CFZ002
- To obtain updated estimates of pharmacokinetic parameters
- To evaluate effects of subjects' demographic characteristics and other covariates on PK parameters, in particular, the effect of race, country of origin (Japan versus others), baseline renal/hepatic impairment and baseline albumin on PK of carfilzomib

The previous population PK model (TR-1015-171) identified the structural model of carfilzomib to be a 2-compartment model with first order elimination (Table 3). This compartmental model structure was maintained for the current population PK analysis.

A slight effect of BSA on clearance was observed. However, PK exposure metrics based on the final model found 95% of all subjects taking carfilzomib achieve exposure (Cmax and AUC) within 10% of the exposure for a subject with median BSA. The current population PK analysis (Table 4) did not identify any other clinically meaningful covariates that impacted the pharmacokinetic profile of carfilzomib. The covariates of CrCL, sex, age, weight, race, albumin, renal and liver impairment, Japanese origin, and cancer type had no detectable influence on model parameters. Parameters estimates for carfilzomib in both final PK models are presented in table 3 and 4 below:

Table 3. Parameters Estimates for Carfilzomib Final PK model

Parameter	Estimate	Standard Error	RSE%	IIV CV%
Clearance (L/h)	148	7.23	4.89	59.9
Central volume (L)	9.94	0.74	7.40	119
Intercompartment clearance (L/h)	4.69	0.37	7.96	NA
Peripheral volume (L)	6.63	0.65	9.75	48.6
BSA effect on clearance: exponent for power model	0.44	0.19	43.4	NA
StD of additive residual error on log-transformed data	0.99	0.01	1.59	NA

Source: Table 8 in TR-1015-171
BSA = body surface area; CV = coefficient of variation; IIV = interindividual variability; PK = pharmacokinetic(s); RSE = relative standard error (standard error/parameter estimate); StD = standard deviation; NA = not applicable.

Table 4. Parameter Estimates for Carfilzomib Final PK model (Variation II- 001, including studies 2011-003, CFZ001, and CFZ002)

Parameter	Estimate	RSE%	IIV CV%	Shrinkage%
Clearance (L/h)	154	3.4	36.5	35.5
Central Volume (L)	11.5	5.0	49.4	45.4
Inter-compartment Clearance (L/h)	5.67	8.6	88.5	40.1
Peripheral Volume (L)	7.62	11.7	106	42.1
BSA effect on Clearance[a]	0.638	19.3		
SD of Additive Residual Error on Log-Transformed Data				
Phase 1/2 Studies	0.943	1.4		10.1
Phase 3 Studies	1.41	2.2		8.7
Correlation Matrix	**IIV% CL**	**IIV% V1**		
IIV CL	36.4			
IIV V1	52.7	49.4		
Correlation Matrix	**IIV Q**	**IIV V2**		
IIV Q	88.5			
IIV V2	94.1	106		

CL = clearance; CV = coefficient of variation; IIV = inter subject variability; Q = inter compartment clearance; RSE = residual standard error; SD = standard deviation; V1= central volume of distribution; V2 = peripheral volume of distribution.

Objective Function Value: 6892.190

Final dataset: popPK_ENDEAVOR_42x.csv

Final model: Model 061 in Table 6

[a] Exponent for power model applied on median BSA of 1.88 m^2.

AUC and Cmax predicted in the final population pharmacokinetic models are considered in line although the predictions with different models are slightly different:

Table 5. Mean (SD) of Model-based AUC and Cmax Predicted by Study in the Final Population PK Model

Study	Dose Regimens	C_{max} (Cycle 1 Day 1) (ng/mL)	AUC (Cycle 1 Day 1) (h·ng/mL)	C_{max} (Maximum in Cycle 1) (ng/mL)	AUC (Average in Cycle 1) (h·ng/mL)
PX-171-003 – Part 2 (A1)	20/27 mg/m^2 [a]	2813 (2040)	289 (127)	3648 (3318)	57.6 (28.7)
PX-171-004	20 mg/m^2 20/27 mg/m^2	3408 (1815)	306 (118)	3799 (2091)	63.9 (25.8)
PX-171-005	15/20 mg/m^2	2068 (780)	208 (162)	3079 (4560)	42.3 (34.8)
PX-171-006	15 mg/m^2 20 mg/m^2 20/27 mg/m^2	2082 (1500)	219 (86)	2698 (2181)	43.6 (21.5)
PX-171-007					
(2- to 10-minute infusion)	20 mg/m^2 20/27 mg/m^2 20/36 mg/m^2	2348 (765)	194 (63)	4036 (1473)	51.6 (26.2)
(30-minute infusion)	36 mg/m^2 45 mg/m^2 20/36 mg/m^2 20/45 mg/m^2 20/56 mg/m^2 20/70 mg/m^2	570 (386)	283 (152)	1338 (1418)	(46.6)
PX-171-009	20/27 mg/m^2 [a]	1555 (1173)	319 (229)	3063 (3228)	(55.5)

AUC = area under the concentration-time curve; C_{max} = maximum concentration
[a] Dose escalation to 27 mg/m^2 for Study PX-171-003 occurred in cycle 2, while dose escalation to 27 mg/m^2 for Study PX-171-009 occurred on day 8 in cycle 1.
Source: TR-1015-171 in Module 5.3.3.5

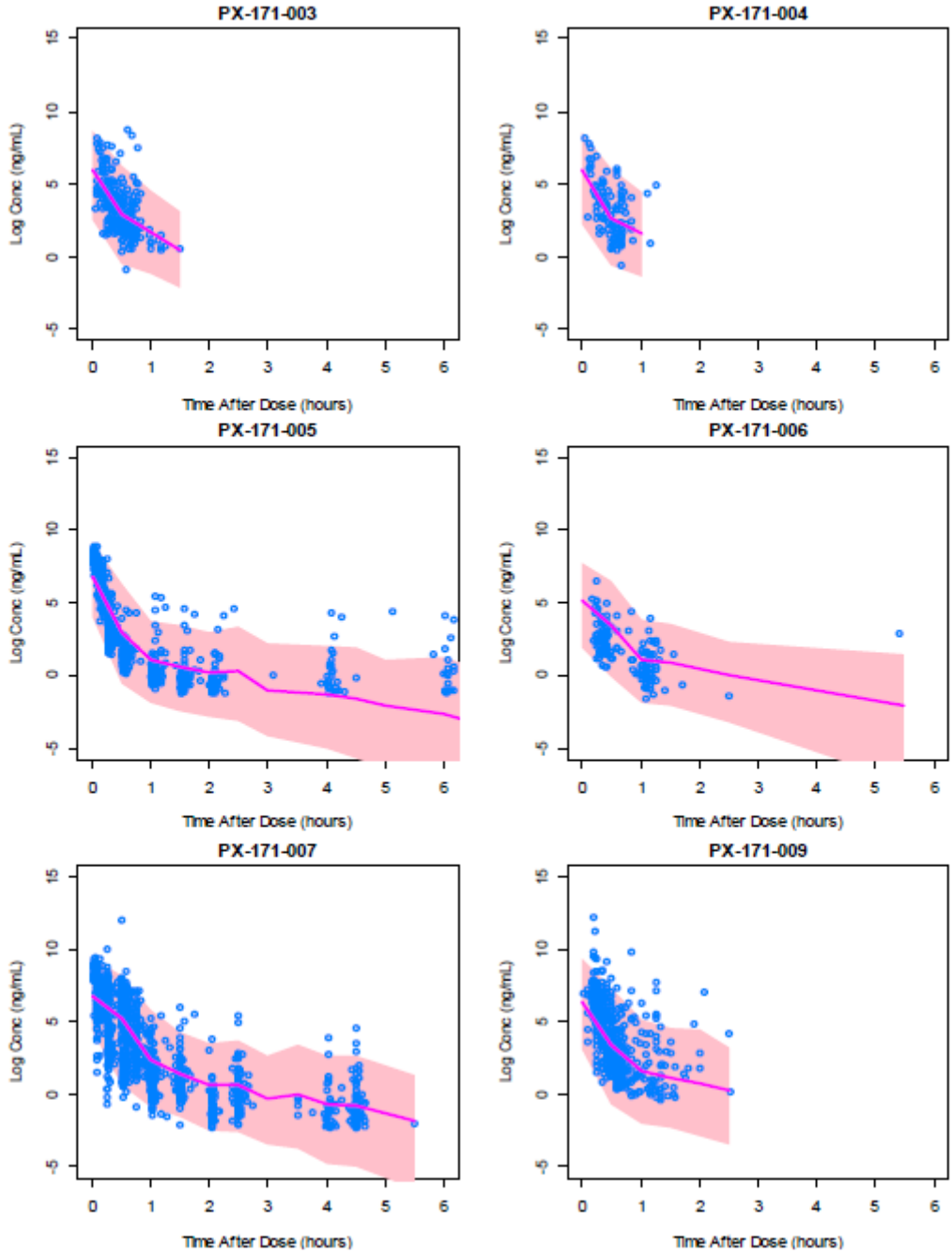
Study	Number of Subjects	Carfilzomib Dosing and Schedule	C_{max}.C1D1 (cycle 1 day 1, ng/mL)	AUC.C1D1 (cycle 1 day 1, h•ng/mL)	C_{max}.peak (Maximum in cycle 1 ng/mL)	AUC.C1avg (Average in cycle 1 h•ng/mL)
PX-171-003 – Part 2 (A1)	102	2 to 10 minute IV infusion days 1, 2, 8, 9, 15, and 16 cycle 1: 20 mg/m^2 cycles ≥ 2: 27 mg/m^2	2160 (857)	250 (52)	2440 (885)	49.3 (14.3)
PX-171-004	51	2 to 10 minute IV infusion days 1, 2, 8, 9, 15, and 16 Part 1: All cycles: 20 mg/m^2 Part 2: cycle 1: 20 mg/m^2 cycle ≥ 2: 27 mg/m^2	2700 (709)	265 (60.2)	2880 (632)	55.2 (13.2)
PX-171-005	43	2 to 10 minute IV infusion days 1, 2, 8, 9, 15, and 16 cycle 1: 15 mg/m^2 cycle 2: 20 mg/m^2 cycle ≥ 3: 27 mg/m^2	1850 (444)	176 (46.5)	2100 (411)	36.1 (10.5)
PX-171-006	39	2 to 10 minute IV infusion cycles 1 to 12: days 1, 2, 8, 9, 15, and 16. cycles ≥ 13: days 1, 2, 15, and 16 Cohorts 1 to 3: 15 mg/m^2 Cohorts 4 to 5: 20 mg/m^2 Cohort 6: 20 mg/m^2 on days 1 and 2 of cycle 1, 27 mg/m^2 thereafter	1670 (789)	194 (41)	2040 (803)	38.5 (13.4)

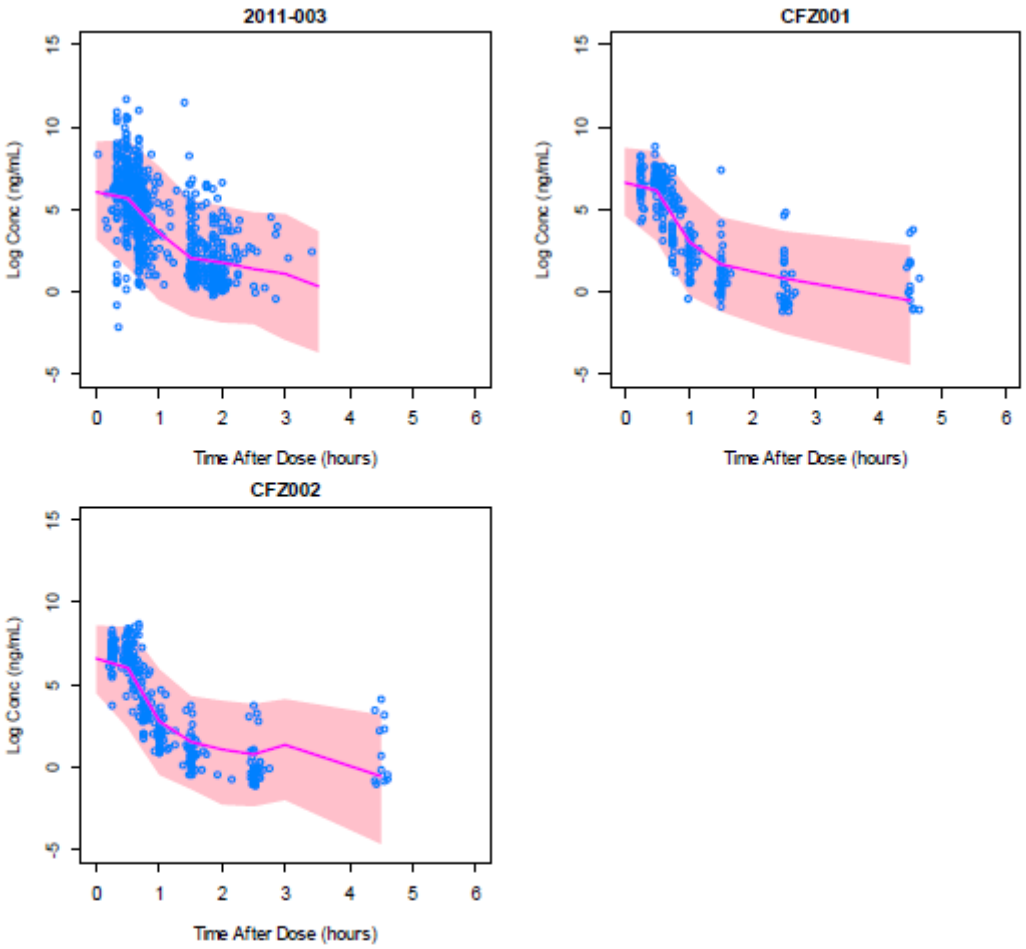
Study	Number of Subjects	Carfilzomib Dosing and Schedule	C_{max}.C1D1 (cycle 1 day 1, ng/mL)	AUC.C1D1 (cycle 1 day 1, h•ng/mL)	C_{max}.peak (Max in cycle 1 ng/mL)	AUC.C1avg (Average in cycle 1 h•ng/mL)
PX-171-007 Solid tumors	29	2 to 10 minute IV infusion 20 mg/m^2: All cycles 20/27 mg/m^2: 20 mg/m^2 on days 1 and 2 of cycle 1, 27 mg/m^2 thereafter 20/36 mg/m^2: 20 mg/m^2 on days 1 and 2 of cycle 1, 36 mg/m^2 thereafter	2560 (539)	211 (43)	4250 (1120)	55.9 (22.5)
PX-171-007 Solid tumors and multiple myeloma	73	30 minute IV infusion 20/36 mg/m^2: 20 mg/m^2 on days 1 and 2 of cycle 1, 36 mg/m^2 thereafter 20/45 mg/m^2: 20 mg/m^2 on days 1 and 2 of cycle 1, 45 mg/m^2 thereafter 20/56 mg/m^2: 20 mg/m^2 on days 1 and 2 of cycle 1, 56 mg/m^2 thereafter 20/70 mg/m^2: 20 mg/m^2 on days 1 and 2 of cycle 1, 70 mg/m^2 thereafter	568 (279)	295 (135)	1240 (555)	90.2 (40.6)

Study	Number of Subjects	Carfilzomib Dosing and Schedule	C_{max}.C1D1 (cycle 1 day 1, ng/mL)	AUC.C1D1 (cycle 1 day 1, h•ng/mL)	C_{max}.peak (Max in cycle 1 ng/mL)	AUC.C1avg (Average in cycle 1 h•ng/mL)
PX-171-009	106	2 to 10 minute IV infusion 28-day treatment cycles. Up to 18 cycles. 20/27 mg/m^2: 20 mg/m^2 on days 1 and 2 of cycle 1, 27 mg/m^2 on days 8, 9, 15, and 16 of cycle 1 and continuing on days 1, 2, 8, 9, 15, and 16 of cycles 2 to 12 In cycles 13 to 18, 27 mg/m^2 on days 1, 2, 15, and 16	1200 (272)	260 (67.7)	1760 (359)	63.5 (19.1)
2011-003	133	Carfilzomib 30 min IV infusion 28-day cycles 20/56 mg/m^2: 20 mg/m^2 on days 1 and 2 of cycle 1, 56 mg/m^2 on days 8, 9, 15, and 16 of cycle 1 and subsequent cycles Dexamethasone 20 mg oral on days 1, 2, 8, 9, 15, 16, 22, and 23 until progressive disease	485 (181)	266 (112)	1370 (397)	116 (43.9)

AUC.C1avg (ng•h/mL) = average daily AUC in cycle 1; AUC.C1D1 (ng•h/mL) = AUC on day 1 of cycle 1; C_{max}.C1D1 (ng/mL) = maximum concentration on day 1 of cycle 1; C_{max}.peak (ng/mL) = maximum concentration corresponding to highest dose in cycle 1; IV = intravenous

Figure 1. Visual Predictive Check of the Final Population PK Model





The blue circles indicate observed data. Solid red line indicates predicted median and the pink area indicates the 95% prediction interval.

Renal impairment

The renal impairment study, CFZ001, was conducted to characterize the pharmacokinetics (PK) and safety of carfilzomib 56 mg/m^2 using a 30-minute infusion in patients with ESRD. The Phase 3 Study 2011-003 (ENDEAVOR) enrolled subjects with varying degrees of renal impairment as measured by creatinine clearance as low as 15 mL/minute, but excluded those subjects with ESRD. Thus, the PK and safety data from CFZ001 will complement the Phase 3 ENDEAVOR study.

A summary of plasma carfilzomib PK parameters after intravenous infusion of carfilzomib 27 mg/m2 on Day 16 of Cycle 1, and 56 mg/m2 on Day 1 of Cycle 2 in subjects with multiple myeloma and normal renal function or ESRD is presented in Table 6.

Table 6. Summary of plasma carfilzomib PK parameters after intravenous infusion of carfilzomib 27 mg/m2 on Day 16 of Cycle 1, and 56 mg/m2 on Day 1 of Cycle 2 in subjects with multiple myeloma and normal renal function or ESRD

	Cycle 1 Day 16: 27 mg/m^2		Cycle 2 Day 1: 56 mg/m^2	
PK Parameters	Normal (N = 13)	ESRD (N = 7)	Normal (N = 10)	ESRD (N = 7)
AUC_{0-last} (hr•ng/mL)	344 (24.8)	444 (37.2)	563 (41.9)	712 (162)
AUC_{0-inf} (hr•ng/mL)	347 (26.3)[a]	450 (49.3)[b]	563 (41.9)	718 (163.0)
C_{max} (ng/mL)	819 (29.8)	932 (36.8)	1389 (26.8)	1500 (144)
T_{max} (hr)	0.583 (0.467–0.733)	0.467 (0.250–0.750)	0.467 (0.250–0.733)	0.467 (0.250–0.583)
$t_{½}$ (hr)	0.318 (60.7)[a]	1.81 (185.8)[b]	0.308 (49.4)	0.875 (202.8)
CL (L/hr)	146 (23.0)	97.7 (59.9)	167 (46.4)	138 (154.8)
MRT_{inf} (hr)	0.222 (16.6)[a]	0.509 (158.6)[b]	0.135 (62.6)	0.256 (86.5)
V_{ss} (L)	32.0 (29.7)	65.7 (164.2)	22.5 (48.7)	35.4 (146.4)

AUC_{0-inf} = area under the curve extrapolated to infinity; AUC_{0-last} = area under the curve to the last measurable concentration; CL = clearance; C_{max} = maximum drug concentration in plasma (observed); ESRD = end-stage renal disease; IV = intravenous; MRT_{inf} = mean residence time extrapolated to infinity; PK = pharmacokinetic(s); $t_{1/2}$ = terminal elimination half-life; T_{max} = time to maximum plasma concentration; V_{ss} = volume of distribution at steady state.
Geometric mean (percent coefficient of variation) is provided for all parameters, unless otherwise stated; T_{max} median (minimum–maximum) is provided.
Descriptive statistics are provided without Subject 14
[a] n = 11
[b] n = 5

A summary of plasma PR-389/M14 PK parameters following IV administration of 27 mg/m2 carfilzomib on Day 16 of Cycle 1 and of 56 mg/m2 carfilzomib on Day 1 of Cycle 2 in Multiple Myeloma patients with normal renal function or ESRD is presented in table 7.

Table 7. Summary of plasma PR-389/M14 PK parameters following IV administration of 27 mg/m2 carfilzomib on Day 16 of Cycle 1 and of 56 mg/m2 carfilzomib on Day 1 of Cycle 2 in Multiple Myeloma patients with normal renal function or ESRD

PK Parameters	Cycle 1, Day 16: 27 mg/m^2		Cycle 2, Day 1: 56 mg/m^2	
	Normal (N = 13)	ESRD (N = 7)	Normal (N = 10)	ESRD (N = 7)
AUC_{0-last} (hr·ng/mL)	320 (32.8)	1522 (36.6)	584 (17.5)	2034 (150)
$AUC_{0-\infty}$ (hr·ng/mL)	355 (25.1)[a]	NC (NC)	650 (22.5)	NC (NC)
C_{max} (ng/mL)	153 (25.4)	421 (36.3)	302 (16.5)	579 (145)
t_{max} (hr)	1.00 (0.75 - 1.13)	1.50 (1.00 - 2.67)	0.983 (0.583 - 1.02)	2.50 (1.45 - 4.47)
$t_{1/2}$ (hr)	1.41 (18.4)[a]	NC (NC)	1.18 (21.8)	NC (NC)

NC: not calculated.
Notes: geometric mean (geometric CV%) is presented for all parameters, unless otherwise stated; t_{max} median (minimum–maximum) is presented.
Descriptive statistics are presented without subject 14
[a] n = 10.

Carfilzomib is rapidly and extensively metabolized mainly to M14 and M16. A fast transformation of M16 into M14 is expected due to their low levels in urine and faeces and its short t1/2. As consequence, carfilzomib will be mainly eliminated in urine as metabolite M14 or incorporated into normal biosynthetic pathways due to its peptidic nature and its irreversible binds to its target. The percent of M14 excreted in urine relative to the dose of carfilzomib was approximately 30%, M14 has a short half-life, no

accumulation is expected for this metabolite and M14 is described as a no pharmacological active metabolite.

Hepatic impairment

The hepatic impairment study CFZ002 is currently ongoing and the final study report is expected during the second quarter of 2016 (please refer to the Risk management plan section).

Study CFZ002 was designed to assess the safety and pharmacokinetic characteristics of carfilzomib in subjects with normal hepatic function or varying degrees of chronic hepatic impairment (mild, moderate, or severe hepatic impairment). Subjects with relapsed or progressive advanced malignancies (solid tumors or hematologic malignancies) are enrolled into cohorts based on their degree of hepatic impairment. Each cohort is to be composed of approximately 10 evaluable subjects. Carfilzomib was administered as a 30-minute intravenous infusion at 20 mg/m2 on cycle 1 days 1 and 2, followed by escalation to 27 mg/m^2 on cycle 1 days 8, 9, 15, and 16 of a 28-day cycle. Subjects who adequately tolerated dosing at 27 mg/m^2 in cycle 1 were administered carfilzomib at 56 mg/m^2 in cycle 2 and beyond. Pharmacokinetics samples were collected on cycle 1 day 16 (carfilzomib 27 mg/$m^{2)}$ and cycle 2 day 1 (carfilzomib 56 mg/m^2).

Based on data cutoff of 02 February 2015, a total of 30 subjects were enrolled in the study, including 28 subjects with solid tumors and 2 subjects with multiple myeloma. Preliminary pharmacokinetic data based on approximately 90% of the final planned evaluable subjects in cohorts 1 to 3 (normal hepatic function, and mild and moderate hepatic impairment) have been analyzed. As of 08 June 2015, data were available from 2 additional subjects in cohort 3 and results were similar to those summarized below based on the data cutoff of 02 February 2015.

As of 02 February 2015, no pharmacokinetic data have been collected for cohort 4 (severe hepatic impairment). Enrollment for cohort 4 has been challenging. Although 13 subjects have been screened for potential enrollment in cohort 4, only 4 subjects have qualified and none of them were able to stay on treatment long enough to enable collection of pharmacokinetic samples on cycle 1 day 16, the primary pharmacokinetic time point for this study. All 4 subjects enrolled in cohort 4 of the study have died or discontinued treatment prior to reaching cycle 1 day 16. All deaths were confounded by multiple comorbidities in the setting of advanced solid tumors with generally extensive hepatic and/or pulmonary metastases. Due to continued enrollment challenge and the lack of demonstrable efficacy with carfilzomib monotherapy in this population of mostly solid tumor subjects, on 22 July 2015, the United States Food and Drug Administration accepted the proposed protocol amendment to close cohort 4.

The pharmacokinetic parameters after carfilzomib administration at 27 or 56 mg/m2 in subjects with hepatic impairment are shown in Table 8.

Table 8. Summary of plasma carfilzomib PK parameters after IV infusion in patients with advanced malignancies categorized by dose and hepatic function

	27 mg/m^2			56 mg/m^2		
PK Parameters	Normal (N = 10)	Mild (N = 14)	Moderate (N = 5)	Normal (N = 8)	Mild (N = 8)	Moderate (N = 1)
AUC_{0-last} (ng·hr/mL)	378 (40.8)	546 (39.2)	446 (42.1)	760 (99.9)	1107 (73.7)	733
AUC_{0-inf} (ng·hr/mL)	348 (35.4)[a]	529 (40.3)[b]	457 (48.9)[c]	604 (98.3)[d]	1108 (73.7)	733
C_{max} (ng/mL)	932 (58.4)	1290 (47.5)	906 (49.4)	1697 (93.7)	2733 (67.0)	1750
T_{max} (hr)	0.292 (0.250–0.500)	0.458 (0.250–0.667)	0.483 (0.233–0.600)	0.283 (0.250–0.583)	0.408 (0.250–0.683)	0.250
$t_{1/2}$ (hr)	0.469 (22.8)[a]	0.541 (75.9)[b]	0.267 (107.2)[c]	0.508 (54.7)[d]	0.621 (47.7)	0.489
CL (L/hr)	157 (32.5)[a]	86.8 (48.6)[e]	117 (50.8)	136 (105.4)	92.0 (77.2)	123
MRT_{inf} (hr)	0.108 (60.6)[a]	0.167 (45.7)[b]	0.161 (17.0)[d]	0.0815 (192.5)[e]	0.161 (43.6)	0.105
V_{ss} (L)	16.9 (37.0)[a]	14.5 (55.3)[e]	19.6 (45.6)	24.8 (188.0)	14.8 (51.9)	12.9

AUC_{0-inf} = area under the concentration-time curve extrapolated to infinity; AUC_{0-last} = area under the concentration-time curve to the last measurable concentration; CL = clearance; C_{max} = maximum drug concentration in plasma (observed); MRT_{inf} = mean residence time extrapolated to infinity; PK = pharmacokinetic; $t_{1/2}$ = terminal elimination half-life; T_{max} = time to maximum concentration; V_{ss} = volume of distribution at the steady state
Geometric mean (geometric percent coefficient of variation) is presented for all parameters except as follows; T_{max} median (minimum–maximum) is presented.
Descriptive statistics are presented without Subject 1[illegible] cycle 2 day 1 (normal hepatic function).
As of 02 February 2015, no subjects were enrolled in cohort 4, severe hepatic impairment.
[a] n = 8
[b] n = 12
[c] n = 4
[d] n = 6
[e] n = 13

Pharmacokinetic interaction studies

In vitro, Carfilzomib displayed a modest direct, time-dependent inhibitory effect on human cytochrome P450 3A4/5 (CYP3A4/5).

In the study conducted in subjects with solid tumours (PX-171-008), single and repeat dosing of carfilzomib at 27 mg/m2 did not affect the PK of midazolam, a sensitive CYP3A substrate.

Table 9. Summary of PK parameters and ratios for midazolam (Study PX-171-008)

Study PX-171-008: Summary of PK Parameters for Midazolam

Parameters		Midazolam Day -7 (n = 17)			Midazolam Day 1 (n = 17)			Midazolam Day 16 (n = 12)		
		Mean	StD	CV (%)	Mean	StD	CV (%)	Mean	StD	CV (%)
AUC_{0-t}	(pg·h/mL)	49771.08	30854.24	61.99	47268.14	26361.40	55.77	48423.68	22981.09	47.46
AUC_{0-12}	(pg·h/mL)	42513.28	23185.19	54.54	40344.22	19077.71	47.29	48423.68	22981.09	47.46
AUC_{0-inf} [a]	(pg·h/mL)	54265.39	35979.31	66.30	51505.37	30279.56	58.79	59858.41	32476.98	54.26
C_{max}	(pg/mL)	16322.93	7607.32	46.61	15740.30	6224.33	39.54	15967.58	7692.31	48.17
T_{max}	(h)	0.496	0.225	45.37	0.688	0.286	41.58	0.842	0.715	84.95
$t_{½}$ [a]	(h)	6.63	2.19	33.09	6.33	1.90	30.03	5.48	1.50	27.36

AUC_{0-t} = area under the concentration–time curve from time zero to last measurable concentration; AUC_{0-12} = area under the concentration–time curve from time zero to 12 hours; AUC_{0-inf} = area under the concentration–time curve extrapolated to infinity; C_{max} = maximum observed concentration; CV = coefficient of variation; K_{el} = elimination rate constant; PK = pharmacokinetic(s); StD = standard deviation; $t_{½}$ = terminal elimination half-life.
[a] For these parameters, n = 11 on Day 16.

Study PX-171-008: Summary of Midazolam PK Parameters Ratios

Statistical Analysis	Treatment Comparisons	Ratio[a]	90% Geometric CI[b]		Intrasubject CV
			Lower	Upper	
AUC_{0-t}	Midazolam Day 1 vs. Midazolam Day -7	95.04%	84.62%	106.74%	19.58%
AUC_{0-12}	Midazolam Day 16 vs. Midazolam Day -7	113.08%	96.81%	132.07%	21.42%
AUC_{0-inf}	Midazolam Day 1 vs. Midazolam Day -7	95.24%	84.67%	107.12%	20.30%
	Midazolam Day 16 vs. Midazolam Day -7	108.16%	94.07%	124.36%	
C_{max}	Midazolam Day 1 vs. Midazolam Day -7	98.95%	82.85%	118.18%	31.11%
	Midazolam Day 16 vs. Midazolam Day -7	98.12%	80.05%	120.25%	

AUC_{0-t} = area under the concentration–time curve from time zero to last measurable concentration; AUC_{0-12} = area under the concentration–time curve from time zero to 12 hours; AUC_{0-inf} = area under the concentration–time curve extrapolated to infinity; CI = confidence interval; C_{max} = maximum observed concentration; CV = coefficient of variation.
[a] Calculated using least-squares means (LSM) of the ln-transformed data according to the formula: $e^{(\text{Treatment a-Treatment b})} \times 100$.
[b] 90% geometric CI using ln-transformed data.

2.3.3. Pharmacodynamics

Primary pharmacology

Despite the rapid clearance of carfilzomib from the plasma compartment, IV administration resulted in potent and prolonged proteasome inhibition in whole blood and peripheral blood mononuclear cells (PBMCs) in subjects with multiple myeloma or solid tumours.

Following the first dose of carfilzomib (15 to 56 mg/m^2), a dose-dependent inhibition of CT-L active sites of the 20S proteasome was observed (≥ 67% and ≥ 75% in whole blood and PBMCs, respectively). A similar inhibition profile was observed in bone marrow-derived CD138$^+$ tumour cells. Proteasome inhibition with carfilzomib was found to be durable, with minimal recovery in PBMCs after 24 hours but near-complete recovery between carfilzomib dosing cycles. At the higher dose at 56 mg/m^2, there was not only a greater inhibition of CT-L subunits compared to those at 15 to 20 mg/m^2, but also a greater inhibition of other proteasome subunits, which may be associated with an increased likelihood of achieving a clinical response (DD-0176R-00). Similar proteasome inhibition by carfilzomib was achieved with 2- to 10-minute and 30-minute infusions at the 2 dose levels (20 and 36 mg/m^2) at which it was tested.

Secondary Pharmacology

<u>QT Effects</u>

In Study PX-171-007, 26% of patients treated with a dose of 20/56 had a change from baseline in QTcB between 30 and 60 msec. Additionally, case of Torsade de pointes-QT prolongation (SMQB), syncope and sudden death had been observed in 1.9%, 1.1% and 0.4% of patients.

Exploratory Exposure-response Analysis

The MAH has provided an updated analysis to a previously conducted exposure-response analysis (TR-1092-171) by incorporating additional data from randomized phase 3 Study 2011-003 (ENDEAVOR).

Methods

The exposure efficacy analysis of overall response rate (ORR), clinical benefit rate (CBR), duration of response (DOR), and progression-free survival (PFS) was performed based on 133 of the 464 (28.7%) subjects with relapsed multiple myeloma who were randomized to the carfilzomib plus dexamethasone arm received a 30-minute intravenous (IV) infusion of 20/56 mg/m2 carfilzomib in the phase 3 Study 2011- 003 (ENDEAVOR).

The pooled exposure-efficacy analysis was based on 507 subjects with multiple myeloma across seven studies from 15 to 20/56 mg/m^2 dose levels including a randomized phase 3 Study 2011-003 (ENDEAVOR), a randomized phase 3 Study (PX-171-009) and 5 phase 1b and phase 2 studies (PX-171-003 – Part 2 (A1),PX-171-004, PX-171-005, PX-171-006, and PX-171-007). This pooled analysis included data from different populations (relapsed or relapsed/refractory), different treatments (carfilzomib monotherapy, carfilzomib combination therapy with lenalidomide and dexamethasone [KRd] or carfilzomib combination therapy with dexamethasone [Kd]), different infusion lengths (2 to 10 minutes or 30 minutes), and different doses (from 15 to 20/56 mg/m2). Duration of response and PFS were not included in the pooled analysis, as different assessment criteria of PFS and DOR between the phase 1b/2 studies and phase 3 studies were used.

For safety endpoints, a pooled analysis was performed in 576 subjects (507 subjects with multiple myeloma and 69 subjects with solid tumors). The safety endpoints included any grade adverse events leading to carfilzomib discontinuation, any grade 3 or higher adverse events, and cardiac- and hepatic/renal-related adverse events.

Subjects received IV infusion of carfilzomib over 2 to 10 minutes (over 10 minutes in Study PX-171-009) or over 30 minutes (in Study PX-171-007 and phase 3 Study 2011-003) on 2 consecutive days each week for 3 weeks (days 1, 2, 8, 9, 15, and 16), this was followed by a 12-day rest period (days 17 to 28) for each 28-day cycle. A population pharmacokinetic (PK) model was used to derive exposure metrics (various estimates of area under the concentration-time curve [AUC] and maximum concentration [Cmax]) that were explored in relation to efficacy and safety. To assess the relationship of carfilzomib exposure with the responses or adverse event, logistic models were used for binary endpoints and standard survival analyses (such as log-rank test, linear Cox regression) were performed for time–to event endpoints. Subject baseline characteristics, including demographics, ECOG PS, number of prior regimens, serum beta-2 microglobulin levels, concomitant medication (dexamethasone or lenalidomide) and other covariates, were included in the multiple regression analysis.

Results:

The exposure response analysis of efficacy endpoints was consistent with the previously reported results (TR-1092-171) demonstrating a relationship between carfilzomib cycle 1 average AUC and response categories ORR/CBR across subjects receiving doses from 15 mg/m^2 to 20/56 mg/m^2. In the exposure response analysis of safety endpoints, no statistically significant relationship was identified to indicate a correlation between increasing exposure and increasing risk of adverse events in subjects with multiple myeloma or solid tumors.

Study 2011-003 (ENDEAVOR): Specifically, the exposure-response analysis of efficacy endpoints in subjects from Study 2011-003 alone, in which all subjects received the 20/56 mg/m^2 dose, did not show any statistically significant relationship between carfilzomib exposure (AUC or Cmax) and the primary efficacy endpoints, PFS and ORR/CBR.

Of note, the median (95% CI) of cycle 1 average AUC in Study 2011-003 (ENDEAVOR) was 108 (48.5 to 211) ng•h/mL, approximately two times higher than the median (95%CI) of the other studies included in the analysis.

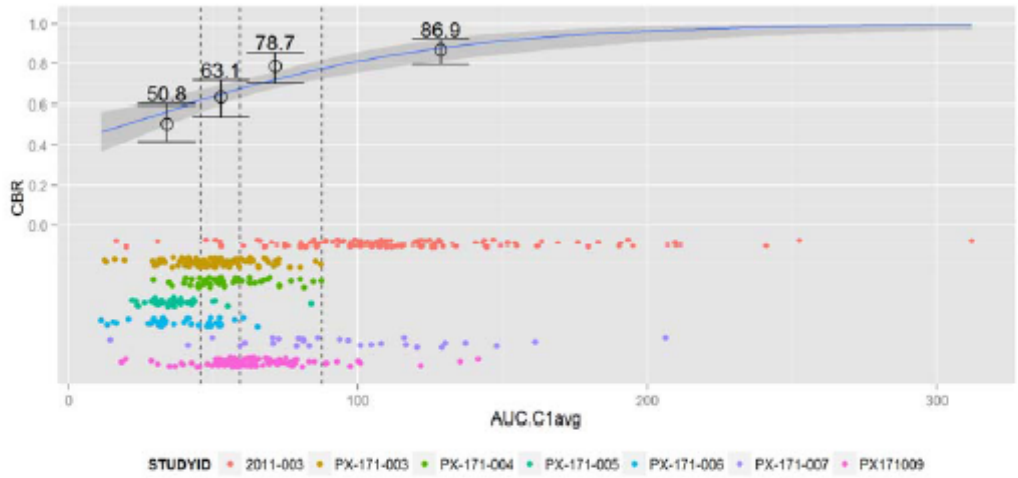
No apparent relationship between carfilzomib exposure and efficacy endpoints was observed in Study 2011-003 (ENDEAVOR), indicating that multiple myeloma subjects may benefit from carfilzomib regardless of potential PK differences within a 30-minute infusion of the 20/56 mg/m2 dosing regimen.

Pooled Analysis of Clinical Studies: When combining data from all the studies in a pooled exposure response analysis of efficacy endpoints, the results of the logistic regression model indicated a relationship between carfilzomib cycle 1 average AUC and response categories ORR/CBR with increasing cycle 1 average AUC associated with increases in ORR/CBR over a dose range of 15 mg/m2 to 20/56 mg/m2. The mean ORR in the first and fourth quartiles of the cycle 1 average AUC were 38.5% and 84.4%, respectively.

After adjusting for baseline characteristics and prognostic factors, an increase in cycle 1 average AUC from the first to the fourth quartile (45.6 to 87.5 ng•h/mL) was associated with an increase of the ORR by a factor of 1.75 (odds ratio = 1.75; 95% confidence interval [CI]: 1.24 to 2.52).

No positive relationships between Cmax and ORR/CBR were identified.

Figure 2. 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.

The pooled efficacy analysis also identified several statistically significant covariate effects ($p < 0.05$) for ORR and CBR. The model for ORR indicated that subjects refractory to bortezomib (odds ratio = 0.48; 95% CI: 0.28 to 0.84) or black race (odds ratio = 0.41; 95% CI: 0.19 to 0.87) had a decreased

probability of overall response while having baseline platelet count ≥ 150 (x 109/L) (odds ratio = 1.90; 95% CI: 1.20 to 3.03), having one prior line of therapy (odds ratio = 1.97; 95% CI: 1.11 to 3.57), KRd combination therapy (odds ratio = 7.93; 95% CI: 4.38 to 14.96), or Kd combination therapy (odds ratio = 2.10; 95%CI: 1.00 to 4.45) increased the probability of overall response.

Table 10. Multiple logistic model for ORR (pooled analysis)

Model Term	Estimate	CI Lower	CI Upper
Intercept	0.27	0.13	0.53
AUC.C1avg fourth quartile versus first	1.75	1.24	2.52
Combo therapy (dexamethasone) Y:N	2.1	1	4.45
Combo therapy (lenalidomide + dexamethasone) Y:N	7.93	4.38	14.96
Plat.bin ≥ 150	1.9	1.2	3.03
Bortezomib Refractory Y:N	0.48	0.28	0.84
Race black	0.41	0.19	0.87
Prior lines of therapy = 1	1.97	1.11	3.57

AUC.C1avg = average daily AUC in cycle 1; CI = confidence interval; Plat.bin = indicator for platelet count ≥ 150 x 10^9/L
Estimate and 95% CI lower and upper bounds presented as odds ratios.

Despite inclusion of different populations (relapsed or relapsed/refractory), different treatments (carfilzomib monotherapy or KRd or Kd combination therapy), different infusion lengths (2 to 10 minutes or 30 minutes), and different doses (from 15 to 20/56 mg/m2) in the pooled dataset, the pooled exposure response analysis of efficacy endpoints across studies showed that after adjusting for baseline characteristics and prognostic factors, higher exposure (cycle 1 average AUC) of carfilzomib is associated with improved ORR/CBR across a dose range of 15 to 20/56 mg/m2

2.3.4. Discussion on clinical pharmacology

New data for the 30-minute infusion dose of 20/56 mg/m_2 mainly comes from the previously submitted trial PX-171-007: A Phase 1b/2, multicentre open label study of the safety and activity of carfilzomib in subjects with relapsed solid tumours, relapsed and/or refractory multiple myeloma or refractory lymphoma. Of note, the initial assessment of this trial was focused on the currently approved dose of 20/27 mg/m_2.

Based on data from studies PX-171-005 and PX-171-007, the exposure (AUC and C_{max}) increased in a dose-dependent manner from 15 to 56 mg/m^2 when looking at similar infusion durations. Dose-proportionality was assessed but was limited by the high variability in PK parameters and small sample size. Based on these data, Section 5.2 of the SmPC has been updated to reflect it.

The impact of 30-minute infusion compared to 2 to 10-minute infusion was assessed in the initial MA as part of study PX-171-007. Changes included in section 5.2. of SmPC come from study PX-171-007 and are acceptable:

"A 30-minute infusion resulted in a similar half-life and AUC, but 2- to 3-fold lower C_{max} compared to that observed with a 2- to 10-minute infusion of the same dose. Following a 30-minute infusion of the 56 mg/m_2 dose, the AUC (948 ng•hr/mL) was approximately 2.5-fold that observed at the 27 mg/m_2 level, and C_{max} (2079 ng/mL) was lower compared to that of 27 mg/m_2 over the 2- to 10-minute infusion".

Hence the following recommendation has been included in Section 5.2 of the SmPC:

"The Cmax and AUC following a 2- to 10-minute intravenous infusion of 27 mg/m^2 was 4,232 ng/mL and 379 ng•hr/mL, respectively. Following repeated doses of Kyprolis at 15 and 20 mg/m^2, systemic

exposure (AUC) and half-life were similar on days 1 and 15 or 16 of cycle 1, suggesting there was no systemic carfilzomib accumulation. At doses between 20 and ~~36~~ **56** mg/m^2, there was a dose-dependent increase in exposure".

An updated population PK model has been presented including, in addition to the previous clinical trials, data from study 2011-003 as well as preliminary data from the currently ongoing trials in patients with renal and hepatic impairment (CFZ001, CFZ002). Using the previously identified structural model for carfilzomib, a slight effect of BSA on clearance was observed. However, PK exposure metrics based on the final model found 95% of all subjects taking carfilzomib achieve exposure (Cmax and AUC) within 10% of the exposure for a subject with median BSA. The current population PK analysis did not identify any other clinically meaningful covariates that impacted the pharmacokinetic profile of carfilzomib. Shrinkage (%) is higher than 30% in the final PK model (Variation II- 001). In fact, because of the high (> 40%) shrinkage in the V1 random effects in the base model, visual assessment of the random effects versus the covariates was not used to select covariate models. Instead, an automated stepwise selection was used. It should be also noted that BQL (13.3%) has been omitted in this population PK. The "M3 BLQ method" which exclude data errors and assume all non-zero trough measurements to be BLQ observations (Beal 2001), was not explored in the current analysis as the previous population PK analysis (TR-1015-171-Marketing Authorization procedure) did not find that using the M3 BLQ replacement method resulted in substantially better fits. Of note due to the high shrinkage detected in the final PK model, the conclusion of this population PK model should be interpreted with caution. Regarding methods, the execution and results with NONMEN and Prediction corrected VPC were provided during the evaluation and were considered adequate.

Regarding renal impairment, study PX-171-005 and preliminary data on Study CFZ001 showed that the pharmacokinetics of carfilzomib was similar between subjects with normal renal function and subjects on dialysis (end-stage renal disease [ESRD]). These data suggest that the pharmacokinetics of carfilzomib is not influenced by the degree of baseline renal impairment; however this will be reviewed when the final study report for CFZ001 will be submitted through a variation by the second quarter of 2016.

Considering the metabolism of carfilzomib and its routes of excretion, hepatic impairment is not expected to have meaningful impact on pharmacokinetic of carfilzomib. However, its biological activity per se could be responsible of hepatic safety consequences. The hepatic impairment study CFZ002 is currently ongoing and the final study report will be submitted through a variation by the second quarter of 2016.

No new drug interaction studies have been performed. Taking into account that Carfilzomib displayed a modest direct, time-dependent inhibitory effect on human cytochrome P450 3A4/5 (CYP3A4/5), a DDI study with midazolam was conducted at the time of initial MA. Taking into account that doses higher than 27mg have not been tested in DDI study with midazolan, DDI cannot be ruled out at doses as high as 20/56 mg/m2. The applicant has developed a physiologically-based pharmacokinetic (PBPK) model to predict the potential effect of carfilzomib at doses of 56 and 70 mg/m2 on the pharmacokinetics of CYP3A substrate midazolam. Simulations using the PBPK model indicated no impact of carfilzomib on midazolam PK for the doses of 56 and 70 mg/m2, similar to the clinical data observed at 27 mg/m2. Hence, in order to properly address the issue, the CHMP recommends the submission of the PBPK report which is expected to be finalised by May 2016. In the meantime, the information included in the SmPC about this issue has been updated to reflect that the study with midazolam was conducted with dose of 27 mg/m2 (2-10 min infusion) and no data are available with dose of 56 mg/m2 (30 min infusion).

The following recommendation was made in section 5.1 of the SmpC with regards to the higher dose of 56 mg/m^2:

"At the higher dose of 56 mg/m^2, there was not only a greater inhibition of CT-L subunits (≥ 90%) compared to those at 15 to 20 mg/m^2, but also a greater inhibition of other proteasome subunits (LMP7, MECL1, and LMP2). There was an approximately 8%, 23% and 34% increase in the inhibition of LMP7, MECL1, and LMP2 subunits respectively at the dose of 56 mg/m^{2}compared to those at 15 to 20 mg/m^2. Similar proteasome inhibition by carfilzomib was achieved with 2- to 10-minute and 30-minute infusions at the 2 dose levels (20 and 36 mg/m^2) at which it was tested."

In Study PX-171-007, 26% of patients treated with a dose of 20/56 had a change from baseline in QTcB between 30 and 60 msec. Additionally, case of Torsade de pointes-QT prolongation (SMQB), syncope and sudden death had been observed in 1.9%, 1.1% and 0.4% of patients. However, as there was no clear signal of a dose/concentration-related effect of carfilzomib on cardiac repolarization using the QT interval with Fridericia's correction (QTcF interval) or from the analysis of concentration-QTc analysis in the initial marketing procedure, the current warning about QT interval prolongation included in the section 4.4 of SmPC is still considered adequate. Cardiac arrhythmias associated with carfilzomib treatment will continue to be monitored with routine pharmacovigilance.

Results from the updated exposure-response analysis were overall in line with the previously submitted report. Only a relationship was found in the pooled analysis between carfilzomib cycle 1 average AUC and ORR/CBR with increasing AUC associated with higher probability of response. No relation between exposure and safety endpoints was found.

2.3.5. Conclusions on clinical pharmacology

The pharmacology of Kyprolis for the new combination has been reasonably well investigated.

Changes under sections 4.5 (in relation with DDI study with midazolam), 5.1 and 5.2 (regarding pharmacodynamics of the newly proposed dose) have been implemented.

The CHMP recommends the submission of the PBPK report by October 2016.

In addition, the final study reports for the currently ongoing trials in patients with renal and hepatic impairment (CFZ001, CFZ002) will be provided in Q2 2016 in line with the RMP.

2.4. Clinical efficacy

2.4.1. Dose response studies

The carfilzomib dose of 20/56 mg/m^2 was selected for this head-to-head study based on evidence of a dose-response relationship and the hypothesis that a greater depth and duration of proteasome inhibition, which could be achieved with higher doses, could drive greater efficacy. Preclinical studies in rats showed that when comparable doses were tested, an increased infusion time led to lower maximum drug concentration in plasma (Cmax), comparable area under the plasma drug concentration time curve (AUC) and proteasome inhibition, and better tolerability (Jiang 2011; Yang 2011). A phase 1b study, PX-171-007 showed high response rates at higher doses of carfilzomib and identified 56 mg/m^2 as the

maximum tolerated dose (MTD) when infused over 30 minutes in subjects with relapsed or refractory multiple myeloma. Carfilzomib was highly active and well tolerated at a dose of 56 mg/m^2 when given alone or in combination with dexamethasone.

Main study

Study 2011-003 (ENDEAVOR)

Methods

Study 2011-003 was a randomized, open-label, phase 3 study of carfilzomib plus dexamethasone versus bortezomib plus dexamethasone in patients with relapsed multiple myeloma.

Study participants

Main inclusion criteria

- Multiple myeloma with relapsing or progressing disease at study entry
- Subjects must have evaluable multiple myeloma with at least 1 of the following (assessed by the central laboratory within 21 days prior to randomization):
    - Serum M-protein ⩾ 0.5 g/dL, or
    - Urine M-protein ⩾ 200 mg/24 hour, or
    - In subjects without detectable serum or urine M-protein, serum free light chain (SFLC) > 100 mg/L (involved light chain) and an abnormal serum Kappa/Lambda (κ/λ) ratio or
    - For immunoglobulin A (IgA) subjects whose disease can only be reliably measured by serum quantitative immunoglobulin (qIgA) ⩾ 750 mg/dL (0.75 g/dL).
- Subjects must have documented at least PR to at least 1 line of prior therapy. PR documentation can be based on investigator assessment.
- Received at least 1, but no more than 3 prior treatment regimens or lines of therapy for multiple myeloma. (Induction therapy followed by stem cell transplant and consolidation/maintenance therapy will be considered as 1 line of therapy.)
- Prior therapy with bortezomib is allowed as long as the subject had at least a PR to prior bortezomib therapy, was not removed from bortezomib therapy due to toxicity, and will have at least a 6-month bortezomib treatment-free interval from last dose received until first study treatment. (Subjects may receive maintenance therapy with drugs that are not in the proteasome inhibitor class during this 6-month bortezomib treatment-free interval.)
- Prior therapy with carfilzomib is allowed as long as the subject had at least a PR to prior carfilzomib therapy, was not removed from carfilzomib therapy due to toxicity, and had at least a 6-month carfilzomib treatment-free interval from last dose received until first study treatment.

(Subjects may receive maintenance therapy with drugs that are not in the proteasome inhibitor class during this 6-month carfilzomib treatment-free interval.) The exception to this is subjects randomized or previously randomized in any other Onyx-sponsored Phase 3 trial.

- Left ventricular ejection fraction ≥ 40%.
- Calculated or measured creatinine clearance (CrCL) of ≥ 15 mL/min within 21 days prior to randomization

Main exclusion criteria

- Multiple myeloma of immunoglobulin M (IgM) subtype
- Glucocorticoid therapy (prednisone > 30 mg/day or equivalent) within 14 days prior to randomization
- Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS) syndrome
- Plasma cell leukemia or circulating plasma cells $\geqslant 2 \times 109/L$
- Focal radiation therapy within 7 days prior to randomization. Radiation therapy to an extended field involving a significant volume of bone marrow within 21 days prior to randomization (i.e., prior radiation must have been to less than 30% of the bone marrow)
- Immunotherapy within 21 days prior to randomization
- Active congestive heart failure (New York Heart Association [NYHA] Class III to IV; refer to protocol Appendix H), symptomatic ischemia, or conduction abnormalities uncontrolled by conventional intervention. Myocardial infarction within 4 months prior to randomization
- Subjects with myelodysplastic syndrome
- Significant neuropathy (Grades 3 to 4, or Grade 2 with pain) within 14 days prior to randomization.

Treatments

Patients were randomized (1:1) to receive either carfilzomib with dexamethasone (Cd arm) or bortezomib with dexamethasone (Vd arm). Study treatment was administered to subjects in both arms until confirmed disease progression, physician decision, intolerable side effects necessitating discontinuation, withdrawal of consent, or death.

The treatments administered in each study arm are summarized below.

Carfilzomib Plus Dexamethasone Arm

Subjects randomized to the Cd arm received their assigned treatment in 28-day cycles as follows:

- Dexamethasone 20 mg was to be given on Days 1, 2, 8, 9, 15, 16 , 22, and 23 at least 30 minutes (but no more than 4 hours) prior to carfilzomib, on a schedule of every 28 days.

- On nonclinic days, dexamethasone oral (PO) could be self-administered at home. Missed doses of dexamethasone were not to be made up.
- Subjects were to maintain a diary of outpatient dexamethasone PO administration.

- Carfilzomib 20 mg/m^2 IV over 30 minutes (± 5 minutes) on Days 1 and 2 of Cycle 1, followed by escalation to 56 mg/m^2 over 30 minutes (± 5 minutes) on Days 8, 9, 15, and 16 of Cycle 1.
  - Subjects who tolerated 56 mg/m^2 in Cycle 1 were to be kept at this dose on Days 1, 2, 8, 9, 15, and 16 every 28 days until PD or intolerable side effects.

Carfilzomib was to be administered within ± 2 days of the scheduled dose. Anticipated treatment delays greater than 2 days were to be discussed with the medical monitor.

Bortezomib Plus Dexamethasone Arm

Subjects randomized to the Vd arm received their assigned treatment in 21-day cycles as follows:

- Dexamethasone 20 mg was to be given on Days 1, 2, 4, 5, 8, 9, 11, and 12 every 21 days at least 30 minutes (but no more than 4 hours) prior to bortezomib.
  - On nonclinic days, dexamethasone PO could be self-administered at home. Missed doses of dexamethasone were not to be made up.
  - Subjects were to maintain a diary of outpatient PO dexamethasone administration.
- Bortezomib 1.3 mg/m^2 IV push or SC (per regulatory approval) was to be given on Days 1, 4, 8, and 11 of each 21-day cycle until PD or intolerable side effects. Subjects were to continue to receive bortezomib with the same route of administration (SC or IV) throughout the study. A switch of route of administration for medical reasons could be made per the physician's discretion.

  Bortezomib was to be administered within ± 2 days of the scheduled dose. Anticipated treatment delays greater than 2 days were to be discussed with the medical monitor.

Intravenous hydration was to be given immediately prior to carfilzomib during Cycle 1 and at the investigator's discretion in Cycle 2 and higher. This was to consist of 250 to 500 mL normal saline or other appropriate IV fluid. The goal of the hydration program was to maintain robust urine output (e.g., $\geqslant$ 2 L/day). Subjects were to be monitored periodically during this period for evidence of fluid overload.

For subjects thought to be at particularly high risk for the development of tumour lysis syndrome (TLS), based on high tumor burden, guidance to begin oral hydration up to 48 hours before starting carfilzomib could be given.

The dose of carfilzomib was to be calculated using the subject's actual body surface area (BSA) at baseline. Subjects with a BSA > 2.2 m2 were to receive a dose based upon a 2.2 m2 BSA. Dose adjustments did not need to be made for weight gains/losses of $\leqslant$ 20%.

At Cycle 1 Day 1, the following treatments were also started:

- Valacyclovir 500 mg PO, once daily (or equivalent antiviral), continuing for the duration of treatment (additional prophylaxis was at the investigator's discretion).L
- Lansoprazole 15 mg PO, once daily (or other oral proton-pump inhibitor to prevent peptic ulcer disease according to institutional practice) for the duration of treatment with dexamethasone

Optional and allowed concomitant medications were:

- Allopurinol (or other approved uric acid-lowering agent) could be prescribed at the investigator's discretion in subjects at high risk for TLS due to high tumor burden.
- Mycostatin or oral fluconazole could be prescribed at the investigator's discretion to prevent oral thrush.
- Antiemetics and antidiarrheal agents could be administered as necessary.
- Myeloid growth factors could be used if neutropenia occurred but were not to be given prophylactically.
- Red blood cell transfusions, erythropoietin stimulating agents, or platelet transfusions were permitted if clinically indicated in accordance with institutional guidelines.
- Palliative radiation for pain management was permitted with the written approval of the medical monitor.
- Bisphosphonates were permitted as indicated and in accordance with institutional guidelines.

Objectives

The primary objective of this study was to compare PFS in subjects with multiple myeloma who relapsed after 1 to 3 prior therapies treated with carfilzomib plus dexamethasone (Cd) or bortezomib plus dexamethasone (Vd).

The secondary objectives of this study were to compare the following between the study arms: Overall survival (OS): Overall response rate (ORR); Neuropathy events; Safety and tolerability (assess change from baseline in left ventricular ejection fraction (LVEF), right ventricular (RV) function, and pulmonary artery pressure in a subset of subjects from both treatment groups).

Outcomes/endpoints

The primary endpoint of the study was PFS as determined by the IRC, defined as the time from randomization to the earlier of disease progression or death due to any cause.

The secondary endpoints were:

- OS, defined as the time from randomization to the date of death (whatever the cause).
- ORR, defined as the proportion of subjects in each study arm who achieved confirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) as their best response.
- Duration of response (DOR), defined as the time in months from the initial start of response (PR or better) to the earlier of documented progressive disease (PD) or death due to any cause.
- Neuropathy events, defined as the incidence of Grade 2 or higher peripheral neuropathy (PN), as specified by peripheral neuropathy Standardised MedDRA Query, narrow (scope) (SMQN) terms.

The study had the following exploratory objectives:

- Evaluate population pharmacokinetics (PK) for a subset of Cd subjects and pharmacokinetic/pharmacodynamic (PK/PDn) relationships for safety and efficacy
- Evaluate pharmacodynamic (PDn) and proteomic biomarkers in a subset of subjects from both treatment groups
- Analyse genetic and gene expression biomarkers that may potentially predict for response and

resistance following treatment with proteasome inhibitors from all subjects who consent to optional genomic biomarker analysis

- Compare TTP between the treatment groups
- Compare CBR (defined as ORR + minimal response [MR]) between the treatment groups
- Compare DCR (defined as ORR + MR + stable disease [SD] lasting at least 8 weeks) between the treatment groups
- Compare Global Health Status/Quality of Life (QoL) (measured by EORTC Quality of Life Questionnaire QLQ-C30)
- Compare subscales of the EORTC QLQ-C30, QLQ-MY20, and FACT/GOG-Ntx (Version 4; "Additional Concerns" questionnaire) between the treatment groups and describe Medical Resource Utilization (MRU)
- Evaluate minimal residual disease (MRD) status: The frequency of MRD negativity when CR, sCR, or VGPR is achieved

Sample size

It was estimated that 526 PFS events would provide 90% power to detect a PFS hazard ratio (HR) of 0.75 with 1-sided overall Type-I error of 0.025 when 1 interim analysis was performed at 75% of information time (i.e., 75% of 526 PFS events) using O'Brien-Fleming type alpha spending function. A total of 888 subjects enrolled over a 22-month period, including 9 months of enrolment ramp-up period and followed for an additional 8 months after the planned closure of enrolment, was expected to result in the required 526 events. Additional assumptions that informed sample size calculation included exponential distribution for PFS, 10.0 months median PFS for Regimen Vd (i.e., 13.3 months median PFS for Regimen Cd), and a 3% rate for loss to follow-up.

The final analysis of OS was to be performed after approximately 496 deaths occurred. A total of 496 deaths would provide 69% power to detect a HR of 0.8 corresponding to a 20% reduction in risk of death for Cd versus Vd, with a 1-sided significance level of 0.025 and 2 planned OS interim analyses. This is based on historical data and is under the assumption of 29.8 months of median OS for the Vd arm and the exponential distribution of OS (Richardson 2005). A 2% loss to follow-up for the OS endpoint was also assumed in this calculation.

Randomisation

Subjects were randomized in a 1:1 ratio to receive either Cd or Vd through an interactive voice or interactive web response system (IXRS). Randomization was stratified based on:

- Prior proteasome inhibitor treatment (Yes or No)
- International Staging System (ISS) Stage (Stage 1 versus Stages 2 or 3)
- Lines of prior treatment (1 versus 2 or 3 lines)
- Choice of route of bortezomib administration (IV versus SC - in accordance with local regulatory approved route of administration)

Blinding (masking)

This was an open-label study.

Statistical methods

General considerations

Summary statistics were to be provided for the primary, secondary, and exploratory endpoints. For continuous variables, the number of subjects with non-missing data, mean, either the standard of error or the standard deviation, median, 25th percentile (first quartile), 75th percentile (third quartile), minimum, and maximum were to be presented for each study arm. The distribution of time-to-event endpoints was to be summarized by Kaplan-Meier method. Quartiles, including median were to be estimated by Kaplan-Meier method along with their 95% CIs by Klein and Moeschberger (1997) with log-log transformation for each study arm. Duration of follow-up for time-to-event endpoints was to be summarized for each study arm by reverse Kaplan-Meier method (Schemper 1996). For discrete variables, frequencies and percentages were to be presented. Point estimates were to be accompanied by 2-sided 95% CIs.

Analysis populations

The Intent-to-Treat (ITT) Population was the basis for the primary analysis of efficacy in this study, and it consisted of all randomized subjects. Subjects in the ITT Population were included in the treatment group to which they were randomized. All efficacy endpoints (PFS, OS, ORR, TTP, CBR, and DCR) were analysed in the ITT Population.

Independent review committee and Independent Data Monitoring Committee

The primary responsibility of the IRC was the independent assessment of subject efficacy outcomes in accordance with the IMWG-URC. The IRC assessments were made without knowledge of the randomization assignments, subject, site, investigator identity, or individual subject efficacy outcomes, as determined by the local investigators and ORCA. The outcomes determined by the IRC were to serve as the primary data source for the primary interim and final analysis for PFS. The IRC was not responsible for assessing safety. The IRC was composed of 3 independent multiple myeloma experts

An IDMC was convened for this study and acted in an advisory capacity to the sponsor with respect to safeguarding the interests of study subjects, assessing interim safety and efficacy data, and monitoring the overall conduct of the study. The IDMC provided recommendations for stopping or continuing the study. The IDMC was composed of 3 experts in multiple myeloma and 1 biostatistician

Study endpoints

Progression-free survival was defined as the duration in months from randomization to the earlier of disease progression or death due to any cause. Response and disease progression were to be centrally reviewed by the IRC and also, for supportive analyses, determined by the sponsor using Onyx Response Computational Assessment (ORCA), a computer algorithm prespecified before the unblinded interim efficacy analysis, as well as investigators. The primary data source for the final analysis was to be the results determined by the IRC. Analyses of concordance and discordance between the IRC, local investigators, and ORCA assessments of disease response and progression were also to be performed. The discordance between the results from the local investigator, ORCA evaluation, and IRC were to be summarized overall and by study arm.

The robustness of the PFS analysis based on disease outcomes determined by the IRC was evaluated using the following prespecified sensitivity analyses: Progression-free survival assessed by local

investigators; Progression-free survival assessed by the sponsor using disease ORCA; Unstratified analysis; Initiation of nonprotocol anticancer therapy treated as a PFS event; Initiation of nonprotocol anticancer therapy treated as neither a PFS event nor a censoring event; Missing assessments treated as censoring events in Vd arm and as PFS events in the Cd arm

- Changes over time in QLQ-C30 Global Health Scale/QoL score were to be compared between treatment groups using a restricted maximum likelihood-based mixed model for repeated measures (MMRM). The dependent variable of this model was the QLQ-C30 Global Health Scale/QoL visit score measured every 4 weeks (every 28 days ± 4 days), including baseline visits. The model was to include treatment effect (Cd versus Vd), as well as the 4 randomization stratification factors, as fixed effects. Analyses of selected subscales of QLQ-C30 and QLQ-MY20 were also performed.

- The FACT/GOG-Ntx scores were analyzed using the same MMRM modeling approach that was used for analysis of the QLQ-C30 Global Health Scale/QoL scale

Interim analysis

The PFS interim analysis was to be performed using a group sequential monitoring plan. The monitoring plan included an O'Brien-Fleming type of efficacy stopping boundary constructed using the Lan-DeMets alpha spending function (Lan 1983; DeMets 1995) to ensure a 1-sided Type I error rate $\leqslant$ 0.025. The monitoring boundary was adjusted by the IDMC to correspond to the actual events observed at the interim analysis using the same design method as described.

Table 1. Monitoring Criteria and Alpha Spending at the Interim and Final Analyses of Progression-Free Survival

Information Fraction	Number of Events	Estimated Study Month	Crossing Boundary for Efficacy		
			Nominal Significance Level	Alpha Spent	Cumulative Alpha Spent
75%	395	25	0.0096	0.0096	0.0096
100%	526	36	0.0216	0.0135	0.025

The OS analysis at the primary PFS analysis (either interim or final PFS analysis time) was the first OS interim analysis. All other secondary endpoints will be final at the primary PFS analysis time.

Results

Participant flow

Table 2: Subject Disposition (Study 2011-003)

	Vd (N = 465) n (%)	Cd (N = 464) n (%)	Total (N = 929) n (%)
Screened	—	—	1096
Screened but Not Randomized	—	—	167
Randomized (ITT Population)	465 (50.1)	464 (49.9)	929 (100.0)
Randomized but Not Dosed	9 (1.9)	1 (0.2)	10 (1.1)
Number of Subjects Currently being Treated	105 (22.6)	200 (43.1)	305 (32.8)
Number of Subjects Discontinued from Treatment	351 (75.5)	263 (56.7)	614 (66.1)
Reason for Study Treatment Discontinuation			
Disease progression	168 (36.1)	117 (25.2)	285 (30.7)
Adverse event	73 (15.7)	65 (14.0)	138 (14.9)
Patient request	45 (9.7)	40 (8.6)	85 (9.1)
Investigator decision	35 (7.5)	18 (3.9)	53 (5.7)
Withdrew consent	19 (4.1)	6 (1.3)	25 (2.7)
Death	9 (1.9)	13 (2.8)	22 (2.4)
Protocol noncompliance	1 (0.2)	4 (0.9)	5 (0.5)
Lost to follow-up	1 (0.2)	0	1 (0.1)
Number of Subjects in LTFU	298 (64.1)	218 (47.0)	516 (55.5)
Disease progression[a]	63 (13.5)	32 (6.9)	95 (10.2)
Reason for Discontinuation from LTFU			
Death	69 (14.8)	58 (12.5)	127 (13.7)
Lost to follow-up	9 (1.9)	2 (0.4)	11 (1.2)
Withdrew consent	5 (1.1)	5 (1.1)	10 (1.1)

Cd = carfilzomib plus dexamethasone arm; ITT = intent-to-treat; LTFU = long-term follow-up;
n = number of subjects assessed for this event; N = number of subjects in ITT Population;
Vd = bortezomib (Velcade) plus dexamethasone arm.

[a] Subjects who discontinue treatment prior to PD enter LTFU until subject withdraws consent, subject is lost to follow-up, subject has died, or the sponsor makes a decision to close the study.

Recruitment

In total, 929 subjects from 198 sites in 27 countries (located in Asia-Pacific, Eastern and Western Europe, North America, and Brazil) were enrolled. The study started on 20 June 2012 and completed on 10 November 2014.

Conduct of the study

There were 3 protocol amendments after the original protocol. Protocol amendments and protocol deviations are summarized below.

Table 3. Protocol amendments (Study 2011-003)

Amendment Number	Version Date	Main Purpose(s) for the Protocol Amendment
Original	13 March 2012	Not applicable
Amendment 1.0	19 December 2012	The main purpose of this amendment was to incorporate the changes from the carfilzomib Investigator's Brochure, Version 11.0 (dated 22 August 2012). Updated text of importance was included in the background information regarding relevant Phase 1 and 2 carfilzomib studies; safety and efficacy text due the carfilzomib marketing approval by the US FDA (July 2012). This amendment also included the addition of assessments for the cardiac and pulmonary substudy safety monitoring, as specified in the study objectives, as follows: • Right ventricular (RV) function, RV size, RV wall thickness; and • Pulmonary artery pressure in all subjects at baseline as well as every 12 weeks, and at the end of study for those subjects who participate in the echocardiogram substudy. The following exploratory objectives were added: • Evaluate PK/PDn relationships for safety and efficacy. • Analyze genetic and gene expression biomarkers that may potentially predict for response and resistance following treatment with proteasome inhibitors from all subjects who consent to optional genomic biomarker analysis. The amendment also provided administrative updates, editorial changes, and style and formatting revisions to improve clarity and consistency. Changes to inclusion/exclusion criteria based on this amendment are presented in Appendix 16.1.1.1.
Amendment 2.0	02 October 2014	The main purpose of this amendment was to specify that the Global Health Status/QoL Scale (measured by EORTC) subscale was to be analyzed as a secondary endpoint and that other subscales were to be analyzed as exploratory endpoints (EORTC QLQ-C30, QLQ-MY20, FACT-GOG/Ntx, and MRU). Additional major changes included the following: • Added the MRD status exploratory endpoint. • Specified the timing and details regarding bone marrow aspirate samples that were to be collected as part of the optional MRD analysis. • Clarified procedures for survival follow-up in order to collect OS data using ad hoc survival sweeps • Clarified that plasma concentrations of carfilzomib, along with other potential excipients, were to be determined as needed based on carfilzomib PK data analysis. The amendment also provided administrative updates, editorial changes, and style and formatting revisions to improve clarity and consistency. There were no changes to inclusion/exclusion criteria based on this amendment.
Amendment 3.0	09 January 2015	The main purpose of this amendment was to specify that the number of OS events to study end was changed from 631 to 496, the number of interim analyses for OS was changed from 1 to 2, and the selected landmarks for estimating survival rate were changed from "6 months, 9 months, and 1 year" to "1 year, 2 years, and 3 years" from randomization. Additional major changes included the following: • Changes in statistical analyses of secondary endpoints resulting from changes in final number of OS events were included as necessary. • The Global Health Status/QoL subscale (measured by EORTC QLQ-C30) was moved from a secondary endpoint to an exploratory endpoint • The FACT/GOG-Ntx questionnaire score was removed from the definition of neuropathy events and the joint model. The amendment also provided administrative updates, editorial changes, and style and formatting revisions to improve clarity and consistency. Changes to inclusion/ exclusion criteria based on this amendment are presented in Appendix 16.1.1.1.

EORTC = European Organization for Research and Treatment of Cancer;
FACT-GOG/Ntx = Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity (subscale questionnaire); MRD = minimal residual disease; MRU = Medical Resource Utilization;
OS = overall survival; RV = right ventricular; PDn = pharmacodynamics; PK = pharmacokinetic;
QoL = Quality of Life; QLQ-C30 = Quality of Life Questionnaire Core Module; QLQ-MY20 = Quality of Life Questionnaire for Multiple Myeloma; US FDA = United States Food and Drug Administration.

Table 4. Important protocol deviations (Study 2011-003)

Protocol Deviation Category, n (%)	Vd (n = 465)	Cd (n = 464)	Total (N = 929)
Important Protocol Deviations	**72 (15.5)**	**75 (16.2)**	**147 (15.8)**
Eligibility Criteria Not Met	5 (1.1)	6 (1.3)	11 (1.2)
I04: No prior treatment or more than three prior treatments	2 (0.4)	0	2 (0.2)
I05: Patient does not have at least a PR to any prior bortezomib, or had bortezomib discontinued due to toxicity, or has less than a 6-month bortezomib treatment-free interval	1 (0.2)	1 (0.2)	2 (0.2)
E02: Glucocorticoid therapy within 14 days prior to randomization	1 (0.2)	0	1 (0.1)
Deviation from E07: Chemotherapy within 21 days prior to randomization	0	1 (0.2)	1 (0.1)
Deviation from E08: Patients randomized or previously randomized in any other Onyx-Sponsored Phase 3 trial	1 (0.2)	0	1 (0.1)
Deviation from E09: Focal radiation therapy within 7 days prior to randomization; radiation therapy to an extended field within 21 days prior to randomization	0	1 (0.2)	1 (0.1)
Deviation from E16: Second malignancy within the past 3 years	0	1 (0.2)	1 (0.1)
Deviation from I11: Absolute neutrophil count of $< 1 \times 10/L$ within 21 days prior to randomization	0	1 (0.2)	1 (0.1)
Deviation from I12: Hemoglobin of < 8 g/dL within 21 days prior to randomization	0	1 (0.2)	1 (0.1)
Deviation from Drug Administration Routine	7 (1.5)	12 (2.6)	19 (2.0)
Continuing to receive treatment after confirmed PD	3 (0.6)	6 (1.3)	9 (1.0)
Concomitant use of marketed or investigational anticancer therapy before discontinuation of study treatment	3 (0.6)	2 (0.4)	5 (0.5)
Receiving more than 20% over the protocol specified dose	2 (0.4)	4 (0.9)	6 (0.6)
Deviation from Randomization Schema	64 (13.8)	61 (13.1)	125 (13.5)
Randomized to wrong strata	64 (13.8)	61 (13.1)	125 (13.5)
Deviation Regarding Safety Assessments	0	1 (0.2)	1 (0.1)
Missing pregnancy test for childbearing age females	0	1 (0.2)	1 (0.1)

Cd = carfilzomib plus dexamethasone arm; ITT = intent to treat; PD = progressive disease;
PR = partial response; Vd = bortezomib (Velcade) plus dexamethasone arm;.
Note: Subjects could be counted in more than 1 row.

Baseline data

Table 5. Demographics (Intent-to-Treat Population; Study 2011-003)

Demographic	Vd (N = 465) n (%)	Cd (N = 464) n (%)	Total (N = 929) n (%)
Age (years)			
Median (minimum, maximum)	65.0 (30.0, 88.0)	65.0 (35.0, 89.0)	65.0 (30.0, 89.0)
Age Group (years)			
< 65	210 (45.2)	223 (48.1)	433 (46.6)
65–74	189 (40.6)	164 (35.3)	353 (38.0)
≥ 75	66 (14.2)	77 (16.6)	143 (15.4)
Sex			
Female	236 (50.8)	224 (48.3)	460 (49.5)
Male	229 (49.2)	240 (51.7)	469 (50.5)
Ethnicity			
Hispanic or Latino	21 (4.5)	19 (4.1)	40 (4.3)
Not Hispanic or Latino	385 (82.8)	379 (81.7)	764 (82.2)
Not Reported	59 (12.7)	66 (14.2)	125 (13.5)
Race			
White	353 (75.9)	348 (75.0)	701 (75.5)
Black	9 (1.9)	8 (1.7)	17 (1.8)
Asian	57 (12.3)	56 (12.1)	113 (12.2)
Native Hawaiian/Other Pacific Islander	0	2 (0.4)	2 (0.2)
Not Reported	45 (9.7)	50 (10.8)	95 (10.2)
Multiple	1 (0.2)	0 (0.0)	1 (0.1)
Geographic Region			
Eastern Europe	121 (26.0)	135 (29.1)	256 (27.6)
Western Europe	169 (36.3)	182 (39.2)	351 (37.8)
North America	49 (10.5)	35 (7.5)	84 (9.0)
South America	15 (3.2)	10 (2.2)	25 (2.7)
Asia-Pacific	111 (23.9)	102 (22.0)	213 (22.9)

Table 6. Baseline patient characteristics (Intent-to-treat population; Study 2011-003)

	Vd (N = 465)	Cd (N = 464)	Total (N = 929)
Height (cm)			
N	452	460	912
Median (minimum, maximum)	164.0 (130.0, 194.0)	165.0 (131.0, 201.0)	165.0 (130.0, 201.0)
Weight (kg)			
N	456	463	919
Median (minimum, maximum)	73.2 (40.0, 162.8)	75.0 (37.0, 140.0)	74.0 (37.0, 162.8)
BSA (m^2)			
N	455	463	918
Median (minimum, maximum)	1.8 (1.2, 2.8)	1.8 (1.2, 3.0)	1.8 (1.2, 3.0)
ECOG Performance Status – n (%)			
0	232 (49.9)	221 (47.6)	453 (48.8)
1	203 (43.7)	211 (45.5)	414 (44.6)
2	30 (6.5)	32 (6.9)	62 (6.7)
Creatinine Clearance (Sponsor calculated[a]) (mL/min)			
N	465	464	929
Mean (StD)	75.1 (32.4)	76.7 (31.8)	75.9 (32.1)
Median (minimum, maximum)	72.0 (12.0, 208.0)	73.0 (14.0, 185.0)	73.0 (12.0, 208.0)
Creatinine Clearance – n (%)			
< 30 mL/min	28 (6.0)	28 (6.0)	56 (6.0)
30 – < 50 mL/min	71 (15.3)	57 (12.3)	128 (13.8)
50 – < 80 mL/min	177 (38.1)	186 (40.1)	363 (39.1)
≥ 80 mL/min	189 (40.6)	193 (41.6)	382 (41.1)
LDH (U/L)			
N	465	464	929
Mean (StD)	195.1 (107.3)	217.7 (172.0)	206.4 (143.7)
Median (minimum, maximum)	170.0 (70.0, 1033.0)	180.5 (24.0, 2130.0)	174.0 (24.0, 2130.0)
LVEF %			
N	461	457	918
Mean (StD)	63.5 (6.6)	63.1 (6.9)	63.3 (6.8)
Median (minimum, maximum)	64.0 (40.0, 84.0)	63.0 (40.0, 83.0)	63.9 (40.0, 84.0)
Subjects with Any History of Neuropathy			
Yes	244 (52.5)	215 (46.3)	459 (49.4)
No	221 (47.5)	249 (53.7)	470 (50.6)
Neuropathy Ongoing at screening			
Grade 1 (mild)	159 (34.2)	133 (28.7)	292 (31.4)
Grade 2 (moderate)	10 (2.2)	10 (2.2)	20 (2.2)

BSA = body surface area; Cd = carfilzomib plus dexamethasone arm; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; LVEF = left ventricular ejection fraction; min = minute; N = number of subjects in Intent-to-Treat Population; n = number of subjects assessed for this Baseline Characteristic; StD = standard deviation; Vd = bortezomib (Velcade) plus dexamethasone arm.

[a] Creatinine clearance was calculated using the Cockcroft-Gault formula.

Table 7. Baseline disease characteristics (Intent-to-treat population; Study 2011-003)

	Vd (N = 465)	Cd (N = 464)	Total (N = 929)
Time from initial diagnosis to randomization (months)			
N	464	464	928
Mean (StD)	54.4 (39.5)	54.0 (38.9)	54.2 (39.2)
Median (minimum, maximum)	43.3 (5.4, 306.2)	44.3 (4.0, 246.6)	44.0 (4.0, 306.2)
Subjects with measureable disease at baseline – n (%)			
Yes	462 (99.4)	463 (99.8)	925 (99.6)
Both SPEP and UPEP	90 (19.4)	124 (26.7)	214 (23.0)
SPEP only	278 (59.8)	240 (51.7)	518 (55.8)
UPEP only	62 (13.3)	71 (15.3)	133 (14.3)
SFLC only	32 (6.9)	28 (6.0)	60 (6.5)
No*	3 (0.6)	1 (0.2)	4 (0.4)
M-protein heavy and light chain isotypes – n (%)			
IgG	284 (61.1)	286 (61.6)	570 (61.4)
Kappa	200 (43.0)	177 (38.1)	377 (40.6)
Lambda	84 (18.1)	108 (23.3)	192 (20.7)
Unknown	0	1 (0.2)	1 (0.1)
IgA	105 (22.6)	90 (19.4)	195 (21.0)
Kappa	64 (13.8)	52 (11.2)	116 (12.5)
Lambda	41 (8.8)	37 (8.0)	78 (8.4)
Unknown	0	1 (0.2)	1 (0.1)
IgD	4 (0.9)	6 (1.3)	10 (1.1)
Kappa	1 (0.2)	3 (0.6)	4 (0.4)
Lambda	3 (0.6)	3 (0.6)	6 (0.6)
Unknown	72 (15.5)	82 (17.7)	154 (16.6)
Kappa	42 (9.0)	48 (10.3)	90 (9.7)
Lambda	30 (6.5)	33 (7.1)	63 (6.8)
Unknown	0	1 (0.2)	1 (0.1)

Serum free light chain Kappa/Lambda ratio – n (%)			
Normal	45 (9.7)	30 (6.5)	75 (8.1)
Abnormal	418 (89.9)	433 (93.3)	851 (91.6)
Unknown	2 (0.4)	1 (0.2)	3 (0.3)
Presence of any plasmacytoma - n (%)			
Yes	24 (5.2)	29 (6.3)	53 (5.7)
No	441 (94.8)	435 (93.8)	876 (94.3)
Presence of any lytic bone lesion – n (%)			
Yes	340 (73.1)	348 (75.0)	688 (74.1)
No	125 (26.9)	116 (25.0)	241 (25.9)
Plasma cell involvement in bone marrow (%)			
N	438	437	875
Mean (StD)	25.9 (27.2)	24.5 (25.7)	25.2 (26.5)
Median (minimum, maximum)	16.0 (0.0, 100.0)	14.0 (0.0, 100.0)	15.0 (0.0, 100.0)
Albumin level (g/dL)			
N	465	463	928
Mean (StD)	4.0 (0.5)	4.0 (0.6)	4.0 (0.6)
Median (minimum, maximum)	4.1 (2.0, 5.6)	4.1 (1.6, 5.5)	4.1 (1.6, 5.6)
Group by albumin level – n (%)			
< 3.5 g/dL	62 (13.3)	62 (13.4)	124 (13.3)
≥ 3.5 g/dL	403 (86.7)	401 (86.4)	804 (86.5)
Unknown	0	1 (0.2)	1 (0.1)
Corrected serum calcium[b] (mg/dL)			
N	465	464	929
Mean (StD)	9.6 (0.8)	9.6 (0.7)	9.6 (0.8)
Median (minimum, maximum)	9.6 (7.0, 16.8)	9.6 (4.2, 15.2)	9.6 (4.2, 16.8)
Group by corrected serum calcium level – n (%)			
≤ 11.5 g/dL	456 (98.1)	457 (98.5)	913 (98.3)
> 11.5 g/dL	9 (1.9)	7 (1.5)	16 (1.7)

Beta-2 microglobulin level (mg/L)			
N	465	464	929
Mean (StD)	4.8 (3.9)	4.6 (3.0)	4.7 (3.5)
Median (minimum, maximum)	3.7 (1.2, 35.3)	3.6 (1.4, 24.2)	3.6 (1.2, 35.3)
Group by beta-2 microglobulin level – n (%)			
< 3.5 g/dL	216 (46.5)	220 (47.4)	436 (46.9)
≥ 3.5 g/dL	249 (53.5)	244 (52.6)	493 (53.1)
Risk group as determined by FISH – n (%)[c]			
High-risk cytogenetics group	113 (24.3)	97 (20.9)	210 (22.6)
del(17p)	52 (11.2)	40 (8.6)	92 (9.9)
t(14;16)	9 (1.9)	10 (2.2)	19 (2.0)
t(4;14)	61 (13.1)	50 (10.8)	111 (11.9)
Standard risk cytogenetics group	291 (62.6)	284 (61.2)	575 (61.9)
Unknown	30 (6.5)	55 (11.9)	85 (9.1)
Missing	31 (6.7)	28 (6.0)	59 (6.4)
ISS stage per IVRS – n (%)			
Stage 1	204 (43.9)	205 (44.2)	409 (44.0)
Stage 2 or 3	261 (56.1)	259 (55.8)	520 (56.0)
ISS stage at baseline – n (%)			
Stage 1	205 (44.1)	212 (45.7)	417 (44.9)
Stage 2	151 (32.5)	138 (29.7)	289 (31.1)
Stage 3	109 (23.4)	114 (24.6)	223 (24.0)

Cd = carfilzomib plus dexamethasone arm; FISH = fluorescence in situ hybridization; Ig = immunoglobulin (IgA, IgD, IgG); ISS = International Staging System; ITT = intent-to-treat; IXRS = interactive voice recognition system or Interactive Web Response System; n = number of subjects assessed for this Baseline Disease Characteristic; N = number of subjects in ITT Population; SFLC = serum free light chain; SPEP = serum protein electrophoresis; StD = standard deviation; UPEP = urine protein electrophoresis; Vd = bortezomib (Velcade) plus dexamethasone arm.

Note: The baseline value was defined as the last available measurement taken before Cycle 1 Day 1.

[a] Subjects were measurable at screening.

[b] When albumin < 4 g/dL, serum calcium (mg/dL) was corrected as: serum calcium (mg/dL) + (0.8 × (4 – albumin [g/dL]).

[c] High-risk subjects have genetic subtypes t(4; 14), t(14;16), or del(17p), whereas standard-risk subjects do not. The unknown risk group included subjects who have FISH assessment, but the result of one or more genetic subtypes are not available.

Table 8. Prior therapy for Multiple Myeloma (Study 2011-003)

	Vd (N = 465)	Cd (N = 464)	Total (N = 929)
Prior systemic cancer therapy for multiple myeloma – n (%)			
Yes	465 (100.0)	464 (100.0)	929 (100.0)
Number of prior regimens by subject			
1	232 (49.9)	232 (50.0)	464 (49.9)
2	145 (31.2)	157 (33.8)	302 (32.5)
3	87 (18.7)	75 (16.2)	162 (17.4)
4	1 (0.2)	0 (0.0)	1 (0.1)
Prior transplant for multiple myeloma – n (%)			
Yes	272 (58.5)	266 (57.3)	538 (57.9)
No	193 (41.5)	198 (42.7)	391 (42.1)
Type of transplant[a]			
Autologous	268 (57.6)	262 (56.5)	530 (57.1)
Allogenic	4 (0.9)	6 (1.3)	10 (1.1)
Prior IMiD treatment – n (%)			
Lenalidomide	177 (38.1)	177 (38.1)	354 (38.1)
Thalidomide	247 (53.1)	211 (45.5)	458 (49.3)
Prior proteasome inhibitor treatment – n (%)			
Carfilzomib	1 (0.2)	2 (0.4)	3 (0.3)
Bortezomib	252 (54.2)	250 (53.9)	502 (54.0)
No prior carfilzomib or bortezomib	212 (45.6)	212 (45.7)	424 (45.6)
Time since last prior proteasome inhibitory treatment (months)			
N	253	252	505
Mean (StD)	26.4 (17.7)	28.1 (18.4)	27.2 (18.0)
Median (minimum, maximum)	21.0 (6.0, 92.6)	22.7 (4.4, 96.5)	21.6 (4.4, 96.5)
Best response to last prior systemic regimen – n (%)			
Stringent complete response	12 (2.6)	10 (2.2)	22 (2.4)
Complete response	117 (25.2)	103 (22.2)	220 (23.7)
Very good partial response	107 (23.0)	105 (22.6)	212 (22.8)
Partial response	177 (38.1)	192 (41.4)	369 (39.7)
Minimal response	1 (0.2)	0	1 (0.1)
Stable disease	32 (6.9)	36 (7.8)	68 (7.3)
Progressive disease	18 (3.9)	17 (3.7)	35 (3.8)
Unknown	1 (0.2)	1 (0.2)	2 (0.2)
Refractory to last prior systemic therapy – n (%)			
Yes	188 (40.4)	184 (39.7)	372 (40.0)
No	277 (59.6)	280 (60.3)	557 (60.0)
Refractory to any prior bortezomib therapy – n (%)			
Yes	19 (4.1)	15 (3.2)	34 (3.7)
No	446 (95.9)	449 (96.8)	895 (96.3)
Time since end of last prior systemic regimen (months)			
N	464	464	928
Mean (StD)	17.3 (21.3)	17.5 (22.2)	17.4 (21.7)
Median (minimum, maximum)	10.0 (0.0, 150.6)	11.0 (0.2, 195.1)	10.5 (0.0, 195.1)

Cd = carfilzomib plus dexamethasone arm; IMiD = immunomodulatory drug;
n = number of subjects assessed for prior therapy; N = number of subjects in Intent-to-Treat Population;
StD = standard deviation; Vd = bortezomib (Velcade) plus dexamethasone arm.

Note: Refractory was defined as disease not achieving a minimal response or better, progressing during therapy, or within 60 days after completion of therapy.

[a] Subjects may be counted in more than one subcategory.

Numbers analysed

Table 9. Analysis sets (Study 2011-003)

	Vd (N = 465) n (%)	Cd (N = 464) n (%)	Total (N = 929) n (%)
ITT Population	465 (100.0)	464 (100.0)	929 (100.0)
Safety Population	456 (98.1)	463 (99.8)	919 (98.9)
Received randomized treatment	456 (98.1)	463 (99.8)	919 (98.9)
Received nonrandomized treatment	0	0	0
Safety Population Exclusion[a]	9 (1.9)	1 (0.2)	10 (1.1)
Cardiac/Pulmonary Evaluable Population[b]	76 (16.3)	75 (16.2)	151 (16.3)

Cd = carfilzomib plus dexamethasone arm; ITT = intent-to-treat; n = number of subjects assessed for this event;
N = number of subjects in ITT Population; Vd = bortezomib (Velcade) plus dexamethasone arm.

[a] Excluded are subjects who did not receive any study drug.

[b] This population was defined as all randomized subjects who are enrolled in the cardiac function and pulmonary artery pressure substudy with evaluable baseline echocardiogram scans per central lab.

Outcomes and estimation

Primary endpoint – PFS by IRC

Table 10. Summary of PFS by IRC (Study 2011-003)

	Vd (N = 465)	Cd (N = 464)
Total PFS events – n (%)	243 (52.3)	171 (36.9)
Progressed	228 (49.0)	150 (32.3)
Died without disease progression	15 (3.2)	21 (4.5)
Censored – n (%)	222 (47.7)	293 (63.1)
Reasons censored		
No baseline assessment	0	0
Alive without progression	157 (33.8)	258 (55.6)
Event after consecutively missed more than 1 assessment[a]	6 (1.3)	4 (0.9)
Started new anticancer treatment before PD or death	29 (6.2)	23 (5.0)
Lost to follow-up or withdrew consent	30 (6.5)	8 (1.7)
Hazard ratio (Cd/Vd) (95% CI) stratified[b]	0.533 (0.437, 0.651)	
Log-rank p-value (1-sided) stratified[b]	< 0.0001	
PFS Duration (months)[c]		
N	465	464
25th percentile (95% CI)	4.6 (3.8, 5.6)	6.8 (5.8, 8.3)
Median (95% CI)	9.4 (8.4, 10.4)	18.7 (15.6, NE)
75th percentile (95% CI)	16.6 (15.1, NE)	NE (NE, NE)
Minimum, maximum (+ for censored)	0+, 24+	0, 26+
PFS Event-Free Rate (95% CI)[c]		
3 months	83.2 (79.4, 86.4)	88.4 (85.1, 91.0)
6 months	65.8 (61.0, 70.1)	79.0 (74.9, 82.5)
9 months	51.9 (46.8, 56.7)	68.9 (64.3, 73.0)
12 months	41.5 (36.1, 46.9)	62.7 (57.6, 67.3)
15 months	31.5 (25.6, 37.6)	56.9 (51.1, 62.3)
18 months	22.2 (15.3, 29.8)	52.4 (45.7, 58.6)
21 months	22.2 (15.3, 29.8)	49.4 (42.0, 56.5)
24 months	22.2 (15.3, 29.8)	43.9 (31.8, 55.5)
Follow-up time for PFS (months)[d]		
N	465	464
25th percentile (95% CI)	8.2 (7.4, 8.5)	9.3 (8.5, 9.3)
Median (95% CI)	11.1 (10.2, 11.4)	11.9 (11.2, 12.4)
75th percentile (95% CI)	14.3 (13.5, 15.7)	16.1 (14.9, 16.9)
Minimum, maximum (+ for censored)	0+, 24+	0, 26+

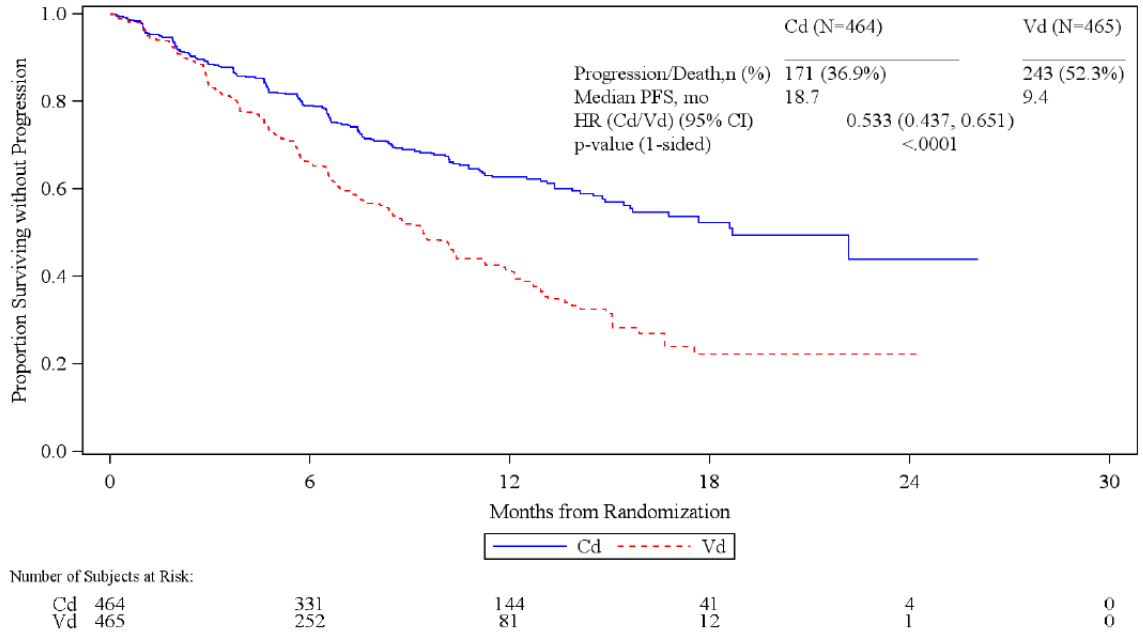
Cd = carfilzomib plus dexamethasone arm; CI = confidence interval; IV = intravenous; n = number of subjects assessed for this event; N = number of subjects in Intent-to-Treat Population; NE = not estimable; PD = progressive disease; PFS = progression-free survival; SC = subcutaneous; Vd = bortezomib (Velcade) plus dexamethasone arm.

[a] Defined as missing disease assessments for more than 64 days, or more than 71 days if relative to randomization.

[b] Randomization stratification factors: Prior proteasome inhibitor treatment (prior carfilzomib or bortezomib versus no prior carfilzomib or bortezomib treatment); lines of prior treatment (1 versus 2 or 3); International Staging System stage (1 versus 2 or 3); choice of route of bortezomib administration (IV versus SC).

[c] Median, percentiles, and event-free rate were estimated using the Kaplan-Meier method. CIs for median and percentiles were estimated using the method by Klein and Moeschberger (1997) with log-log transformation. CIs for event-free rates were estimated using the method by Kalbfleisch and Prentice (1980) with log-log transformation.

[d] Medians and percentiles of follow-up time were estimated using reverse Kaplan-Meier method (Schemper 1996). Corresponding 95% CIs were estimated using the method by Klein and Moeschberger (1997) with log-log transformation.



Cd = carfilzomib plus dexamethasone arm; CI = confidence interval; HR = hazard ratio; mo = months; n = number of subjects assessed for this event; N = number of subjects in Intent-to-Treat Population; PFS = progression-free survival; Vd = bortezomib (Velcade) plus dexamethasone arm.

Note: The survival curves in this plot and the median PFS in this plot were derived by the unstratified Kaplan-Meier method, while other statistics reported in the figure were from Cox proportional hazards model stratified by the randomization stratification factors.

Figure 3. Kaplan-Meier curve of PFS by IRC (Intent-to-treat population; Study 2011-003)

Table 10. Sensitivity/Supportive analyses of PFS (Intent-to-treat population; Study 2011-003)

Analysis[a]	Vd (N = 465)		Cd (N = 464)		Hazard Ratio (Cd/Vd) (95% CI)[b]	P-value[c] (1-sided)
	Events/Subjects (%)	Median (months) (95% CI)	Events/Subjects (%)	Median (months) (95% CI)		
Primary analysis	243/465 (52.3)	9.4 (8.39, 10.39)	171/464 (36.9)	18.7 (15.63, —)	0.53 (0.437, 0.651)	< 0.0001
PFS as assessed by the investigators	249/465 (53.5)	9.4 (8.36, 10.39)	177/464 (38.1)	17.7 (14.87, 21.55)	0.52 (0.424, 0.630)	< 0.0001
PFS as assessed by the sponsor using ORCA	241/465 (51.8)	9.3 (8.32, 10.39)	175/464 (37.7)	18.5 (15.69, —)	0.55 (0.448, 0.668)	< 0.0001
Unstratified analysis	243/465 (52.3)	9.4 (8.39, 10.39)	171/464 (36.9)	18.7 (15.63, —)	0.53 (0.434, 0.644)	< 0.0001
Initiation of AMT treated as a PFS event	270/465 (58.1)	8.6 (7.40, 9.47)	191/464 (41.2)	17.7 (14.24, 22.17)	0.53 (0.439, 0.642)	< 0.0001
Initiation of AMT Treated as neither a PFS event nor a censoring event	251/465 (54.0)	9.4 (8.39, 10.39)	176/464 (37.9)	18.7 (15.43, —)	0.54 (0.443, 0.656)	< 0.0001
Analysis after adjusting for the bias due to stopping at interim[d]	243/465 (52.3)	9.4 (8.39, 10.39)	171/464 (36.9)	18.7 (15.63, —)	0.53 (0.438, 0.650)	< 0.0001
Missing assessments treated as censoring events in Vd arm and as PFS events in Cd arm	203/465 (43.7)	10.4 (9.31, 12.93)	196/464 (42.2)	15.7 (13.13, 22.17)	0.72 (0.593, 0.886)	0.0008

AMT = nonprotocol antimyeloma therapy; Cd = carfilzomib plus dexamethasone arm; CI = confidence interval; IV = intravenous; N = number of subjects in Intent-to-Treat Population; ORCA = Onyx Response Computational Assessment; PFS = progression-free survival; SC = subcutaneous; Vd = bortezomib (Velcade) plus dexamethasone arm.

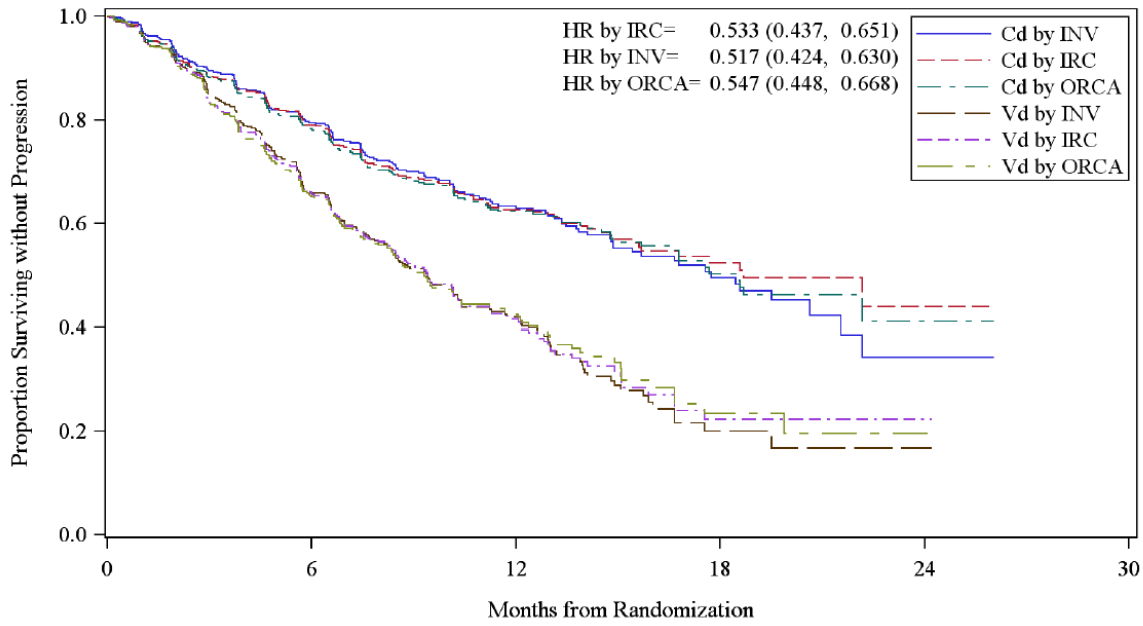
Notes: Randomization stratification factors: prior proteasome inhibitor treatment (prior carfilzomib or bortezomib versus no prior carfilzomib or bortezomib treatment); lines of prior treatment (1 versus 2 or 3 lines); International Staging System stage (1 versus 2 or 3); choice of route of bortezomib administration (IV versus SC).

[a] Included: the prespecified sensitivity analyses of PFS as described in the SAP Version 2.0. Unless specified otherwise, stratified analyses were conducted.

[b] Hazard ratios and corresponding 95% CIs were estimated using a stratified (or unstratified) Cox proportional hazards model as specified.

[c] P-values were calculated using stratified (or unstratified) log-rank test as specified.

[d] Based on Jennison 1999.



Source: Figure 14.2.8.3.

Cd = carfilzomib plus dexamethasone arm; HR = hazard ratio; INV = investigator; IV = intravenous; IRC = Independent Review Committee; ORCA = Onyx Response Computation Assessment; SC = subcutaneous; Vd = bortezomib (Velcade) plus dexamethasone arm.

Note: Randomization stratification factors: prior proteasome inhibitor treatment (prior carfilzomib or bortezomib versus no prior carfilzomib or bortezomib treatment); lines of prior treatment (1 versus 2 or 3 lines); International Staging System stage (1 versus 2 or 3); choice of route of bortezomib administration (IV versus SC).

Figure 4. Concordance in PFS assessment (Intent-to-treat population; Study 2011-003)

An ad hoc analysis of PFS was conducted using a cutoff date of 3 March 2016 with a retrospective data cut on 28 April 2015 to include 526 investigator-confirmed PFS events and 520 ORCA-confirmed PFS events. Data are presented in following table 12:

Table 12. **Progression-Free Survival as Determined by Investigators and Onyx Response Computational Assessment (ITT Population; cutoff 3 March 2016))**

	Vd (N = 465)		Cd (N = 464)			
Analysis	Events/ Subjects (%)	Median (months) (95% CI)	Events /Subjects (%)	Median (months) (95% CI)	Hazard Ratio (Cd/Vd) (95% CI)[a]	P-value[b] (1-sided)
PFS as assessed by the investigators	294/465 (63.2)	9.4 (8.4, 10.3)	232/464 (50.0)	17.6 (15.1, 20.3)	0.504 (0.421, 0.602)	< 0.0001
PFS as assessed by the sponsor using ORCA	288/465 (61.9)	9.3 (8.4, 10.4)	232/464 (50.0)	16.8 (14.8, 20.4)	0.528 (0.441, 0.632)	< 0.0001

CI = confidence interval; Cd = carfilzomib plus dexamethasone arm; ITT = intent to treat; N = number of subjects in ITT Population; ORCA = Onyx Response Computational Assessment; PFS = progression-free survival; Vd = bortezomib (Velcade) plus dexamethasone arm.

Notes: Randomization stratification factors: prior proteasome inhibitor treatment (yes versus no); lines of prior treatment (1 versus 2 or 3 lines); ISS (1 versus 2 or 3); choice of route of bortezomib administration (IV versus SC).

[a] Hazard ratios and corresponding 95% CIs were estimated using a stratified (or unstratified) Cox proportional hazards model as specified.

P-values were calculated using stratified (or unstratified) log-rank test as specified.

Secondary endpoint – Overall Survival

Table 11. Overall Survival (Intent-to-treat population; Study 2011-003)

	Vd (N = 465)	Cd (N = 464)
Subject Status		
Death – n (%)	88 (18.9)	75 (16.2)
Censored – n (%)	377 (81.1)	389 (83.8)
Reasons Censored		
Alive	342 (73.5)	377 (81.3)
Lost to follow-up	5 (1.1)	5 (1.1)
Withdrew consent	30 (6.5)	7 (1.5)
Log-rank p-value (1-sided)		
Stratified[a]	0.0650	
Unstratified	0.0570	
Hazard ratio (Cd/Vd) (95% CI)		
Stratified[a]	0.786 (0.575, 1.075)	
Unstratified	0.780 (0.573, 1.062)	

OS Duration (months)[b]		
N	465	464
25th percentile (95% CI)	16.1 (14.7, 18.5)	22.8 (17.0, NE)
Median (95% CI)	24.3 (24.3, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (24.3, NE)	NE (NE, NE)
Minimum, maximum (+ for censored)	0+, 25+	0, 28+
OS event-free rate (%) (95% CI)[b]		
12 months	83.8 (79.7, 87.1)	83.2 (79.1, 86.6)
24 months	63.8 (54.0, 72.1)	72.2 (57.5, 82.5)
Follow-up time (months)[c]		
N	465	464
25th percentile (95% CI)	9.3 (8.9, 9.5)	9.6 (9.4, 10.1)
Median (95% CI)	11.9 (11.2, 12.6)	12.5 (11.9, 13.2)
75th percentile (95% CI)	15.9 (15.0, 16.8)	16.6 (16.0, 17.4)
Minimum, maximum (+ for censored)	0+, 25+	0, 28+

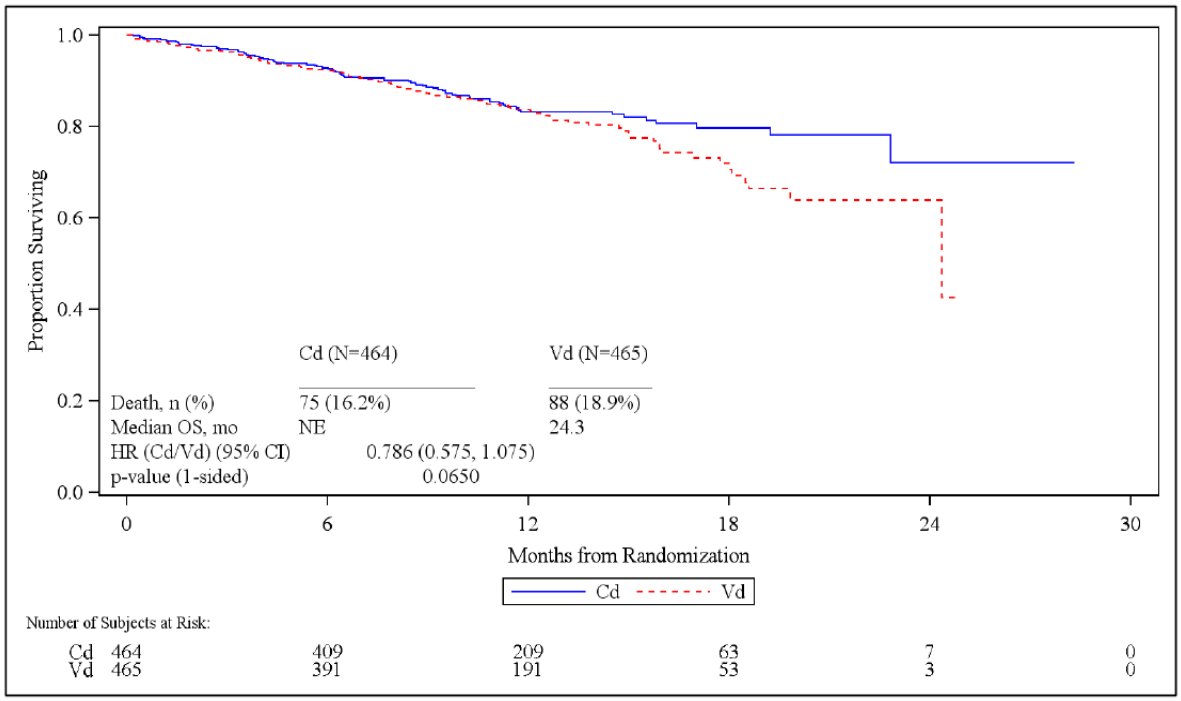
Cd = carfilzomib plus dexamethasone arm; CI = confidence interval; IV = intravenous; n = number of subjects assessed for this event; N = number of subjects in the Intent-To-Treat population; NE = not estimable; OS = overall survival; SC = subcutaneous; Vd = bortezomib (Velcade) plus dexamethasone arm.

Note: Randomization stratification factors: prior proteasome inhibitor treatment (prior carfilzomib or bortezomib versus no prior carfilzomib or bortezomib treatment); lines of prior treatment (1 versus 2 or 3 lines); International Staging System stage (1 versus 2 or 3); choice of route of bortezomib administration (IV versus SC).

[a] The stratified analysis was the primary analysis for OS.

[b] Median, percentiles, and event-free rates were estimated using the Kaplan-Meier method. CIs for median and percentiles were estimated using the method by Klein and Moeschberger (1997) with log-log transformation. CIs for event-free rates were estimated using the method by Kalbfleisch and Prentice (1980) with log-log transformation.

[c] Medians and percentiles of follow-up times were estimated using reverse Kaplan-Meier method (Schemper 1996). Corresponding 95% CIs were estimated using the method by Klein and Moeschberger (1997) with log-log transformation.



Source: Figure 14.2.2.1.

Cd = carfilzomib plus dexamethasone arm; CI = confidence interval; HR = hazard ratio; mo = month; n = number of subjects assessed for this event; N = number of subjects in Intent-to-Treat Population; NE = not estimable; OS = overall survival; Vd = bortezomib (Velcade) plus dexamethasone arm.

Note: The survival curves in this plot and the median OS in this plot were derived by unstratified Kaplan-Meier method, while other statistics reported in the figure were from Cox proportional hazards model stratified by randomization stratification factors.

Figure 5. Kaplan-Meier curve of Overall Survival (Intent-to-treat population; Study 2011-003)

An ad hoc analysis of overall survival (OS) was conducted using a cutoff date of 3 March 2016 and included 322 events. Data from this analysis are shown in the following table:

Table 12. Analysis of Overall Survival (ITT Population; cutoff 03 March 2016)

	Vd (N=465)	Cd (N=464)	Treatment Difference
Subject status			
Death - n (%)	169 (36.3)	153 (33.0)	
Censored - n (%)	296 (63.7)	311 (67.0)	
Alive	248 (53.3)	284 (61.2)	
Lost to follow up	6 (1.3)	5 (1.1)	
Withdrawn consent	42 (9.0)	22 (4.7)	
Log-rank p-value (1-sided)			
Stratified[a]			0.0263
Unstratified			0.0275
Cox model hazard ratio (Cd/Vd) (95% CI)			
Stratified[a]			0.805 (0.646, 1.003)
Unstratified			0.807 (0.648, 1.005)
OS duration (months)[b]			
N	465	464	
25th percentile (95% CI)	16.4 [14.7, 18.5)	19.2 [15.0, 23.8)	
Median (95% CI)	NE [31.0, NE)	NE [NE, NE)	
75th percentile (95% CI)	NE [NE, NE)	NE [NE, NE)	
Min, Max (+ for censored)	0+, 40+	0, 42+	
OS event-free rate (%) (95% CI)[b]			
12 months	83.4 (79.5, 86.5)	83.6 (79.8, 86.7)	
24 months	64.7 (59.9, 69.1)	70.8 (66.3, 74.8)	
36 months	51.1 (43.9, 57.9)	58.6 (52.0, 64.6)	
Follow-up time (months)[c]			
N	465	464	
25th percentile (95% CI)	23.3 [22.3, 23.8)	24.6 [23.8, 25.0)	
Median (95% CI)	26.2 [25.3, 26.9)	27.3 [26.8, 28.1)	
75th percentile (95% CI)	30.0 [29.0, 31.4)	32.0 [30.6, 32.8)	
Min, Max (+ for censored)	0+, 40+	0, 42+	

CI = confidence interval; ITT = intent-to-treat; NE = not estimable; OS = overall survival

[a] The stratified analysis is the primary analysis for OS. Stratification factors: prior proteasome inhibitor (yes vs. no); lines of prior treatment (1 vs. 2 or 3); ISS stage (1 vs. 2 or 3); route of bortezomib administration (IV vs. SC).

[b] Median, percentiles and event-free rate were estimated using the Kaplan-Meier method. CIs for median and percentiles were estimated using the method by Klein and Moeschberger (1997) with log-log transformation. CIs for event-free rates were estimated using the method by Kalbfleisch and Prentice (1980) with log-log transformation.

[c] Medians and percentiles of follow-up times were estimated using reverse Kaplan-Meier method (Schemper and Smith, 1996). Corresponding 95% CIs were estimated using the method by Klein and Moeschberger (1997) with log-log transformation.

Secondary endpoint – Overall Response Rate (ORR)

Table 13. ORR by IRC (Intent-to-treat population; Study 2011-003)

	Vd (N = 465)	Cd (N = 464)
Best Overall Response[a] – n (%)		
Stringent complete response	9 (1.9)	8 (1.7)
Complete response	20 (4.3)	50 (10.8)
Very good partial response	104 (22.4)	194 (41.8)
Partial response	157 (33.8)	104 (22.4)
Minimal response	53 (11.4)	24 (5.2)
Stable disease	53 (11.4)	40 (8.6)
Progressive disease	31 (6.7)	25 (5.4)
Unable to evaluate	38 (8.2)	19 (4.1)
Overall Response Rate[a]		
Number of subjects who achieved overall response	291	357
ORR (95% CI)[b]	62.6 (58.0, 67.0)	76.9 (72.8, 80.7)
P-value (1-sided)[c]	< 0.0001	
Odds ratio of Cd/Vd (95% CI)[c]	2.032 (1.519, 2.718)	
Response rate ≥ complete response		
Number of subjects who achieved ≥ complete response	29	58
Complete response or better (95% CI)	6.2 (4.2, 8.8)	12.5 (9.6, 15.9)
p-value (1-sided)[c]	0.0005	
Odds ratio (Cd/Vd) (95% CI)[c]	2.140 (1.344, 3.408)	
Response rate ≥ very good partial response		
Number of subjects who achieved ≥ very good partial response	133	252
Very good partial response or better (95% CI)	28.6 (24.5, 32.9)	54.3 (49.7, 58.9)
P-value (1-sided)[c]	<.0001	
Odds ratio of Cd/Vd (95% CI)[c]	3.063 (2.322, 4.040)	

Cd = carfilzomib plus dexamethasone; CI = confidence interval; CR = complete response; ORR = overall response rate; PR = partial response; sCR = stringent complete response; Vd = bortezomib (Velcade) plus dexamethasone; VGPR = very good partial response.

[a] Best overall response was defined as a subject's best response during the study. Overall response was defined as achieving a best overall response of PR, VGPR, CR, or sCR.

[b] Clopper-Pearson interval

[c] The odds ratio and 95% CI and p-values were calculated using the stratified Cochran-Mantel-Haenszel method.

Assessment of overall response was 97% consistent between IRC and ORCA, 75.3% consistent between

the IRC and investigators, and 76% consistent between investigators and ORCA. In comparison, concordance rates for assessment of best overall response were notably lower, with higher concordance between the IRC and ORCA (81.3%) than between the IRC and investigators (55.8%), or between investigators and ORCA (52.5%). Probably, this was due to the fact that the CRF page capturing best overall response by investigator (BOR) was not expected to be completed until the patient discontinues therapy

Duration of Response (DOR)

Table 14. Duration of Response (Intent-to-treat population; Study 2011-003)

	Vd (N = 465)	Cd (N = 464)
Duration of response (months)[a]		
Subject status - n (%)	291 (62.6)	357 (76.9)
Events	122 (26.2)	92 (19.8)
Progressed	120 (25.8)	84 (18.1)
Death	2 (0.4)	8 (1.7)
Censored	169 (36.3)	265 (57.1)
25th percentile (95% CI)	6.5 (5.6, 7.5)	9.3 (8.3, 13.0)
Median (95% CI)	10.4 (9.3, 13.8)	21.3 (21.3, NE)
75th percentile (95% CI)	NE (14.9, NE)	NE (NE, NE)
Minimum, maximum (+ for censored)	0+, 23+	0+, 25+
Follow-up time for DOR (months)[b]		
n	291	357
25th percentile	7.2 (5.9, 7.4)	7.4 (7.4, 8.3)
Median (95% CI)	9.4 (8.6, 11.2)	10.4 (9.4, 11.1)
75th percentile	13.8 (2.5, 14.9)	14.7 (13.8, 15.9)
Minimum, maximum (+ for censored)	0+, 23+	0+, 25+

Cd = carfilzomib plus dexamethasone arm; CI = confidence interval;
DOR = duration of response; n = number of subjects assessed for this event;
N = number of subjects in Intent-to-Treat Population NE = not estimable;
Vd = bortezomib (Velcade) plus dexamethasone arm.

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

[b] Median and percentiles were estimated using the Kaplan-Meier method (Schemper 1996). CIs for median were estimated using the method by Klein and Moeschberger (1997) with log-log transformation.

Exploratory endpoints

Time to progression (TTP)

The median TTP was longer in the Cd arm (22.2 months [95% CI: 17.7, NE]) than in the Vd arm (10.1 months [95% CI: 8.8, 11.7]). The median follow-up for disease progression was 11.3 months (95% CI: 11.1, 12.1) in the Cd arm and 11.0 months (95% CI: 9.5, 11.3) in the Vd arm.

Clinical Benefit Rate (CBR)

The CBR by IRC in the Cd arm (81.9% [95% CI: 78.1, 85.3]) was higher than in the Vd arm (73.8% [95% CI: 69.5, 77.7]). As determined by ORCA, the CBR was 82.1% (95% CI: 78.3, 85.5) in the Cd arm and 76.3% (95% CI: 72.2, 80.1) in the Vd arm. By investigators, the CBR was 61.6% (95% CI: 57.0, 66.1) in the Cd arm and 64.7% (95% CI: 60.2, 69.1) in the Vd arm.

Disease Control Rate (DCR)

By IRC, the DCR was 90.5% (95% CI: 87.5, 93.0) in the Cd arm and 85.2% (95% CI: 81.6, 88.3) in the Vd arm). As determined by ORCA, the DCR was 88.8% (95% CI: 85.6, 91.5) in the Cd arm and 83.4% (95% CI: 79.7, 86.7) in the Vd arm. By investigators, the DCR was 69.6% (95% CI: 65.2, 73.8) in the Cd arm and 77.2% (95% CI: 73.1, 80.9) in the Vd arm.

Patient reported outcomes: QLQ-C30

Table 17. HRQoL Analysis of Treatment Difference Over Time in QLC-C30 Global Health Status/Quality of Life Based on Mixed Model for Repeated Measures (ITT Population; Study 2011-003)

Summary of Study Subjects			Vd (N = 465)		Cd (N = 464)	
With at least one assessment before EOT			452		459	
Least Squares Mean Estimates						
Visit	Mean Estimate		Difference: Cd – Vd (SE)	DF	95% CI	P-Value (2-Sided)
	Vd	Cd				
Overall[a,b]	57.15	60.66	3.51 (0.789)	2918	(1.97, 5.06)	<0.0001

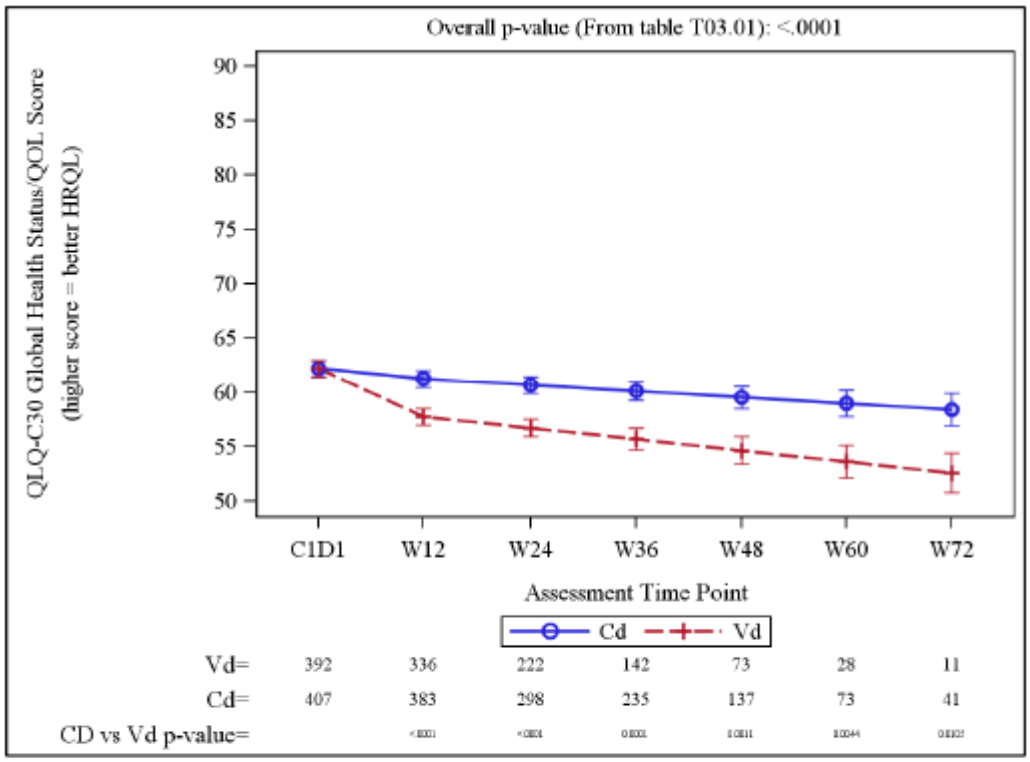
Source: Tables 3.01 in the PRO Results Report.

Cd = carfilzomib plus dexamethasone arm; CI = confidence interval; DF = degrees of freedom; EOT = End of Treatment; IV = intravenous; N = number of subjects in Intent-to-Treat Population; PRO = Patient-Reported Outcomes; SE = standard of error; SC = subcutaneous; Vd = bortezomib (Velcade) plus dexamethasone arm.

Note: Scores range from 0 to 100 with a higher score representing better health status.

[a] Analysis was performed based on a linear mixed effects model. The model included the fixed, categorical effects of treatment (all baseline responses were modeled with a dummy treatment); the randomization stratification factors - prior proteasome inhibitor treatment (prior carfilzomib or bortezomib versus no prior carfilzomib or bortezomib treatment); lines of prior treatment (1 versus 2 or 3 lines); International Staging System stage (1 versus 2 or 3); choice of route of bortezomib administration (IV versus SC); and random effects of subject intercept and coefficient on time.

[b] The least squares mean estimates were the overall estimates under the assumption that the treatment effect was the same across visits.



Source: Table 03.01 (overall p-value), Table 04.01 (data points), Figure 02.03.01 in the PRO Results Report.
C1D1 = Cycle 1 Day 1; Cd = carfilzomib plus dexamethasone arm; HRQL = health-related quality of life; PRO = Patient-Reported Outcome; QLQ-C30 = Quality of Life Questionnaire Core Module; QOL = quality of life; Vd = bortezomib (Velcade) plus dexamethasone arm; W = week.
Note: Cycle p-values were 2-sided p-values from mixed model for repeated measures model.

Figure 6. Least Squares Mean Difference (Cd−Vd) and 95% CI on the QLQ-C30 Global Health Status/Quality of Life Based on Mixed Model for Repeated Measures Model (ITT Population; Study 2011-003)

Patient reported outcomes: Additional Subscales of the EORTC QLQ-C30 and QLQ-MY20

Table 15. Treatment Difference Over Time in QLC-C30 and QLQ-MY20 Subscales Based on Mixed Model for Repeated Measures (ITT Population; Study 2011-003)

Summary of Study Subjects			Vd (N = 465)		Cd (N = 464)	
Number of subjects with at least 1 assessment			452		459	
QLQ-C30 Fatigue: Least Squares Mean Estimates						
Visit	Mean Estimate Vd	Mean Estimate Cd	Difference: Cd – Vd (SE)	DF	95% CI	P-Value (2-Sided)
Overall	40.10	38.21	-1.89 (0.915)	3434	-3.69, -0.10	0.0387
QLQ-C30 Pain: Least Squares Mean Estimates						
Visit	Mean Estimate Vd	Mean Estimate Cd	Difference: Cd – Vd (SE)	DF	95% CI	P-Value (2-Sided)
Overall	28.38	26.04	-2.35 (0.997)	3172	-4.30, -0.39	0.0186
QLQ-C30 Physical Functioning: Least Squares Mean Estimates						
Visit	Mean Estimate Vd	Mean Estimate Cd	Difference: Cd – Vd (SE)	DF	95% CI	P-Value (2-Sided)
Overall	71.07	72.23	1.16 (0.733)	4908	-0.27, 2.60	0.1120
QLQ-C30 Role Functioning: Least Squares Mean Estimates						
Visit	Mean Estimate Vd	Mean Estimate Cd	Difference: Cd – Vd (SE)	DF	95% CI	P-Value (2-Sided)
Overall	68.40	70.14	1.74 (1.042)	3184	-0.30, 3.79	0.0941
QLQ-C30 Nausea/Vomiting: Least Squares Mean Estimates						
Visit	Mean Estimate Vd	Mean Estimate Cd	Difference: Cd – Vd (SE)	DF	95% CI	P-Value (2-Sided)
Overall	4.46	3.84	-0.62 (0.414)	1602	-1.43, 0.19	0.1362
QLQ-MY20 Disease Symptoms: Least Squares Mean Estimates						
Visit	Mean Estimate Vd	Mean Estimate Cd	Difference: Cd – Vd (SE)	DF	95% CI	P-Value (2-Sided)
Overall	19.70	19.52	-0.18 (0.648)	4115	-1.45, 1.09	0.7842
QLQ-MY20 Side Effects of Treatment: Least Squares Mean Estimates						
Visit	Mean Estimate Vd	Mean Estimate Cd	Difference: Cd – Vd (SE)	DF	95% CI	P-Value (2-Sided)
Overall	21.32	18.99	-2.33 (0.509)	4768	-3.33, -1.33	<0.0001

Source: Tables 05.01 through 5.07 in the PRO Results Report.

Cd = carfilzomib plus dexamethasone arm; CI = confidence interval; DF = degrees of freedom; N = number of subjects in Intent-to-Treat Population; PRO = Patient-Reported Outcome; QLQ-C30 = Quality of Life Questionnaire Core Module; QLQ-MY20 = Quality of Life Questionnaire for Multiple Myeloma; SE = standard of error; Vd = bortezomib (Velcade) plus dexamethasone arm.

Note: For functional scales, a higher score represents a better health status; for symptom scores, a lower score represents a better health status.

Patient reported outcomes: Functional Assessment of Cancer Therapy / Gynecologic Oncology Group-Neurotoxicity (FACT-GOG / Ntx)

Table19. Analysis of Treatment Difference Over Time in FACT/GOG-Ntx "Additional Concerns" Subscales Based on Mixed Model for Repeated Measures (ITT Population; Study 2011-003)

Summary of Study Subjects			Vd (N = 465)		Cd (N = 464)
With at least 1 assessment before EOT			452		459
Least Squares Mean Estimates					
Visit	Mean Estimate Vd	Mean Estimate Cd	Difference: Cd – Vd (SE)	DF	95% CI	P-Value (2-Sided)
Overall[a,b]	35.19	36.03	0.84 (0.225)	5794	0.40, 1.28	0.0002

Source: Table 5.08 in the PRO Results Report.

Cd = carfilzomib plus dexamethasone arm; CI = confidence interval; DF = degrees of freedom;
EOT = End of Treatment; IV = intravenous; N = number of subjects in Intent-to-Treat Population;
PRO = Patient-Reported Outcome; SC = subcutaneous; SE = standard of error;
Vd = bortezomib (Velcade) plus dexamethasone arm.

Note: Scores range from 0 to 44, with a higher scores representing better health status.

[a] Analysis was performed based on a linear mixed effects model. The model included the fixed, categorical effects of treatment (all baseline responses were modeled with a dummy treatment); the randomization stratification factors - prior proteasome inhibitor treatment (prior carfilzomib or bortezomib versus no prior carfilzomib or bortezomib treatment); lines of prior treatment (1 versus 2 or 3 lines); International Staging System stage (1 versus 2 or 3); choice of route of bortezomib administration (IV versus SC); and random effects of subject intercept and coefficient on time.

[b] The least squares mean estimates were the overall estimates under the assumption that the treatment effect was the same across visits.

Ancillary analyses

Subgroup analysis of PFS by IRC

Table 20. Subgroup Analyses of PFS by IRC (Intent-to-treat population; Study 2011-003)

	Vd (N=465)		Cd (N=464)			
	Events/ Subjects (%)	Median (months) (95% CI)	Events/ Subjects (%)	Median (months) (95% CI)	Hazard Ratio (Cd/Vd) (95% CI)[a]	P-value[b] (1-sided)
All randomized subjects	243/465(52.3)	9.4[8.39, 10.39)	171/464(36.9)	18.7[15.63, -)	0.53(0.437, 0.653)	<.0001
Age (years)						
<65	110/210(52.4)	9.5[7.96, 12.17)	83/223(37.2)	-	0.58(0.437, 0.775)	<.0001
65-74	97/189(51.3)	9.5[7.30, 11.28)	62/164(37.8)	15.6[13.36, -)	0.53(0.383, 0.729)	<.0001
>=75	36/ 66(54.5)	8.9[6.09, 11.88)	26/ 77(33.8)	18.7[14.87, -)	0.38(0.227, 0.647)	<.0001
Sex						
Male	115/229(50.2)	9.5[8.45, 12.17)	93/240(38.8)	17.7[14.51, -)	0.61(0.463, 0.804)	0.0002
Female	128/236(54.2)	9.0[7.27, 10.39)	78/224(34.8)	-	0.46(0.343, 0.605)	<.0001
Geographical region						
Eastern Europe	61/121(50.4)	10.4[7.27, 14.90)	40/135(29.6)	-	0.39(0.259, 0.584)	<.0001
Western Europe	104/169(61.5)	8.8[7.40, 10.39)	80/182(44.0)	15.4[11.25, -)	0.56(0.419, 0.754)	<.0001
Asia Pacific	53/111(47.7)	8.5[5.99, 11.22)	36/102(35.3)	17.7[10.16, -)	0.62(0.402, 0.940)	0.0116
Body surface area (m^2)						
<=2.2	235/437(53.8)	9.4[8.36, 10.39)	169/447(37.8)	18.6[14.87, -)	0.54(0.442, 0.659)	<.0001
>2.2	7/ 18(38.9)	9.9[4.77, -)	2/ 16(12.5)	-	0.25(0.051, 1.217)	0.0321
Missing	1/ 10(10.0)	-	0/ 1(0)	-		

Baseline ECOG PS						
0	118/232(50.9)	10.2[9.05, 12.17)	75/221(33.9)	22.2[15.43, -)	0.51(0.378, 0.680)	<.0001
1	103/203(50.7)	9.5[6.71, 12.63)	85/211(40.3)	18.7[12.50, -)	0.60(0.452, 0.805)	0.0003
>=2	22/ 30(73.3)	5.0[2.83, 6.91)	11/ 32(34.4)	-	0.25(0.118, 0.547)	<.0001
Baseline Hemoglobin (g/L)						
<105	94/162(58.0)	6.5[5.10, 8.75)	79/154(51.3)	10.3[7.20, 14.87)	0.66(0.484, 0.888)	0.0030
>=105	149/303(49.2)	11.2[9.41, 12.83)	92/310(29.7)	-	0.45(0.350, 0.591)	<.0001
Baseline ANC (10^9/L)						
<1.5	26/ 48(54.2)	8.5[4.84, 14.11)	12/ 28(42.9)	12.5[10.16, -)	0.48(0.240, 0.958)	0.0163
>=1.5	217/417(52.0)	9.4[8.39, 11.22)	159/436(36.5)	22.2[15.63, -)	0.54(0.437, 0.660)	<.0001
Baseline Corrected Calcium (mg/dL)						
<=11.5	236/456(51.8)	9.5[8.49, 10.39)	165/457(36.1)	22.2[15.69, -)	0.53(0.430, 0.642)	<.0001
>11.5	7/ 9(77.8)	4.3[1.97, 7.53)	6/ 7(85.7)	6.4[0.72, 14.11)	0.68(0.213, 2.186)	0.2560
Baseline Creatinine Clearance[c] (mL/min)						
<30	12/ 28(42.9)	12.6[3.36, -)	15/ 28(53.6)	8.6[6.64, 22.17)	0.99(0.459, 2.158)	0.4949
30 - <50	43/ 71(60.6)	6.1[4.90, 9.31)	20/ 57(35.1)	17.7[13.13, -)	0.35(0.202, 0.600)	<.0001
50 - <80	101/177(57.1)	9.4[6.74, 10.30)	70/186(37.6)	18.6[12.93, -)	0.48(0.351, 0.653)	<.0001
>=80	87/189(46.0)	12.2[8.78, 14.90)	66/193(34.2)	-	0.60(0.434, 0.827)	0.0008
Presence of peripheral neuropathy history						
No	113/221(51.1)	9.5[7.96, 12.14)	89/249(35.7)	17.7[14.87, -)	0.52(0.395, 0.693)	<.0001
Yes	130/244(53.3)	9.4[7.53, 10.39)	82/215(38.1)	18.7[13.88, -)	0.54(0.410, 0.715)	<.0001
Grade 1	76/159(47.8)	11.2[9.41, 14.90)	53/140(37.9)	18.7[13.36, -)	0.62(0.436, 0.884)	0.0038
Grade >=2	53/ 81(65.4)	5.6[4.47, 7.40)	28/ 71(39.4)	18.6[10.20, -)	0.42(0.266, 0.677)	0.0001
Unknown	1/ 4(25.0)	-	1/ 4(25.0)	-	1.15(0.072, 18.59)	0.5404
ISS stage per IVRS[d]						
I	88/204(43.1)	12.2[10.30, 13.65)	52/205(25.4)	-	0.45(0.317, 0.631)	<.0001
II or III	155/261(59.4)	7.0[6.02, 8.75)	119/259(45.9)	14.1[11.12, 18.68)	0.57(0.446, 0.724)	<.0001
Degree of Plasma Cell Involvement						
<50%	179/355(50.4)	9.9[8.68, 11.68)	116/359(32.3)	22.2[17.66, -)	0.48(0.378, 0.605)	<.0001
>=50%	52/ 83(62.7)	6.5[4.61, 9.47)	40/ 78(51.3)	10.8[6.38, -)	0.61(0.402, 0.932)	0.0104
Missing	12/ 27(44.4)	13.7[3.62, -)	15/ 27(55.6)	9.3[6.55, 18.59)	1.03(0.479, 2.198)	0.5265
Serum B-2 Microglobulin level (mg/L)						
<3.5	98/216(45.4)	12.2[10.16, 13.88)	61/220(27.7)	-	0.45(0.327, 0.624)	<.0001
>=3.5	145/249(58.2)	6.8[5.72, 8.75)	110/244(45.1)	14.5[11.09, 18.68)	0.58(0.453, 0.747)	<.0001
LDH (U/L)						
<300	216/427(50.6)	9.5[8.55, 11.28)	132/404(32.7)	-	0.47(0.381, 0.589)	<.0001
>=300	27/ 38(71.1)	3.9[2.73, 7.40)	39/ 60(65.0)	6.4[3.82, 13.88)	0.66(0.399, 1.078)	0.0463
Risk group by FISH[e]						
High	71/113(62.8)	6.0[4.93, 8.13)	56/ 97(57.7)	8.8[6.94, 11.25)	0.65(0.453, 0.922)	0.0075
Standard	142/291(48.8)	10.2[9.31, 12.17)	81/284(28.5)	-	0.44(0.334, 0.579)	<.0001
Unknown	16/ 30(53.3)	9.3[4.01, -)	20/ 55(36.4)	18.6[11.48, -)	0.45(0.228, 0.873)	0.0077
Missing	14/ 31(45.2)	13.2[5.72, 16.64)	14/ 28(50.0)	7.9[4.70, -)	1.53(0.678, 3.451)	0.8490
Lines of prior treatment per IVRS						
1	107/229(46.7)	10.3[8.75, 12.93)	69/231(29.9)	22.2[17.66, -)	0.45(0.329, 0.608)	<.0001
2-3	136/236(57.6)	8.4[6.55, 10.16)	102/233(43.8)	14.5[10.76, -)	0.60(0.467, 0.782)	<.0001
Lines of prior treatment						
1	109/232(47.0)	10.1[8.78, 12.70)	70/232(30.2)	22.2[17.66, -)	0.45(0.330, 0.607)	<.0001
2	83/145(57.2)	8.4[6.55, 11.22)	69/157(43.9)	14.9[10.20, -)	0.60(0.434, 0.828)	0.0008
>=3	51/ 88(58.0)	7.4[6.02, 11.68)	32/ 75(42.7)	13.9[7.63, -)	0.61(0.392, 0.952)	0.0136
Prior transplant for multiple myeloma						
Yes	135/272(49.6)	10.2[8.49, 12.17)	99/266(37.2)	-	0.61(0.470, 0.792)	<.0001
No	108/193(56.0)	8.5[6.55, 10.16)	72/198(36.4)	17.7[14.11, -)	0.43(0.321, 0.587)	<.0001
Prior proteasome inhibitor per IVRS						
Yes	145/259(56.0)	8.4[6.61, 10.13)	107/258(41.5)	15.6[13.13, -)	0.56(0.433, 0.719)	<.0001
No	98/206(47.6)	10.4[9.31, 13.03)	64/206(31.1)	-	0.49(0.355, 0.668)	<.0001

Prior bortezomib						
Yes	141/252(56.0)	8.1[6.58, 9.54)	105/250(42.0)	15.6[12.93, -)	0.56(0.436, 0.728)	<.0001
No	102/213(47.9)	11.2[9.38, 12.83)	66/214(30.8)	-	0.48(0.355, 0.661)	<.0001
Prior lenalidomide						
Yes	103/177(58.2)	7.3[6.41, 10.16)	85/177(48.0)	12.9[8.78, 15.63)	0.69(0.516, 0.918)	0.0052
No	140/288(48.6)	10.2[8.75, 12.14)	86/287(30.0)	22.2[18.68, -)	0.43(0.324, 0.561)	<.0001
Prior thalidomide						
Yes	136/247(55.1)	9.0[7.96, 10.16)	85/211(40.3)	17.7[14.51, -)	0.54(0.409, 0.709)	<.0001
No	107/218(49.1)	10.2[7.53, 12.93)	86/253(34.0)	-	0.53(0.401, 0.709)	<.0001
Prior Imid						
Yes	186/348(53.4)	9.0[7.96, 10.16)	136/325(41.8)	15.6[12.93, -)	0.60(0.479, 0.749)	<.0001
No	57/117(48.7)	11.9[7.73, 13.65)	35/139(25.2)	-	0.38(0.247, 0.577)	<.0001
Prior Imid and bortezomib						
Yes	101/167(60.5)	6.8[5.95, 8.78)	80/158(50.6)	10.8[8.55, 14.87)	0.64(0.473, 0.861)	0.0015
No	142/298(47.7)	11.3[9.41, 12.93)	91/306(29.7)	-	0.47(0.358, 0.608)	<.0001
Refractory to any prior bortezomib treatment						
Yes	11/ 19(57.9)	5.7[2.04, -)	6/ 15(40.0)	14.9[6.94, -)	0.37(0.128, 1.080)	0.0290
No	232/446(52.0)	9.5[8.49, 10.39)	165/449(36.7)	18.7[15.63, -)	0.54(0.439, 0.657)	<.0001
Refractory to any prior lenalidomid treatment						
Yes	76/122(62.3)	6.6[5.23, 7.53)	66/113(58.4)	8.6[6.61, 11.25)	0.80(0.573, 1.110)	0.0891
No	167/343(48.7)	10.4[9.31, 12.17)	105/351(29.9)	-	0.44(0.341, 0.559)	<.0001
Administration route of bortezomib per IVRS						
SC	183/357(51.3)	9.5[8.36, 11.22)	134/356(37.6)	-	0.57(0.459, 0.719)	<.0001
IV	60/108(55.6)	9.4[6.55, 12.17)	37/108(34.3)	22.2[15.69, -)	0.41(0.270, 0.621)	<.0001

ANC=absolute neutrophil count; ECOG PS=Eastern Cooperative Oncology Group Performance Status; FISH=fluorescent in situ hybridization; imid= Lenalidomide or Thalidomide or Pomalidomide; LDH=lactate dehydrogenase.
Analysis of "All randomized subjects" is stratified as in the protocol-specified primary PFS analysis. Analyses of all other subgroups are unstratified.
[a] Hazard ratios and corresponding 95% CIs were estimated using a stratified or unstratified Cox proportional hazards model as specified.
[b] P-values were calculated using the stratified or unstratified log-rank test as specified.
[c] Creatinine clearance was calculated by sponsor using the Cockcroft-Gault formula.
[d] ISS stage: stage I, serum B-2 microglobulin less than 3.5 mg/L plus serum albumin >= 3.5 g/dL; stage II, neither stage I nor III; and stage III, serum B-2 microglobulin >= 5.5 mg/L
[e] High-risk subjects have genetic subtypes t(4; 14), t(14;16), or del(17p), while standard-risk subjects do not. The unknown risk group are subjects with FISH result not done, failed or quantity was not sufficient.

Subgroup analysis of ORR

Table 216. Subgroup Analyses of ORR by IRC (Intent-to-treat population; Study 2011-003)

	Vd (N=465)		Cd (N=464)			
	Events/ Subjects	ORR (%) (95% CI)[a]	Events/ Subjects	ORR (%) (95% CI)[a]	Odds Ratio (Cd/Vd) (95% CI) [b]	P-value[b] (1-sided)
All randomized subjects	291/465	62.6(58.0, 67.0)	357/464	76.9(72.8, 80.7)	2.032 (1.519, 2.718)	<.0001
Age (years)						
<65	128/210	61.0(54.0, 67.6)	165/223	74.0(67.7, 79.6)	1.822 (1.212, 2.740)	0.0019
65-74	124/189	65.6(58.4, 72.4)	127/164	77.4(70.3, 83.6)	1.799 (1.121, 2.889)	0.0073
>=75	39/66	59.1(46.3, 71.0)	65/77	84.4(74.4, 91.7)	3.750 (1.706, 8.241)	0.0004
Sex						
Male	143/229	62.4(55.8, 68.7)	172/240	71.7(65.5, 77.3)	1.521 (1.032, 2.242)	0.0169
Female	148/236	62.7(56.2, 68.9)	185/224	82.6(77.0, 87.3)	2.821 (1.826, 4.356)	<.0001

Baseline ECOG PS						
0	156/232	67.2(60.8, 73.2)	173/221	78.3(72.3, 83.5)	1.756 (1.152, 2.676)	0.0043
1	121/203	59.6(52.5, 66.4)	160/211	75.8(69.5, 81.4)	2.126 (1.394, 3.242)	0.0002
>=2	14/30	46.7(28.3, 65.7)	24/32	75.0(56.6, 88.5)	3.429 (1.171, 10.041)	0.0116
Baseline Hemoglobin (g/L)						
<105	86/162	53.1(45.1, 61.0)	100/154	64.9(56.8, 72.4)	1.637 (1.041, 2.573)	0.0163
>=105	205/303	67.7(62.1, 72.9)	257/310	82.9(78.2, 86.9)	2.318 (1.583, 3.394)	<.0001
Baseline ANC (10^9/L)						
<1.5	32/48	66.7(51.6, 79.6)	21/28	75.0(55.1, 89.3)	1.500 (0.528, 4.265)	0.2243
>=1.5	259/417	62.1(57.3, 66.8)	336/436	77.1(72.8, 80.9)	2.050 (1.521, 2.762)	<.0001
Baseline Corrected Calcium (mg/dL)						
<=11.5	288/456	63.2(58.5, 67.6)	353/457	77.2(73.1, 81.0)	1.980 (1.482, 2.646)	<.0001
>11.5	3/9	33.3(7.5, 70.1)	4/7	57.1(18.4, 90.1)	2.667 (0.347, 20.508)	0.1782
Baseline Creatinine Clearance [c] (mL/min)						
<30	17/28	60.7(40.6, 78.5)	22/28	78.6(59.0, 91.7)	2.373 (0.730, 7.713)	0.0749
30-<50	32/71	45.1(33.2, 57.3)	41/57	71.9(58.5, 83.0)	3.123 (1.485, 6.567)	0.0012
50-<80	123/177	69.5(62.1, 76.2)	146/186	78.5(71.9, 84.2)	1.602 (0.997, 2.574)	0.0253
>=80	119/189	63.0(55.7, 69.9)	148/193	76.7(70.1, 82.5)	1.935 (1.239, 3.021)	0.0018
Presence of Neuropathy at Baseline						
No	140/221	63.3(56.6, 69.7)	196/249	78.7(73.1, 83.6)	2.140 (1.422, 3.219)	0.0001
Yes	151/244	61.9(55.5, 68.0)	161/215	74.9(68.5, 80.5)	1.836 (1.228, 2.745)	0.0015
Grade 1	108/159	67.9(60.1, 75.1)	108/140	77.1(69.3, 83.8)	1.594 (0.951, 2.671)	0.0381
Grade >=2	41/81	50.6(39.3, 61.9)	51/71	71.8(59.9, 81.9)	2.488 (1.265, 4.892)	0.0039
Unknown	2/4	50.0(6.8, 93.2)	2/4	50.0(6.8, 93.2)	1.000 (0.063, 15.988)	0.5000
ISS Stage at baseline per IVRS [d]						
I	138/204	67.6(60.8, 74.0)	172/205	83.9(78.1, 88.7)	2.493 (1.552, 4.005)	<.0001
II or III	153/261	58.6(52.4, 64.7)	185/259	71.4(65.5, 76.8)	1.765 (1.225, 2.543)	0.0011
Degree of Plasma Cell Involvement (%)						
<50	239/355	67.3(62.2, 72.2)	289/359	80.5(76.0, 84.5)	2.004 (1.423, 2.823)	<.0001
>=50	37/83	44.6(33.7, 55.9)	51/78	65.4(53.8, 75.8)	2.348 (1.243, 4.437)	0.0041
Missing	15/27	55.6(35.3, 74.5)	17/27	63.0(42.4, 80.6)	1.360 (0.458, 4.042)	0.2916
Serum B-2 Microglobulin Level (mg/L)						
<3.5	149/216	69.0(62.4, 75.1)	182/220	82.7(77.1, 87.5)	2.154 (1.369, 3.388)	0.0004
>=3.5	142/249	57.0(50.6, 63.3)	175/244	71.7(65.6, 77.3)	1.911 (1.314, 2.780)	0.0003
LDH (U/L)						
<300	275/427	64.4(59.7, 68.9)	327/404	80.9(76.8, 84.7)	2.347 (1.709, 3.225)	<.0001
>=300	16/38	42.1(26.3, 59.2)	30/60	50.0(36.8, 63.2)	1.375 (0.606, 3.119)	0.2239
Risk Group by FISH [e]						
High	66/113	58.4(48.8, 67.6)	70/97	72.2(62.1, 80.8)	1.846 (1.033, 3.299)	0.0190
Standard	192/291	66.0(60.2, 71.4)	225/284	79.2(74.0, 83.8)	1.966 (1.351, 2.862)	0.0002
Unknown	16/30	53.3(34.3, 71.7)	42/55	76.4(63.0, 86.8)	2.827 (1.094, 7.306)	0.0151
Missing	17/31	54.8(36.0, 72.7)	20/28	71.4(51.3, 86.8)	2.059 (0.697, 6.080)	0.0960
Lines of prior treatment per IVRS						
1	149/229	65.1(58.5, 71.2)	188/231	81.4(75.8, 86.2)	2.347 (1.529, 3.603)	<.0001
2-3	142/236	60.2(53.6, 66.5)	169/233	72.5(66.3, 78.2)	1.748 (1.186, 2.577)	0.0023
Lines of prior treatment						
1	152/232	65.5(59.0, 71.6)	190/232	81.9(76.3, 86.6)	2.381 (1.549, 3.660)	<.0001
2	89/145	61.4(52.9, 69.3)	109/157	69.4(61.6, 76.5)	1.429 (0.887, 2.301)	0.0711
>=3	50/88	56.8(45.8, 67.3)	58/75	77.3(66.2, 86.2)	2.593 (1.306, 5.147)	0.0030
Prior transplant for multiple myeloma						
Yes	182/272	66.9(61.0, 72.5)	195/266	73.3(67.6, 78.5)	1.358 (0.937, 1.968)	0.0528
No	109/193	56.5(49.2, 63.6)	162/198	81.8(75.7, 86.9)	3.468 (2.190, 5.492)	<.0001

Prior proteasome inhibitor per IVRS						
Yes	158/259	61.0(54.8, 67.0)	183/258	70.9(65.0, 76.4)	1.560 (1.081, 2.251)	0.0087
No	133/206	64.6(57.6, 71.1)	174/206	84.5(78.8, 89.1)	2.984 (1.860, 4.789)	<.0001
Prior bortezomib						
Yes	152/252	60.3(54.0, 66.4)	178/250	71.2(65.2, 76.7)	1.626 (1.121, 2.360)	0.0051
No	139/213	65.3(58.5, 71.6)	179/214	83.6(78.0, 88.3)	2.723 (1.720, 4.309)	<.0001
Prior lenalidomide						
Yes	105/177	59.3(51.7, 66.6)	124/177	70.1(62.7, 76.7)	1.604 (1.033, 2.490)	0.0174
No	186/288	64.6(58.8, 70.1)	233/287	81.2(76.2, 85.5)	2.366 (1.615, 3.467)	<.0001
Prior thalidomide						
Yes	150/247	60.7(54.3, 66.9)	163/211	77.3(71.0, 82.7)	2.196 (1.456, 3.312)	<.0001
No	141/218	64.7(57.9, 71.0)	194/253	76.7(71.0, 81.7)	1.796 (1.201, 2.686)	0.0021
Prior Imid						
Yes	211/348	60.6(55.3, 65.8)	241/325	74.2(69.0, 78.8)	1.863 (1.341, 2.587)	<.0001
No	80/117	68.4(59.1, 76.7)	116/139	83.5(76.2, 89.2)	2.333 (1.289, 4.222)	0.0023
Prior Imid and bortezomib						
Yes	95/167	56.9(49.0, 64.5)	103/158	65.2(57.2, 72.6)	1.419 (0.907, 2.222)	0.0629
No	196/298	65.8(60.1, 71.1)	254/306	83.0(78.3, 87.0)	2.542 (1.734, 3.726)	<.0001
Refractory to any prior bortezomib treatment						
Yes	7/19	36.8(16.3, 61.6)	10/15	66.7(38.4, 88.2)	3.429 (0.827, 14.209)	0.0444
No	284/446	63.7(59.0, 68.1)	347/449	77.3(73.1, 81.1)	1.941 (1.447, 2.602)	<.0001
Refractory to any prior lenalidomid treatment						
Yes	67/122	54.9(45.7, 63.9)	70/113	61.9(52.3, 70.9)	1.336 (0.794, 2.250)	0.1380
No	224/343	65.3(60.0, 70.3)	287/351	81.8(77.3, 85.7)	2.382 (1.678, 3.382)	<.0001
Administration route of bortezomib per IVRS						
IV	63/108	58.3(48.5, 67.7)	87/108	80.6(71.8, 87.5)	2.959 (1.606, 5.452)	0.0002
SC	228/357	63.9(58.6, 68.9)	270/356	75.8(71.1, 80.2)	1.776 (1.284, 2.458)	0.0002

ANC=absolute neutrophil count;ECOG PS=Eastern Cooperative Oncology Group Performance Status; FISH=fluorescent in situ hybridization; imid= Lenalidomide or Thalidomide or Pomalidomide; LDH=lactate dehydrogenase.
Analysis of "All randomized subjects" is stratified as in the primary ORR analysis. Analyses of all other subgroups are unstratified.
[a] 95% CIs were estimated using the Clopper-Pearson method.
[b] The odds ratio and 95% CI and p-values were estimated by a stratified or unstratified analysis, as specified, using the Cochran-Mantel-Haenszel method.
[c] Creatinine clearance was calculated by sponsor using the Cockcroft-Gault formula.
[d] ISS stage: stage I, serum B-2 microglobulin < 3.5 mg/L plus serum albumin >=3.5 g/dL; stage II, neither stage I nor III; and stage III, serum B-2 microglobulin >=5.5 mg/L
[e] High-risk subjects have genetic subtypes t(4; 14), t(14;16), or del(17p), while standard-risk subjects do not. The unknown risk group are subjects with FISH result not done, failed or quantity was not sufficient.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22. Summary of Efficacy for trial 2011-003 (ENDEAVOUR)

Title: A Randomized, Open-label, Phase 3 Study of Carfilzomib Plus Dexamethasone vs. Bortezomib Plus Dexamethasone in Patients with Relapsed Multiple Myeloma		
Study identifier	EudraCT Number: 2012-000128-16	
Design	Randomized, Open-label, Phase 3, controlled	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	20.06.2012-10.11.2014 not applicable not applicable
Hypothesis	Superiority	

Treatments groups	Cd		Dexamethasone 20 mg (PO) or by intravenous (IV) injection on Days 1, 2, 8, 9, 15, 16, 22, and 23, at least 30 minutes prior to carfilzomib Carfilzomib 20 mg/m^2 IV on Days 1 and 2 of Cycle 1, escalating to 56 mg/m2 IV on Days 8, 9, 15, and 16 of Cycle 1 and continuing on Days 1, 2, 8, 9, 15, and 16 for subsequent 28-day cycles until progressive disease (PD) or intolerable side effects N=464
	Vd		Dexamethasone 20 mg (PO or IV) on Days 1, 2, 4, 5, 8, 9, 11, and 12, at least 30 minutes prior to bortezomib Bortezomib 1.3 mg/m^2 as a 3 to 5 second bolus IV injection or subcutaneous (SC) injection on Days 1, 4, 8, and 11 of each 21-day cycle until PD or intolerable side effects N=465
Endpoints and definitions	Primary endpoint	PFS	duration from randomization to disease progression or death due to any cause as determined by an IRC
	Secondary	OS	defined as the time from randomization to the date of death (whatever the cause)
	Secondary	ORR	the proportion of best overall response of sCR, CR, VGPR, and PR
	Secondary	DOR	time from the initial start of response (PR or better) to documented PD or death due to any cause.
Database lock	10 November 2014		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Vd	Cd
	Number of subject	465	464
	PFS (Median months)	9.4	18.7
	95% CI	8.39-10.39	15.63-NE
	OS (Median months)	24.3	NE
	95% CI	24.34-NE	NE
	ORR (%)	62.6	76.9
	95% CI	58.0-67.0	72.8-80.7
	DoR (Median; months) 95% CI	10.4 9.28-13.85	21.3 21.28-NE

Effect estimate per comparison	Primary endpoint PFS	Comparison groups	Cd vs Vd
		HR	0.533
		95% CI	0.437-0.651
		P-value	<0.0001
	Secondary endpoint OS	Comparison groups	Cd vs Vd
		HR	0.786
		95% CI	0.575-1.075
		P-value	0.0650
	Secondary endpoint ORR	Comparison groups	Cd vs Vd
		Odds ratio	2.032
		95% CI	1.519-2.718

		P-value	<0.0001
Notes	Based on the results from the PFS interim analysis, the IDMC recommended stopping the trial for efficacy, and Onyx Pharmaceuticals accepted the recommendation. Monitoring for safety and long-term survival is continuing. Stratification factors were: prior proteasome inhibitor treatment (Yes or No), ISS Stage (Stage 1 versus Stages 2 or 3), lines of prior treatment (1 versus 2 or 3 lines) and choice of route of bortezomib administration (IV versus SC)		

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The 2011-003 study was designed in order to allow the recruitment of patients with MM previously treated with at least one prior line (transplant is considered 1st line of therapy) but not more than three. Both bortezomib and carfilzomib were allowed as previous treatment, provided at least PR was obtained and there was a treatment-free interval of 6 months. Patients refractory to prior lenalidomide treatment were allowed. The requirement for a 6 month treatment-free interval reflects the usual clinical practice with bortezomib, though there are nodata regarding carfilzomib a similar pattern could be expected. In the Cd arm, subjects received carfilzomib 20 mg/m^2 IV over 30 minutes on days 1 and 2 of cycle 1, followed by escalation to 56 mg/m2 over 30 minutes on days 8, 9, 15, and 16 of cycle 1. Subjects who tolerated 56 mg/m^2 in cycle 1 were kept at this dose for each subsequent 28 day cycle until disease progression, intolerable side effects, withdrawal of consent, or death. Bortezomib was administered iv or sc.The bortezomib PI (based on the RETRIEVE trial) recommends that patients achieving a response or a stable disease after 4 cycles of Vd can continue to receive the same combination for a maximum of 4 additional cycles. However, in the ENDEAVOUR study, subjects received bortezomib until disease progression, intolerable side effects, withdrawal of consent, or death. This approach seems reasonable in the context of a clinical trial, especially in those subjects where bortezomib was administered sc.

PFS was the primary endpoint, with OS, ORR and DoR as secondary endpoints. The use of PFS as main outcome variable is acceptable, given that there are different efficacious treatment alternatives that patients could receive, which will likely modify the expected survival. Although the design of the study is unblinded, the use of an IRC to assess response (as defined by IMWG-URC) is endorsed. In addition, the different sensitive analyses planned increase the level of robustness of the results.

No critical protocol deviations or amendments have been identified. One key change to the original design was introduced. It was a reduction in the required number of OS events. This revision was made to shorten the expected study duration and minimize the impact of cross-over.

Efficacy data and additional analyses

The population recruited in the study is the one expected at relapse. The median age of 65 is similar to that in other phase 3 studies in relapsed MM patients. The study enrolled 143 subjects (15%)above 75 years. The majority geographic region is Western Europe (38%).

More than half of patients received previous transplant (vast majority autologous). Patients with at least 2 previous regimens are 50%. Thalidomide and bortezomib were received by 50%, whereas lenalidomide was administered to 38%. Prior Imid and Bortezomib were received in 35% of subjects. Approximately 4% of patients were refractory to any prior bortezomib therapy. Refractory to the last therapy was reported in 40%, with 25% (235 subjects) of patients refractory to lenalidomide.

Repeating protease inhibitor treatment for relapsing MM is a clinical option, especially after a long-lasting remission (>12 months). In patients on 2011-003 whose last prior regimen included bortezomib (n=343) PFS was longer in the Cd arm than in the Vd arm regardless of the length of the bortezomib-free period (data not shown).

After a recommendation of the IDMC based on the first interim analysis of PFS, the study was stopped. The use of Cd provided an increase in PFS of approximately 9 months vs Vd (HR = 0.533 [95% CI: 0.437, 0.651]; log-rank p < 0.0001). The median PFS was 18.7 months (95% CI: 15.6, not estimable [NE]) in the Cd arm versus 9.4 months (95% CI: 8.4, 10.4) in Vd. This result seems robust as the different sensitive analyses offer similar results. In the new analysis provided (cutoff date of 3 March 2016) both the PFS investigator assessed and PFS by ORCA show comparable results to the previous analysis.It is not proven thatthis delay in the progression of MM can be translated into a longer survival, since OS data are not definitive. In this regard the first interim analysis offered a positive trend for Cd vs Vd (HR = 0.786; 95% CI: 0.575, 1.075; p = 0.065) supported with the same trend in a post hoc analysis (65% of total events required) with a HR of 0.805 (95%CI: 0.646, 1.003). The second interim analysis is expected during this year (in second half 2016).

Secondary variables according to IRC support the PFS results. However, the investigator assessment showed no differences between arms (Cd vs Vd) in ORR, CBR and DCR. This unexpected result could be due to the fact that the CRF page capturing best overall response by investigator was not expected to be completed until the patient discontinued therapy. In contrast, the IRC assessed best overall response for all subjects regardless if they had discontinued therapy. Due to the prolonged PFS, two hundred subjects were still on therapy on the Cd arm and 105 on the Vd arm at the time of the IA data cutoff, which resulted in 168 subjects with missing investigator assessed BOR (109 Cd arm subjects and 59 Vd arm subjects). The best overall response of those subjects was imputed as NE in investigator assessed BOR analyses and these subjects were counted as non-responders which resulted in low ORR, CBR and DCR estimates per investigator.

The depth of the response (rate of sCR+CR+VGPR) is higher for the experimental arm (Cd) regardless of the method of analysis (IRC; investigator).

The PFS benefit of Kd was consistently observed in the vast majority of subgroups, including patients ≥ 75 years of age (n = 143), patients with high risk genetic mutations (n = 210), and patients with baseline creatinine clearance of 30 - < 50mL/min (n = 128).

Other subgroups of interest also showed the superiority of the new combination (Cd): prior bortezomib treatment (PFS HR 0.56 95%CI [0.436, 0.728]), prior lenalidomide (PFS HR 0.69 95%CI [0.516, 0.918]) and prior Imid and bortezomib (PFS HR 0.64 95%CI [0.473, 0.861]). However, in one potential population for this combination, patients refractory to lenalidomide, the benefit is less clear (PFS HR 0.80 95%CI [0.573, 1.110]) though there seem to be a higher response in those treated with Cd than those treated with Vd (61.9% vs 54.9%). In addition, patients refractory/intolerant to Bortezomib were excluded from the study. Despite this inclusion criterion, surprisingly there is a very small subgroup of patients labelled as bortezomib refractory (19+15 Vd and Cd) where the treatment with Cd seems to be superior to Vd (PFS HR 0.37 95%CI [0.128, 1.080]) even though it does not seem reasonable to obtain conclusions from this comparison (bortezomib would not be the best comparator and the activity of carfilzomib in these subjects is not totally known).

Finally, although this is a low sample size, in the subgroup of patients who received bortezomib in the line just prior to randomization and had an interval relapse free of 6-12 months, there were not substantial differences between treatments (median PFS duration 6.5 months; 95% CI: 1.1, 17.5 in the Vd arm and

7.2 months (1.5, NE) in the Cd arm with HR=0.963; 95% CI: 0.32, 2.899). Of note, the ORR was 75% (6/8 subjects) in the Vd arm, and 42% (5/12 subjects) in the Cd arm. In those with an interval relapse >12 months, the benefit of Cd seems consistently higher than in those subjects treated with Vd

2.4.3. Conclusions on the clinical efficacy

The superiority of the new combination of Carfilzomib plus Dexamethasone (Cd) vs. Bortezomib plus Dexamethasone (Vd) has been shown in terms of improved PFS, of approximately 9 months, and improved depth of response. PFS results showed a significant benefit for those patients treated with Cd.

The CHMP recommended the submission of the OS second interim analysis of the ENDEAVOUR study by July 2017.

2.5. Clinical safety

Introduction

The Summary of Clinical Safety for carfilzomib presents safety information from the following source of data:

- Company (Onyx/Amgen)-sponsored clinical studies including:

  – Safety data (including adverse events, serious adverse events, deaths, adverse drug reactions, adverse events of interests, and laboratory abnormalities) from Study 2011-003 through 30 June 2015.

  – Serious adverse events (2326 events) from 12 ongoing studies in which 2266 subjects were enrolled.

- Non-company (Onyx/Amgen)-sponsored clinical studies including:

  – Serious adverse events (2187 events) from 76 investigator-sponsored trials (ISTs) in which 3549 subjects were enrolled.

  – Serious adverse events (20 events) from 3 Ono Pharmaceutical-sponsored studies in which 89 subjects were enrolled.

  – Serious adverse events (102 events) in the Early Carfilzomib Access Program (ECAP) in 23 countries in which 571 subjects were enrolled.

  - Serious adverse events (100 events) in the Single Patient Investigational New Drug (SPIND) program in which 35 subjects were enrolled.

  – Adverse events (11145 total events: serious [2528 events] and non-serious [8617 events]) from postmarketing reports, where it is estimated that approximately 20000 patients have been treated with carfilzomib.

Patient exposure

Carfilzomib is currently being evaluated worldwide in several phase 1, 2, and 3 clinical studies as a treatment option for patients with hematologic malignancies and solid tumors. As of 30 June 2015, subjects have been exposed to carfilzomib in the following studies or programs:

• Approximately 4450 individual subjects have been enrolled in 22 clinical studies (Onyx/Amgen sponsored), of which an estimated total of 2940 subjects have been treated with carfilzomib.

• 3549 subjects have been enrolled in 76 ISTs, of which 2413 were treated with carfilzomib.

• 89 subjects have been enrolled in Ono Pharmaceutical sponsored studies.

• 571 subjects have been enrolled in the Early Carfilzomib Access Program (ECAP) in 23 countries.

• 35 subjects have been enrolled in the SPIND program.

• Approximately 20000 patients have received carfilzomib in the postmarketing setting.

In combination with dexamethasone, patients were exposed to carfilzomib in study 2011-003 (ENDEAVOR), which is the main study supporting the present application.

A summary of the ENDEAVOR study if provided in the table below:

Table 23. Overview of Study 2011-003 (ENDEAVOR)

Study ID/ Centers	Study Design	Enrollment Duration/ Total Enrolled/ Total Treated[a]	Study and Control Drugs/ Dose, Route, Regimen, Treatment Duration	Primary Study Objective(s)	Diagnosis and Main Inclusion Criteria	Safety Assessments[b]
2011-003 (ENDEAVOR) 208 centers in 27 countries located in Asia-Pacific, Eastern and Western Europe, North America, and Brazil	Randomized, open-label, active-controlled; phase 3	20 June 2012 through 30 June 2015 - ongoing 929 Cd: 463 Vd: 456	Cd: CFZ (IV 30 min) 20/56 mg/m^2 in 28-d cycles[c] DEX 20 mg on D1, 2, 8, 9, 15, 16, 22, and 23 of 28-d cycles until PD *or* Vd: BTZ 1.3 mg/m^2 on D1, 4, 8, and 11 of 21-d cycles; DEX 20 mg on D1, 2, 4, 5, 8, 9, 11, and 12 of 21-d cycle until PD	PFS	Relapsed MM, 1−3 prior treatments	Routine, Cardiopulmonary substudy, and peripheral neuropathy

BTZ = bortezomib (Velcade); Cd = carfilzomib plus dexamethasone; CFZ = carfilzomib; d or D = day; DEX = dexamethasone; ECG = electrocardiogram; ECHO = echocardiogram; IV = intravenous; MM = multiple myeloma; PD = progressive disease; PFS = progression-free survival; Vd = bortezomib (Velcade) plus dexamethasone

[a] Total number of subjects treated as of the data cutoff date for this safety analysis (30 June 2015).

[b] Standard safety assessments at every study visit consisting of adverse events, physical exams, labs (hematology, blood chemistries, and urinalysis), vital signs, and ECGs (at baseline and End of Treatment), and this is noted as "routine." Only additional study-specific safety assessments are listed here. ECGs were evaluated at baseline. ECHOs were evaluated at baseline for all enrolled subjects and those enrolled in the Study 2011-003 ECHO Cardiopulmonary substudy had ECHOs at baseline, every 12 weeks and at the end of study.

[c] Carfilzomib was administered in 28-day cycles on days 1, 2, 8, 9, 15, and 16. Stepped-up dosing was allowed to occur in cycle 1, day 8.

Table 17. Patient disposition in Study 2011-003 (ENDEAVOR)

	ENDEAVOR sNDA		ENDEAVOR 120-day Safety Update	
	Vd (N = 456) n (%)	Cd (N = 463) n (%)	Vd (N = 456) n (%)	Cd (N = 463) n (%)
Treated	456	463	456	463
Continuing treatment	105 (23.0)	200 (43.2)	52 (11.4)	116 (25.1)
Discontinued treatment	351 (77.0)	263 (56.8)	404 (88.6)	347 (74.9)
Reason for study treatment discontinuation				
Disease progression	168 (36.8)	117 (25.3)	195 (42.8)	153 (33.0)
Adverse event	73 (16.0)	65 (14.0)	86 (18.9)	77 (16.6)
Withdrew consent	19 (4.2)	6 (1.3)	19 (4.2)	8 (1.7)
Death	9 (2.0)	13 (2.8)	10 (2.2)	17 (3.7)
Non-compliance with study treatment	1 (0.2)	4 (0.9)	2 (0.4)	4 (0.9)
Lost to follow-up	1 (0.2)	0	1 (0.2)	0
Patient request/investigator decision	80 (17.5)	58 (12.5)	91 (20.0)	88 (19.0)

Cd = carfilzomib plus dexamethasone; sNDA = Supplemental New Drug Application; Vd = bortezomib (Velcade) plus dexamethasone.
ENDEAVOR sNDA includes cumulative data through 10 November 2014; ENDEAVOR 120-day Safety Update includes cumulative data through 30 June 2015

Table 18. Duration of exposure to study treatments (Study 2011-003)

	ENDEAVOR sNDA		ENDEAVOR 120-day Safety Update	
	Vd (N = 456) n (%)	Cd (N = 463) n (%)	Vd (N = 456) n (%)	Cd (N = 463) n (%)
Number of weeks subjects dosed				
Mean (SD)	30 (19.3)	39.8 (22.8)	34.9 (26.5)	50.6 (32.2)
Median	26.8	39.9	27.0	48.0
Minimum, maximum	1.0, 106.1	1.0, 108.1	1.0, 136.9	1.0, 140.1
Number of subjects treated by week – n (%)				
Week 12	383 (84.0)	407 (87.9)	383 (84.0)	407 (87.9)
Week 24	252 (55.3)	350 (75.6)	257 (56.4)	358 (77.3)
Week 48	84 (18.4)	165 (35.6)	123 (27.0)	237 (51.2)
Week 72	13 (2.9)	48 (10.4)	61 (13.4)	138 (29.8)
Week 96	2 (0.4)	6 (1.3)	14 (3.1)	44 (9.5)
Number of cycles subjects dosed[a] - n (%)				
Mean (SD)	9.3 (5.7)	10.0 (5.6)	10.7 (7.8)	12.6 (7.8)
Median	8.0	10.0	8.0	12.0
Minimum, maximum	1.0, 35.0	1.0, 26.0	1.0, 45.0	1.0, 32.0
Number of subjects on treatment in each cycle[a] - n (%)				
Cycle 6	321 (70.4)	358 (77.3)	322 (70.6)	363 (78.4)
Cycle 12	141 (30.9)	169 (36.5)	154 (33.8)	235 (50.8)
Cycle 18	44 (9.6)	49 (10.6)	88 (19.3)	136 (29.4)
Cycle 24	7 (1.5)	7 (1.5)	41 (9.0)	45 (9.7)
Cycle 30	2 (0.4)	0	13 (2.9)	13 (2.8)
Cumulative carfilzomib dose (mg)				
Mean	–	5405.6	–	6731.7
SD	–	3418.0	–	4660.9
Median	–	5140.80	–	5900.0
Minimum, Maximum	–	52.0, 18564.0	–	52.0, 21942.0
Relative dose intensity of carfilzomib[b](%)				
Mean	–	89.3	–	87.9
SD	–	12.6	–	13.5
Median	–	93.2	–	92.0
Minimum, maximum	–	29.5, 105.0	–	29.5, 107.2

Cd = carfilzomib plus dexamethasone; SD = standard deviation; sNDA = Supplemental New Drug Application; Vd = bortezomib (Velcade) plus dexamethasone.
ENDEAVOR sNDA includes cumulative data through 10 November 2014; ENDEAVOR 120-day Safety Update includes cumulative data through 30 June 2015

[a] Regimen Cd has a 28-day cycle, whereas regimen Vd has a 21-day cycle. For cycle 1, carfilzomib dose is 20 mg/m^2 on day 1 and day 2 and 56 mg/m^2 thereafter.

[b] Relative Dose Intensity (%) = actual dose intensity/planned dose intensity × 100, where actual (planned) dose intensity is the actual (planned) cumulative dose (mg) divided by the actual (planned) duration of carfilzomib administration (weeks).

Adverse events

A summary of safety results from study 2011-003 (ENDEAVOR) is provided below.

Table 19. Summary of adverse events (Study 2011-003)

	ENDEAVOR sNDA		ENDEAVOR 120-day Safety Update	
	Vd (N = 456) n (%)	Cd (N = 463) n (%)	Vd (N = 456) n (%)	Cd (N = 463) n (%)
Subjects with ≥ 1 treatment-emergent adverse event	447 (98.0)	455 (98.3)	451 (98.9)	456 (98.5)
≥ Grade 3	305 (66.9)	339 (73.2)	316 (69.3)	365 (78.8)
Serious adverse event	162 (35.5)	223 (48.2)	175 (38.4)	254 (54.9)
Leading to discontinuation of any investigational product	95 (20.8)	92 (19.9)	108 (23.7)	117 (25.3)
Leading to death[a]	21 (4.6)	25 (5.4)	21 (4.6)	29 (6.3)
Subjects with ≥ 1 treatment-related adverse event[b]	406 (89.0)	404 (87.3)	408 (89.5)	411 (88.8)
≥ Grade 3	230 (50.4)	248 (53.6)	235 (51.5)	267 (57.7)
Serious adverse event	69 (15.1)	110 (23.8)	74 (16.2)	122 (26.3)
Leading to discontinuation of any investigational product	76 (16.7)	60 (13.0)	85 (18.6)	77 (16.6)
Leading to death[a]	2 (0.4)	2 (0.4)	2 (0.4)	5 (1.1)

Cd = carfilzomib plus dexamethasone; sNDA = Supplemental New Drug Application; Vd = bortezomib (Velcade) plus dexamethasone

ENDEAVOR sNDA includes cumulative data through 10 November 2014; ENDEAVOR 120-day Safety Update includes cumulative data through 30 June 2015

[a] Subject death could be due to multiple reasons including adverse event, progressive disease, or other reasons. Adverse events leading to death include adverse events that start before 30 days after last study treatment, but death may have occurred after 30 days after last study treatment.

[b] Treatment-related adverse events were adverse events considered related to ≥ 1 investigational product by the investigator, including those with unknown relationship.

Table 20. Adverse events in ≥ 5% of Subjects in Any Treatment Arm by Preferred Term in Study 2011-003 (Safety Population)

	ENDEAVOR sNDA		ENDEAVOR 120-day Safety Update	
Preferred Term	Vd (N = 456) n (%)	Cd (N = 463) n (%)	Vd (N = 456) n (%)	Cd (N = 463) n (%)
Number of subjects reporting adverse events	447 (98.0)	455 (98.3)	451 (98.9)	456 (98.5)
Anaemia	**123 (27.0)**	**182 (39.3)**	**126 (27.6)**	**189 (40.8)**
Diarrhoea	175 (38.4)	143 (30.9)	183 (40.1)	155 (33.5)
Pyrexia	**63 (13.8)**	**130 (28.1)**	**67 (14.7)**	**145 (31.3)**
Fatigue	130 (28.5)	136 (29.4)	134 (29.4)	144 (31.1)
Dyspnoea	**60 (13.2)**	**132 (28.5)**	**60 (13.2)**	**141 (30.5)**
Hypertension	**40 (8.8)**	**115 (24.8)**	**44 (9.6)**	**138 (29.8)**
Insomnia	119 (26.1)	117 (25.3)	121 (26.5)	125 (27.0)
Cough	**64 (14.0)**	**115 (24.8)**	**68 (14.9)**	**121 (26.1)**
Oedema Peripheral	78 (17.1)	101 (21.8)	**84 (18.4)**	**109 (23.5)**
Upper Respiratory Tract Infection	**67 (14.7)**	**94 (20.3)**	**78 (17.1)**	**108 (23.3)**
Asthenia	75 (16.4)	94 (20.3)	78 (17.1)	102 (22.0)
Nausea	82 (18.0)	90 (19.4)	87 (19.1)	102 (22.0)
Thrombocytopenia	78 (17.1)	95 (20.5)	81 (17.8)	101 (21.8)
Back Pain	71 (15.6)	86 (18.6)	78 (17.1)	100 (21.6)
Bronchitis	**41 (9.0)**	**76 (16.4)**	**46 (10.1)**	**99 (21.4)**
Muscle Spasms	**27 (5.9)**	**86 (18.6)**	**28 (6.1)**	**91 (19.7)**
Headache	**46 (10.1)**	**79 (17.1)**	**49 (10.7)**	**86 (18.6)**
Nasopharyngitis	51 (11.2)	66 (14.3)	56 (12.3)	77 (16.6)
Vomiting	**40 (8.8)**	**65 (14.0)**	**42 (9.2)**	**72 (15.6)**
Constipation	123 (27.0)	68 (14.7)	127 (27.9)	70 (15.1)
Hypokalaemia	45 (9.9)	50 (10.8)	48 (10.5)	56 (12.1)
Platelet Count Decreased	39 (8.6)	55 (11.9)	40 (8.8)	56 (12.1)
Arthralgia	46 (10.1)	47 (10.2)	51 (11.2)	54 (11.7)
Blood Creatinine Increased	26 (5.7)	48 (10.4)	**28 (6.1)**	**52 (11.2)**
Bone Pain	38 (8.3)	47 (10.2)	38 (8.3)	52 (11.2)
Pain in Extremity	49 (10.7)	47 (10.2)	50 (11.0)	51 (11.0)

Cd = carfilzomib plus dexamethasone; sNDA = Supplemental New Drug Application; Vd = bortezomib (Velcade) plus dexamethasone

ENDEAVOR sNDA includes cumulative data through 10 November 2014; ENDEAVOR 120-day Safety Update includes cumulative data through 30 June 2015

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 15.1. **Bold** text identifies events with subject incidence ≥ 5% higher in the carfilzomib arm than in the bortezomib arm. Shaded cells indicate adverse events in the carfilzomib arm that are ≥ 5% in Study 2011-003 in the 120-day Safety Update and were not ≥ 5% in Study 2011-003 in the ENDEAVOR sNDA.

Preferred Term	ENDEAVOR sNDA		ENDEAVOR 120-day Safety Update	
	Vd (N = 456) n (%)	Cd (N = 463) n (%)	Vd (N = 456) n (%)	Cd (N = 463) n (%)
Pneumonia	48 (10.5)	41 (8.9)	51 (11.2)	50 (10.8)
Hyperglycaemia	41 (9.0)	49 (10.6)	40 (8.8)	50 (10.8)
Decreased Appetite	57 (12.5)	40 (8.6)	62 (13.6)	48 (10.4)
Respiratory Tract Infection	29 (6.4)	34 (7.3)	30 (6.6)	47 (10.2)
Neuropathy Peripheral	121 (26.5)	43 (9.3)	125 (27.4)	46 (9.9)
Muscular Weakness	43 (9.4)	36 (7.8)	46 (10.1)	43 (9.3)
Paraesthesia	74 (16.2)	36 (7.8)	74 (16.2)	42 (9.1)
Lymphocyte Count Decreased	18 (3.9)	39 (8.4)	**18 (3.9)**	**42 (9.1)**
Chest Pain	17 (3.7)	38 (8.2)	20 (4.4)	41 (8.9)
Dizziness	67 (14.7)	37 (8.0)	68 (14.9)	40 (8.6)
Musculoskeletal Chest Pain	17 (3.7)	37 (8.0)	18 (3.9)	38 (8.2)
Urinary Tract Infection	27 (5.9)	32 (6.9)	30 (6.6)	36 (7.8)
Rash	27 (5.9)	27 (5.8)	31 (6.8)	36 (7.8)
Dyspepsia	24 (5.3)	31 (6.7)	25 (5.5)	33 (7.1)
Hypophosphataemia	25 (5.5)	26 (5.6)	26 (5.7)	31 (6.7)
Lymphopenia	24 (5.3)	30 (6.5)	25 (5.5)	31 (6.7)
Abdominal Pain	36 (7.9)	30 (6.5)	39 (8.6)	30 (6.5)
Pruritus	24 (5.3)	25 (5.4)	27 (5.9)	29 (6.3)
Creatinine Renal Clearance Decreased	18 (3.9)	26 (5.6)	18 (3.9)	28 (6.0)
Oropharyngeal Pain	18 (3.9)	26 (5.6)	19 (4.2)	28 (6.0)
Hypotension	39 (8.6)	23 (5.0)	40 (8.8)	28 (6.0)
Hyperuricaemia	9 (2.0)	27 (5.8)	8 (1.8)	28 (6.0)
Neutropenia	25 (5.5)	25 (5.4)	25 (5.5)	27 (5.8)
Peripheral Sensory Neuropathy	67 (14.7)	27 (5.8)	69 (15.1)	27 (5.8)
Productive Cough	13 (2.9)	22 (4.8)	15 (3.3)	26 (5.6)
Hypocalcaemia	18 (3.9)	24 (5.2)	18 (3.9)	25 (5.4)

Cd = carfilzomib plus dexamethasone; sNDA = Supplemental New Drug Application; Vd = bortezomib (Velcade) plus dexamethasone

ENDEAVOR sNDA includes cumulative data through 10 November 2014; ENDEAVOR 120-day Safety Update includes cumulative data through 30 June 2015

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 15.1. **Bold** text identifies events with subject incidence ≥ 5% higher in the carfilzomib arm than in the bortezomib arm. Shaded cells indicate adverse events in the carfilzomib arm that are ≥ 5% in Study 2011-003 in the 120-day Safety Update and were not ≥ 5% in Study 2011-003 in the ENDEAVOR sNDA.

Preferred Term	ENDEAVOR sNDA		ENDEAVOR 120-day Safety Update	
	Vd (N = 456) n (%)	Cd (N = 463) n (%)	Vd (N = 456) n (%)	Cd (N = 463) n (%)
Myalgia	16 (3.5)	23 (5.0)	17 (3.7)	25 (5.4)
Chills	10 (2.2)	19 (4.1)	11 (2.4)	25 (5.4)
Rhinitis	8 (1.8)	20 (4.3)	10 (2.2)	25 (5.4)
Cataract	9 (2.0)	17 (3.7)	10 (2.2)	25 (5.4)
Flushing	7 (1.5)	24 (5.2)	7 (1.5)	24 (5.2)
Malaise	8 (1.8)	20 (4.3)	7 (1.5)	23 (5.0)
Musculoskeletal Pain	19 (4.2)	20 (4.3)	23 (5.0)	22 (4.8)
Abdominal Pain Upper	36 (7.9)	18 (3.9)	36 (7.9)	19 (4.1)
Anxiety	31 (6.8)	17 (3.7)	31 (6.8)	19 (4.1)
Abdominal Distension	26 (5.7)	19 (4.1)	26 (5.7)	19 (4.1)
Conjunctivitis	30 (6.6)	12 (2.6)	31 (6.8)	18 (3.9)
Dysgeusia	25 (5.5)	14 (3.0)	26 (5.7)	14 (3.0)
Neuralgia	70 (15.4)	9 (1.9)	70 (15.4)	10 (2.2)
Tremor	23 (5.0)	10 (2.2)	23 (5.0)	10 (2.2)
Polyneuropathy	24 (5.3)	5 (1.1)	24 (5.3)	5 (1.1)

Cd = carfilzomib plus dexamethasone; sNDA = Supplemental New Drug Application; Vd = bortezomib (Velcade) plus dexamethasone
ENDEAVOR sNDA includes cumulative data through 10 November 2014; ENDEAVOR 120-day Safety Update includes cumulative data through 30 June 2015
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 15.1. **Bold** text identifies events with subject incidence ≥ 5% higher in the carfilzomib arm than in the bortezomib arm. Shaded cells indicate adverse events in the carfilzomib arm that are ≥ 5% in Study 2011-003 in the 120-day Safety Update and were not ≥ 5% in Study 2011-003 in the ENDEAVOR sNDA.

Adverse events of special interest

Cardiac Adverse Events

Cardiac Arrhythmias

The cumulative subject incidence during the ENDEAVOR 120-day Safety Update was 17.3% (2.8% ≥ grade 3) in the Cd arm and 10.1% (4.4% ≥ grade 3) in the Vd arm.

Since the ENDEAVOR sNDA, no additional cardiac arrhythmia adverse events led to discontinuation of carfilzomib or bortezomib and there were no additional fatal cardiac arrhythmia adverse events.

The following adverse events were ≥ 2% more frequent in subjects in the Cd arm compared with those in the Vd arm: tachycardia (Cd 4.8%, Vd 2.0%), palpitations (Cd 4.8%, Vd 0.9%), and sinus tachycardia (Cd 2.6%, Vd 0.9%). Syncope was the only event that occurred with a ≥ 2% higher frequency in subjects in the Vd arm compared with those in the Cd arm (Cd 1.3%, Vd 3.7%).

Torsades de pointes-QT prolongation (SMQB) occurred in 1.9% of subjects in the Cd arm compared with 5.0% of subjects in the Vd arm. In the Cd arm, 1.1% of subjects had events that were Grade 3 or higher versus 3.1% of subjects in the Vd arm. For both treatment groups, the most common event, of any grade,

was syncope, which occurred in 5 (1.1%) subjects in the Cd arm and in 17 (3.7%) subjects in the Vd arm. Within this grouping, events leading to the discontinuation of carfilzomib or bortezomib occurred in 0.4% and 0.2% of subjects, respectively. Grade 5 events occurred in 1.1% of subjects in the Cd arm and in 0.4% of subjects in the Vd arm. Since the ENDEAVOR sNDA, 1 additional subject in the Cd arm had an adverse event in the Torsade de pointes-QT prolongation of syncope; the cumulative subject incidence was 2.2% in the Cd arm and 5.0% in the Vd arm.

Cardiac Failure

The cumulative subject incidence during the ENDEAVOR 120-day Safety Update was 8.6% (5.2% ≥ grade 3) in the Cd arm and 3.3% (2.0% ≥ grade 3) in the Vd arm.

Since the ENDEAVOR sNDA, there were no additional fatal cardiac failures. No additional subjects in the Vd arm had a cardiac failure that resulted in discontinuation of bortezomib and 2 additional subjects in the Cd arm had a cardiac failure that resulted in discontinuation of carfilzomib.

The most common events were cardiac failure (Cd 3.7%, Vd 1.1%) and decreased ejection fraction (Cd 2.4%, Vd 0.9%).

Cardiomyopathy

The cumulative subject incidence during the ENDEAVOR 120-day Safety Update was 3.5% (1.9% ≥ grade 3) in the Cd arm and 1.3% (0.4% ≥ grade 3) in the Vd arm. No fatal adverse events were reported for the cardiomyopathy in either treatment arm. One additional subject in the Cd arm had a cardiomyopathy adverse event that resulted in discontinuation of carfilzomib.

The decreased ejection fraction was the most frequently reported event (Cd 2.4%, Vd 0.9%).

Ischemic Heart Disease

The cumulative subject incidence in Study 2011-003 during the ENDEAVOR 120-day Safety Update was 3.0% (1.7% ≥ grade 3) in the Cd arm and 2.0% (1.5% ≥ grade 3) in the Vd arm. Since the ENDEAVOR sNDA, there were no additional fatal adverse events or adverse events leading to discontinuation of carfilzomib or bortezomib.

Angina pectoris was the most frequently reported event (Cd 1.1%, Vd: 0.2%).

Cardiopulmonary Sub- study

A cardiopulmonary substudy was conducted within Study 2011-003 to explore the impact of carfilzomib on echocardiographic parameters and their correlation with cardiac events.

The results of the mixed-model for repeated measures analysis of change in left ventricular ejection fraction, fractional area change, and pulmonary artery systolic pressure have not significantly changed since the ENDEAVOR sNDA.

The substudy did not find echocardiographic evidence of cumulative cardiac injury associated with the use of carfilzomib over a median of approximately 30 weeks of exposure.

Gastrointestinal Events

Gastrointestinal adverse events of diarrhea, nausea, constipation, and vomiting were previously identified as ADRs of carfilzomib. Since the ENDEAVOR sNDA, 1 new adverse drug reaction (gastrointestinal perforation) has been identified.

The cumulative subject incidence during the ENDEAVOR 120-day Safety Update was 59.8% (9.7% ≥ grade 3) in Cd arm and 65.1% (14.3% ≥ grade 3) in the Vd arm. Since the ENDEAVOR sNDA, 2 additional subjects (1 Cd, 1 Vd) had a gastrointestinal adverse event that resulted in discontinuation of carfilzomib or bortezomib. There were no fatal gastrointestinal disorder adverse events.

The most common adverse events in the ENDEAVOR sNDA, were diarrhea (Cd 33.5%, Vd 40.1%), nausea (Cd 22.0%, Vd 19.1%), vomiting (Cd 15.6%, Vd 9.2%), and constipation (Cd 15.1%, Vd 27.9%).

Hematologic Events

Anemia

The cumulative subject incidence during the ENDEAVOR 120-day Safety Update was 41.7% (15.8% ≥ grade 3) in the Cd arm and 28.1% (10.1% ≥ grade 3) in the Vd arm. Since the ENDEAVOR sNDA, 1 additional subject had anemia that led to discontinuation of carfilzomib and no subjects had a fatal anemia adverse event.

Leukopenia

The cumulative subject incidence during the ENDEAVOR 120-day Safety Update was 21.8% (15.3% ≥ grade 3) in the Cd arm and 16.4% (8.6% ≥ grade 3) in the Vd arm. Since the ENDEAVOR sNDA, no additional subjects had leukopenia adverse events that led to discontinuation of carfilzomib or bortezomib and there were no fatal leukopenia adverse events. The decreased lymphocyte count (Cd 9.1%, Vd 3.9%), lymphopenia (Cd 6.7%, Vd 5.5%), and neutropenia (Cd 5.8%, Vd 5.5%) were the 3 most frequently reported adverse events during the ENDEAVOR 120-day Safety Update. Of the ≥ grade 3 adverse events, decreased lymphocyte count (Cd 6.3%, Vd 1.8%) and lymphopenia (Cd 4.5%, Vd 3.1%) occurred at a higher frequency in the Cd arm (≥ 1% difference compared with Vd arm).

Grade 4 neutropenia was balanced in both arms (0.4% in each). None of the subjects with grade 4 neutropenia (Cd 2 subjects, Vd 2 subjects) also had an adverse event of sepsis.

Thrombocytopenia

The cumulative subject incidence during the ENDEAVOR 120-day Safety Update was 31.7% (12.1% ≥ grade 3) in the Cd arm and 26.1% (14.5% ≥ grade 3) in the Vd arm. Since the ENDEAVOR sNDA, there were no additional subjects with thrombocytopenia adverse events that led to discontinuation of carfilzomib or bortezomib and there no fatal thrombocytopenia adverse events.

Hemorrhage

Epistaxis was previously identified as an ADR for carfilzomib. Since the ENDEAVOR sNDA, no new hemorrhages ADRs have been identified. The cumulative subject incidence during the ENDEAVOR 120-day Safety Update was 20.7% (2.6% ≥ grade 3) in the Cd arm and 17.1% (1.3% ≥ grade 3) in the Vd arm. Since the ENDEAVOR sNDA, no additional subjects had a hemorrhage adverse event that led to discontinuation of carfilzomib or bortezomib and there were no fatal hemorrhage adverse events.

Epistaxis (Cd 4.8%, Vd 2.9%), contusion (Cd 3.9%, Vd 4.6%), and hematoma (Cd 2.8%, Vd 1.3%) were the 3 most frequently reported adverse events in this grouping.

Since the sNDA, there were 3 additional ≥ grade 3 hemorrhage adverse events of hemorrhagic anemia, lower gastrointestinal hemorrhage, and vitreous hemorrhage. The cumulative subject incidence during the ENDEAVOR 120-day Safety Update of ≥ grade 3 hemorrhage adverse events was 2.6% in the Cd arm and 1.3% in the Vd arm.

Hepatic Adverse Events

Hepatic Failure, Fibrosis and Cirrhosis

The cumulative subject incidence during the ENDEAVOR 120-day Safety Update was 2.6% (1.3% ≥ grade 3) in the Cd arm and 1.1% (0.2% ≥ grade 3) in the Vd arm. Since the ENDEAVOR sNDA, no additional hepatic adverse events in this grouping led to discontinuation of carfilzomib or bortezomib and there were no additional fatal hepatic failure adverse events.

Hepatitis, Noninfectious

The cumulative subject incidence was 0.2% (0.2% ≥ grade 3) in the Cd arm and 0 in the Vd arm.

Signs and Symptoms

The cumulative subject incidence was 11.9% (3.9% ≥ grade 3) in the Cd arm and 6.4% (1.3% ≥ grade 3) in the Vd arm. The most frequently reported preferred terms in the Cd and Vd arms, were as follows:

- Increased ALT: Cd: 4.8% (1.3% ≥ grade 3) and Vd: 3.9% (0.4% ≥ grade 3)
- Increased AST: Cd: 3.0% (0.4% ≥ grade 3) and Vd: 2.6% (0% ≥ grade 3)
- Increased GGT: Cd: 2.8% (1.7% ≥ grade 3) and Vd: 0.4% (0.2% ≥ grade 3)
- Increased blood bilirubin: Cd: 1.9% (0% ≥ grade 3) and Vd: 0.7% (0.2% ≥ grade 3)
- Hyperbilirubinemia: Cd: 1.5% (0.2% ≥ grade 3) and Vd: 0.2% (0% ≥ grade 3)

Cholestasis and Jaundice of Hepatic Origin

Cholestasis was previously identified as an ADR for carfilzomib.

The cumulative subject incidence during the ENDEAVOR 120-day Safety Update was 2.8% (0.6% ≥ grade 3) in the Cd arm and 0.7% (0 ≥ grade 3) in the Vd arm.

Infections

Infections and Infestations System Organ Class

The cumulative subject incidence during the ENDEAVOR 120-day Safety Update was 76.9% (28.7% ≥ grade 3) in the Cd arm and 66.9% (19.7% ≥ grade 3) in the Vd arm. Since the ENDEAVOR sNDA, 6 additional subjects in the Cd arm and 2 additional subjects in the Vd arm had infection and infestation adverse events that led to discontinuation of carfilzomib or bortezomib.

Two additional subjects in the Cd arm had fatal pneumonia adverse events.

The cumulative infection and infestation fatal adverse events in the Cd arm included pneumonia (3 subjects), bacterial pneumonia (1 subject) and sepsis/septic shock (4 subjects). In the Vd arm, the cumulative fatal adverse events included pneumonia (2 subjects), sepsis/septic shock (4 subjects), pulmonary sepsis (1 subject), and urosepsis (1 subject).

Respiratory Tract Infections

The cumulative subject incidence during the ENDEAVOR 120-day Safety Update was 69.5% (20.3% ≥ grade 3) in the Cd arm and 55.3% (15.1% ≥ grade 3) in the Vd arm. Since the ENDEAVOR sNDA, 4 additional subjects in the Cd arm and 1 additional subject in the Vd arm had respiratory tract infection HLGT (high-level group term) adverse events that led to discontinuation of carfilzomib or bortezomib. Since the sNDA, 2 additional subjects in the Cd arm had a fatal respiratory tract infection HLGT adverse event of pneumonia and no additional subjects in the Vd arm had a fatal respiratory tract infection.

Upper respiratory tract infections (Cd 23.3%, Vd 17.1%), bronchitis (Cd 21.4%, Vd 10.1%), and nasopharyngitis (Cd 16.6%, Vd 12.3%) were the most common adverse events. The incidence of pneumonia and bronchopneumonia was comparable across the 2 arms (pneumonia: Cd 10.8% [8.4% ≥ grade 3], Vd 11.2% [7.9% ≥ grade 3]; bronchopneumonia: Cd 2.6% [1.7% ≥ grade 3], Vd 0.9% [0.4% ≥ grade 3]).

Subject incidence of ≥ grade 3 upper respiratory tract infection (Cd 1.7%, Vd 0.9%) and bronchitis (Cd 2.6%, Vd 1.1%) was higher in the Cd arm compared with the Vd arm.

Herpes Virus Infection

The cumulative subject incidence during the ENDEAVOR 120-day Safety Update was 2.8% (0.6% ≥ grade 3) in the Cd arm and 5.9% (0.4% ≥ grade 3) in the Vd arm. Since the ENDEAVOR sNDA, 1 additional subject in the Cd arm had a herpes viral infection adverse event that led to discontinuation of carfilzomib. No subjects have had a fatal herpes viral infection.

Oral herpes was the most common event in the Cd arm (Cd 1.5%, Vd 0.9%) and herpes zoster the most common adverse event in the Vd arm (Cd 0.4%, Vd 3.7%).

Opportunistic Infections

The cumulative subject incidence was 2.4% in the Cd arm and 1.1% in the Vd arm. Aside from oral candidiasis, opportunistic fungal infection adverse events (ie, fungal skin infection, fungal infection, oral fungal infection, genital fungal infection, and gastrointestinal fungal infection) were reported with a low subject incidence (< 2% for all individual preferred terms) in both treatment arms of Study 2011-003 and differed by < 2% between the treatment and control arms. There were no reports of cytomegalovirus infection in Study 2011-003.

Pulmonary Events

Interstitial Lung Disease

The cumulative subject incidence during the ENDEAVOR 120-day Safety Update was 1.5% (1.3% ≥ grade 3) in the Cd arm and 0.7% (0.4% ≥ grade 3) in the Vd arm. Since the ENDEAVOR sNDA, 1 additional subject had an interstitial lung disease SMQB adverse event that led to discontinuation of carfilzomib and there were no additional fatal interstitial lung disease adverse events.

The most frequently reported preferred terms within this grouping included ILD (Cd 0.6%, Vd 0), pneumonitis (Cd 0.4%, Vd 0.2%), ARDS (Cd 0.2%, Vd 0.2%), and bronchiolitis (Cd 0.2%, Vd 0).

Dyspnea

The cumulative subject incidence of dyspnea adverse events was 33.0% (6.5% ≥ grade 3) in the Cd arm and 17.5% (2.2% ≥ grade 3) in the Vd arm.

There were no additional subjects with a dyspnea adverse event that led to discontinuation of carfilzomib or bortezomib and there were no fatal dyspnea adverse events.

Cough

The cumulative subject incidence of cough during the ENDEAVOR 120-day Safety Update was 26.1% (0 ≥ grade 3) in the Cd arm and 14.9% (0.2% ≥ grade 3) in the Vd arm. No subjects discontinued treatment due to cough and there were no fatal cough adverse events.

Acute Respiratory Failure

The cumulative subject incidence of acute respiratory failure (preferred term) adverse events was 0 in the Cd arm and 0.2% (0.2% ≥ grade 3) in the Vd arm. No subjects discontinued treatment due to acute respiratory failure and there were no fatal acute respiratory failure adverse events.

Renal Adverse Events

Since the ENDEAVOR sNDA, no additional renal adverse events have been identified as ADRs for carfilzomib. The cumulative subject incidence during the ENDEAVOR 120-day Safety Update was 8.9% (4.8% ≥ grade 3) in the Cd arm and 5.9% (3.3% ≥ grade 3) in the Vd arm.

Since the ENDEAVOR sNDA, 1 additional subject in the Cd arm and 1 additional subject in the Vd arm had an acute renal failure that led to discontinuation of carfilzomib or bortezomib.

There were no additional fatal acute renal failure adverse events since the ENDEAVOR sNDA.

The most frequently reported preferred terms included the following:

• Acute renal failure: Cd: 4.8% (2.4% ≥ grade 3), Vd 3.3% (1.5% ≥ grade 3)

• Renal failure: Cd 2.8% (1.7% ≥ grade 3), Vd 1.1% (0.4% ≥ grade 3)

• Renal impairment: Cd 1.7% (0.4% ≥ grade 3), Vd 1.8% (1.3% ≥ grade 3)

Thromboembolic Adverse Events

The cumulative subject incidence during the ENDEAVOR 120-day Safety Update was 16.2% (5.8% ≥ grade 3) in the Cd arm and 6.1% (3.9% ≥ grade 3) in the Vd arm. Since the ENDEAVOR sNDA, 2 additional subjects in the Cd arm and no additional subject in the Vd arm had an embolic and thrombotic adverse event that resulted in discontinuation of carfilzomib or bortezomib.

There was 1 additional fatal embolic and thrombotic adverse event (aortic embolus) in the Cd arm since the ENDEAVOR sNDA. The cumulative fatal adverse events included 1 subject in the Cd arm (aortic

embolus) and 3 subjects in the Vd arm (myocardial infarction [2 subjects] and acute myocardial infarction [1 subject]).

Deep vein thrombosis (Cd 4.8%, Vd 1.1%) and pulmonary embolism (Cd 3.0%, Vd 0.9%) were the most frequently reported embolic and thrombotic adverse events.

Thrombotic Microangiopathy

Thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and thrombotic microangiopathy were previously identified as ADRs for carfilzomib. Since the ENDEAVOR sNDA, no additional thrombotic microangiopathy adverse event ADRs have been identified.

Since the ENDEAVOR sNDA, there have been no additional subjects with thrombotic microangiopathy adverse events. The cumulative subject incidence of thrombotic microangiopathy adverse events in the ENDEAVOR 120-day Safety Update was 0.4% (0.2% ≥ grade 3) in the Cd arm and 0 in the Vd arm.

Peripheral Neuropathy Adverse Events

Study 2011-003 excluded subjects with significant neuropathy at baseline (defined as grade 3 or 4 neuropathy or grade 2 neuropathy with pain), but allowed subjects with low-grade peripheral neuropathy at baseline (grade 2 without pain or grade 1) to enroll because of the high prevalence of peripheral neuropathy in the multiple myeloma population.

The cumulative subject incidence during the ENDEAVOR sNDA Safety Update was 20.1% (2.4% ≥ grade 3) in the Cd arm and 52.6% (8.6% ≥ grade 3) in the Vd arm. Since the ENDEAVOR sNDA, no additional subjects had peripheral neuropathy adverse events that led to discontinuation of carfilzomib and 4 additional subjects had peripheral neuropathy adverse events that led to discontinuation of bortezomib. There were no fatal peripheral neuropathy adverse events.

Peripheral neuropathy (Cd 9.9%, Vd 27.4%), peripheral sensory neuropathy (Cd 5.8%, Vd 15.1%), and neuralgia (Cd 2.2%, Vd 15.4%) were the most common adverse events and all occurred at a higher frequency in the Vd arm.

Based on the ENDEAVOR 120-day Safety Update, the subject incidence of ≥ grade 2 peripheral neuropathy was lower in the Cd arm (6.5%) compared with the Vd arm (33.1%); these percentages were comparable with the sNDA (Cd: 6.0%, Vd: 32.0%).

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) was previously identified as an ADR for carfilzomib. Since the ENDEAVOR sNDA, there were no additional PRES adverse events in Study 2011-003. The cumulative subject incidence of PRES during the ENDEAVOR 120-day Safety Update was 0.4% (0.2% ≥ grade 3) in the Cd arm and 0 in the Vd arm.

Vascular Events

<u>Hypertension</u>

The cumulative subject incidence of hypertension in the ENDEAVOR 120-day Safety Update was 31.5% (13.8% ≥ grade 3) in the Cd arm and 10.3% (3.3% ≥ grade 3) in the Vd arm. Since the ENDEAVOR

sNDA, no additional subjects had a hypertension that resulted in discontinuation of carfilzomib or bortezomib. There were no fatal hypertension adverse events.

The most common preferred term was hypertension (Cd 29.8% [12.7% ≥ grade 3] and Vd 9.6% [3.3% ≥ grade 3]).

Pulmonary Hypertension

Since the ENDEAVOR sNDA, no additional subjects had a pulmonary hypertension adverse event. The cumulative subject incidence of pulmonary hypertension in the ENDEAVOR 120-day Safety Update was 1.3% (0.6% ≥ grade 3) in the Cd arm and 0.2% (0.2% ≥ grade 3) in the Vd arm.

Hypotension

The cumulative subject incidence of vascular hypotensive disorders HLT in the ENDEAVOR 120-day Safety Update was 6.9% (1.1% ≥ grade 3) in the Cd arm and 11.6% (2.9% ≥ grade 3) in the Vd arm. Since the ENDEAVOR sNDA, no additional subjects had vascular hypotensive disorders HLT adverse events that resulted in discontinuation of carfilzomib or bortezomib. There were no fatal vascular hypotensive disorders HLT adverse events.

Tumor Lysis Syndrome Adverse Events

The cumulative subject incidence in the ENDEAVOR 120-day Safety Update was 21.0% (7.3% ≥ grade 3) in the Cd arm and 12.3% (3.5% ≥ grade 3) in the Vd arm.

Two additional subjects (1 in each arm) had a TLS adverse event that resulted in discontinuation of carfilzomib or bortezomib. No events led to death.

Hypersensitivity

Angioedema

The cumulative subject incidence during the ENDEAVOR 120-day Safety Update was 33.3% (2.6% ≥ grade 3) in the Cd arm and 27.9% (2.2% ≥ grade 3) in the Vd arm. Since the ENDEAVOR sNDA, 3 additional subjects in the Cd arm had an angioedema adverse event that led to discontinuation of carfilzomib and there were no additional fatal adverse events.

The most common adverse events in this category were peripheral edema (Cd 23.5%, Vd 18.4%) and edema (Cd 3.9%, Vd 4.6%.

There were 4 events (0.9%) reported of drug hypersensitivity in the Cd arm; none were serious. No events of drug hypersensitivity occurred in subjects in the Vd arm.

Anaphylactic Reactions

The cumulative subject incidence during the ENDEAVOR 120-day Safety Update was 0.4% (0.4% ≥ grade 3) in the Cd arm and 0.2% (0.2% ≥ grade 3) in the Vd arm.

Based on the cumulative data in the ENDEAVOR 120-day Safety Update, none of these cases were reported as anaphylactic reaction as the preferred term.

Two subjects in the Cd arm and 1 subject in the Vd arm had grade 3 circulatory collapse.

Severe Cutaneous Reactions

The cumulative subject incidence during the ENDEAVOR 120-day Safety Update was 0 in the Cd arm and 0.2% (0.2% ≥ grade 3) in the Vd arm.

Infusion Reactions and Infusion Site Reactions

Since the ENDEAVOR sNDA, no additional infusion reaction ADRs have been identified. No infusion reactions within 1 day of the first dose of carfilzomib led to discontinuation of carfilzomib. Asthenia and dyspnea were among the most frequently reported adverse events within 1 day of the first carfilzomib dose. None of the infusion reactions in this category were fatal.

Adverse Events of Electrolyte Changes

Since the ENDEAVOR sNDA, no new ADRs related to electrolyte changes have been identified.

Electrolyte change adverse events that occurred in > 1 additional subject since the ENDEAVOR sNDA included hypokalemia and hypophosphatemia.

The cumulative subject incidence during the ENDEAVOR 120-day Safety Update for hypokalemia was 12.1% (1.7% ≥ grade 3) in the Cd arm and 10.5% (3.5% ≥ grade 3) in the Vd arm and for hypophosphatemia was 6.7% (3.0% ≥ grade 3) in the Cd arm and 5.7% (1.1% ≥ grade 3) in the Vd arm.

No subject in the Cd arm discontinued treatment due to one of these events, and no fatal adverse events were reported.

Malignant or Unspecified Tumors

Since the ENDEAVOR sNDA, no malignant or unspecified tumor ADRs were identified. Since the ENDEAVOR sNDA, 1 additional subject in each treatment arm (Vd and Cd) had a malignant or unspecified tumor in Study 2011-003. Therefore, the cumulative subject incidence of malignant or unspecified tumors during the ENDEAVOR 120-day Safety Update was 6.3% (4.1% ≥ grade 3) in the Cd arm and 1.5% (1.3% ≥ grade 3) in the Vd arm. Since the ENDEAVOR sNDA, no additional malignant or unspecified tumor adverse events led to discontinuation of carfilzomib or bortezomib or were fatal.

Multiple myeloma was reported in 1.3% and 0.2% of subjects in the Cd arm and Vd arm, respectively; plasmacytoma was reported in 2.2% and 0%, respectively. Basal cell carcinoma and acute myeloid leukemia occurred with an incidence of 1.1% and 0.2%, respectively, in the Cd arm and neither event was reported in the Vd arm.

Serious adverse events

Table 21. Summary of Serious Adverse Events Occurring in ≥ 1% of Subjects in any Study arm by Preferred Term (Safety Population; Study 2011-003)

Preferred Term	ENDEAVOR sNDA Vd (N = 456) n (%)	ENDEAVOR sNDA Cd (N = 463) n (%)	ENDEAVOR 120-day Safety Update Vd (N = 456) n (%)	ENDEAVOR 120-day Safety Update Cd (N = 463) n (%)
Number of subjects reporting serious adverse events	162 (35.5)	223 (48.2)	175 (38.4)	254 (54.9)
Pneumonia	39 (8.6)	28 (6.0)	40 (8.8)	36 (7.8)
Dyspnoea	**1 (0.2)**	**14 (3.0)**	**1 (0.2)**	**17 (3.7)**
Pyrexia	**3 (0.7)**	**15 (3.2)**	**3 (0.7)**	**15 (3.2)**
Pulmonary embolism	**3 (0.7)**	**10 (2.2)**	**3 (0.7)**	**10 (2.2)**
Renal failure acute	5 (1.1)	8 (1.7)	7 (1.5)	10 (2.2)
Cardiac failure	**3 (0.7)**	**8 (1.7)**	**3 (0.7)**	**8 (1.7)**
Respiratory tract infection	5 (1.1)	5 (1.1)	5 (1.1)	8 (1.7)
Disease progression	5 (1.1)	7 (1.5)	6 (1.3)	7 (1.5)
Bronchopneumonia	**0**	**6 (1.3)**	**1 (0.2)**	**7 (1.5)**
Bronchitis	2 (0.4)	4 (0.9)	**2 (0.4)**	**7 (1.5)**
Upper respiratory tract infection	3 (0.7)	7 (1.5)	3 (0.7)	6 (1.3)
Sepsis	3 (0.7)	6 (1.3)	3 (0.7)	6 (1.3)
Back pain	2 (0.4)	5 (1.1)	2 (0.4)	6 (1.3)
Plasmacytoma	**0**	**5 (1.1)**	**0**	**6 (1.3)**
Atrial fibrillation	4 (0.9)	5 (1.1)	4 (0.9)	5 (1.1)
Diarrhoea	9 (2.0)	5 (1.1)	10 (2.2)	5 (1.1)
Urinary tract infection	4 (0.9)	5 (1.1)	4 (0.9)	5 (1.1)
Vomiting	2 (0.4)	5 (1.1)	2 (0.4)	5 (1.1)
Deep vein thrombosis	2 (0.4)	4 (0.9)	3 (0.7)	5 (1.1)
Lung infection	3 (0.7)	4 (0.9)	3 (0.7)	5 (1.1)
Thrombocytopenia	6 (1.3)	4 (0.9)	6 (1.3)	4 (0.9)
Hypercalcemia	5 (1.1)	0	5 (1.1)	0

Cd = carfilzomib and dexamethasone; sNDA = Supplemental New Drug Application; Vd = bortezomib (Velcade) and dexamethasone
ENDEAVOR sNDA includes cumulative data through 10 November 2014; ENDEAVOR 120-day Safety Update includes cumulative data through 30 June 2015.
Bold text identifies events with subject incidence ≥ 1% higher in the carfilzomib arm than in the respective comparator arm. Shaded cells indicate adverse events in the carfilzomib arm that are ≥ 1% in the 120-day Safety Update and were not ≥ 1% in the carfilzomib arm in the ENDEAVOR sNDA.

Deaths

In Study 2011-003 (data cut-off 30 June 2015), a cumulative total of 127 subjects (27.4%) in the Cd arm and 144 subjects (31.6%) in the Vd arm died.

Table 22. Summary of Deaths (Safety Population; Study 2011-003)

	ENDEAVOR sNDA Vd (N = 456) n (%)	ENDEAVOR sNDA Cd (N = 463) n (%)	ENDEAVOR 120-day Safety Update Vd (N = 456) n (%)	ENDEAVOR 120-day Safety Update Cd (N = 463) n (%)
Total number of deaths	89 (19.5)	75 (16.2)	144 (31.6)	127 (27.4)
Deaths occurred ≤ 30 days after the date of last dose[a]	21 (4.6)	22 (4.8)	21 (4.6)	26 (5.6)
Primary cause of death				
Adverse event	16 (3.5)	18 (3.9)	16 (3.5)	21 (4.5)
Other	0	0	1 (0.2)	0
Progressive disease	4 (0.9)	4 (0.9)	3 (0.7)	4 (0.9)
Unknown	1 (0.2)	0	1 (0.2)	1 (0.2)
Deaths occurred > 30 days after the date of last dose[a]	68 (14.9)	53 (11.4)	123 (27.0)	101 (21.8)
Primary cause of death				
Adverse event	2 (0.4)	5 (1.1)	5 (1.1)	5 (1.1)
Other	12 (2.6)	4 (0.9)	23 (5.0)	9 (1.9)
Progressive disease	48 (10.5)	39 (8.4)	78 (17.1)	75 (16.2)
Unknown	6 (1.3)	5 (1.1)	17 (3.7)	12 (2.6)

Cd = carfilzomib plus dexamethasone; sNDA = Supplemental New Drug Application; Vd = bortezomib (Velcade) plus dexamethasone
ENDEAVOR sNDA includes cumulative data through 10 November 2014; ENDEAVOR 120-day Safety Update includes cumulative data through 30 June 2015
[a] Last dose of any investigational product, calculated as "event date – last dose date +1."

Table 30. Summary of Deaths Occurring Within 2 Days of any Investigational Product Dosing by Preferred Term (Safety Population; Study 2011-003)

	ENDEAVOR sNDA		ENDEAVOR 120-day Safety Update	
Preferred Term	Vd (N = 456) n (%)	Cd (N = 463) n (%)	Vd (N = 456) n (%)	Cd (N = 463) n (%)
Number of subjects reporting adverse events	2 (0.4)	1 (0.2)	2 (0.4)	2 (0.4)
Cardiac death	0	1 (0.2)	0	1 (0.2)
Myocardial infarction	1 (0.2)	0	1 (0.2)	0
Sepsis	1 (0.2)	0	1 (0.2)	0
Aortic embolus	0	0	0	1 (0.2)

Cd = carfilzomib plus dexamethasone; sNDA = Supplemental New Drug Application; Vd = bortezomib (Velcade) plus dexamethasone
ENDEAVOR sNDA includes cumulative data through 10 November 2014; ENDEAVOR 120-day Safety Update includes cumulative data through 30 June 2015

Laboratory findings

Haematology

Table 31. Treatment-emergent NCI-CTCAE Grade 3 or 4 Laboratory Values and Frequency - Hematology (Safety Population; Study 2011-003)

	ENDEAVOR 120-day Safety Update	
Laboratory Parameter	Vd N = 456 n (%)	Cd N = 463 n (%)
Hemoglobin (decreased) grade 3	64 (14.0)	86 (18.6)
White blood cell count (decreased) grade 3	29 (6.4)	35 (7.6)
White blood cell count (decreased) grade 4	1 (0.2)	1 (0.2)
Neutrophil count (decreased) grade 3	31 (6.8)	33 (7.1)
Neutrophil count (decreased) grade 4	4 (0.9)	6 (1.3)
Lymphocyte count (decreased) grade 3	200 (43.9)	296 (63.9)
Lymphocyte count (decreased) grade 4	42 (9.2)	69 (14.9)
Platelet count (decreased) grade 3	71 (15.6)	86 (18.6)
Platelet count (decreased) grade 4	31 (6.8)	34 (7.3)

Cd = carfilzomib plus dexamethasone; NCI-CTCAE = National Cancer Institute-Common Toxicity Criteria for Adverse Events; Vd = bortezomib (Velcade) plus dexamethasone
ENDEAVOR 120-day Safety Update includes cumulative data through 30 June 2015.
Post-baseline laboratory results through 30 days after the last dose of any investigational product are included. Laboratory abnormalities were graded using NCI-CTCAE Version 4.03 for Study 2011-003.
Subjects were counted only once for each laboratory test.

Chemistry

Table 32. Treatment-emergent NCI-CTCAE Grade 3 or 4 Electrolytes and Other Chemistry Laboratory Values (Safety Population; Study 2011-003)

	ENDEAVOR 120-day Safety Update	
Laboratory Parameter	Vd N = 456 n (%)	Cd N = 463 n (%)
Sodium (decreased) grade 3	40 (8.8)	35 (7.6)
Sodium (decreased) grade 4	1 (0.2)	1 (0.2)
Potassium (decreased) grade 3	25 (5.5)	19 (4.1)
Potassium (decreased) grade 4	3 (0.7)	5 (1.1)
Potassium (increased) grade 3	25 (5.5)	66 (14.3)
Potassium (increased) grade 4	3 (0.7)	20 (4.3)
Corrected calcium (decreased) grade 3	5 (1.1)	28 (6.0)
Corrected calcium (decreased) grade 4	2 (0.4)	12 (2.6)
Corrected calcium (increased) grade 3	5 (1.1)	4 (0.9)
Corrected calcium (increased) grade 4	7 (1.5)	1 (0.2)
Magnesium (decreased) grade 3	1 (0.2)	1 (0.2)
Magnesium (increased) grade 3	0	1 (0.2)
Phosphorus (decreased) grade 3	77 (16.9)	92 (19.9)
Phosphorus (decreased) grade 4	2 (0.4)	3 (0.6)
Glucose (decreased) grade 3	4 (0.9)	3 (0.6)
Glucose (decreased) grade 4	3 (0.7)	7 (1.5)
Uric Acid (increased) grade 3	188 (41.2)	275 (59.4)
Uric Acid (increased) grade 4	20 (4.4)	29 (6.3)

Cd = carfilzomib plus dexamethasone; NCI-CTCAE = National Cancer Institute-Common Toxicity Criteria for Adverse Events; Vd = bortezomib (Velcade) plus dexamethasone
ENDEAVOR 120-day Safety Update includes cumulative data through 30 June 2015.
Post-baseline laboratory results through 30 days after the last dose of any investigational product are included. Laboratory abnormalities were graded using NCI-CTCAE Version 4.03 for Study 2011-003.
Subjects were counted only once for each laboratory test.

Renal and hepatic function

Table 33. Treatment-emergent NCI-CTCAE Grade 3 or 4 Renal and Hepatic Function Laboratory Values (Safety Population; Study 2011-003)

	ENDEAVOR 120-day Safety Update	
Laboratory Parameter	Vd N = 456 n (%)	Cd N = 463 n (%)
Renal function		
Creatinine clearance[a] (decreased) grade 3	47 (10.3)	80 (17.3)
Creatinine clearance[a] (decreased) grade 4	7 (1.5)	5 (1.1)
Serum creatinine (increased) grade 3	20 (4.4)	19 (4.1)
Serum creatinine (increased) grade 4	5 (1.1)	1 (0.2)
Hepatic function		
Alanine aminotransferase (increased) grade 3	2 (0.4)	7 (1.5)
Alanine aminotransferase (increased) grade 4	0	2 (0.4)
Aspartate aminotransferase (increased) grade 3	2 (0.4)	7 (1.5)
Total bilirubin (increased) grade 3	1 (0.2)	1 (0.2)
Total bilirubin (increased) grade 4	0	1 (0.2)
Alkaline phosphatase (increased) grade 3	3 (0.7)	3 (0.6)

Cd = carfilzomib plus dexamethasone; NCI-CTCAE = National Cancer Institute-Common Toxicity Criteria for Adverse Events; Vd = bortezomib (Velcade) plus dexamethasone

ENDEAVOR 120-day Safety Update includes cumulative data through 30 June 2015.
Post-baseline laboratory results through 30 days after the last dose of any investigational product are included. Laboratory abnormalities were graded using NCI-CTCAE Version 4.03 for Study 2011-003.
Subjects were counted only once for each laboratory test.
[a] Creatinine clearance was calculated by sponsor using the Cockcroft-Gault formula.

Vital signs

There were no notable differences in median values of heart rate, blood pressure, and respiratory rate between the Cd and Vd arms at the measured time points in Study 2011-003. There are no additional analyses conducted for the ENDEAVOR 120-day Safety Update.

Electrocardiograms

Electrocardiograms were required for all subjects at baseline only in Study 2011-003.

Safety in special populations

Pregnancy and Lactation

As of 30 June 2015, no pregnancies have been reported in subjects receiving carfilzomib.

Overdose

At the time of the safety update (30 June 2015) there was a cumulative total of 1 overdose and 6 medication errors. The 1 overdose included a patient who received a high dose of carfilzomib in a clinical trial; however, no further details were provided. Two medication errors included administration of carfilzomib with saline.

Drug Abuse

Carfilzomib has no known drug abuse or dependence potential. No signal for drug abuse has been identified in nonclinical studies of carfilzomib, and the pharmacology does not suggest that carfilzomib has the potential for abuse.

Safety related to drug-drug interactions and other interactions

The drug-drug interaction potential of carfilzomib is expected to be low. Please refer to the discussion on Clinical Pharmacology/Non Clinical.

Discontinuation due to adverse events

Table 34. Summary of Adverse Events Leading to Discontinuation of Carfilzomib or Bortezomib in ≥ 1% of Subjects in any arm by Preferred Term (Safety Population; Study 2011-003)

	ENDEAVOR sNDA		ENDEAVOR 120-day Safety Update	
Preferred Term	Vd (N = 456) n (%)	Cd (N = 463) n (%)	Vd (N = 456) n (%)	Cd (N = 463) n (%)
Number of subjects with adverse event leading to discontinuation of carfilzomib or bortezomib	80 (17.5)	79 (17.1)	91 (20.0)	102 (22.0)
Cardiac failure	0	6 (1.3)	0	7 (1.5)
Asthenia	2 (0.4)	3 (0.6)	2 (0.4)	5 (1.1)
Dyspnoea	6 (1.3)	3 (0.6)	6 (1.3)	3 (0.6)
Fatigue	6 (1.3)	1 (0.2)	6 (1.3)	1 (0.2)
Neuropathy peripheral	19 (4.2)	1 (0.2)	21 (4.6)	1 (0.2)
Diarrhoea	4 (0.9)	0	6 (1.3)	0
Neuralgia	6 (1.3)	0	8 (1.8)	0
Peripheral sensory neuropathy	7 (1.5)	0	7 (1.5)	0

Cd = carfilzomib and dexamethasone; sNDA = Supplemental New Drug Application; Vd = bortezomib (Velcade) and dexamethasone
ENDEAVOR sNDA includes cumulative data through 10 November 2014; ENDEAVOR 120-day Safety Update includes cumulative data through 30 June 2015.

Post marketing experience

Based on available marketing data, it is estimated that 20000 patients have been treated with the marketed prduct Kyprolis (carfilzomib) from the international birthdate 20 July 2012 through 10 July 2015.

As of 30 June 2015, the sponsor received a total of 11145 events in 3373 cases from worldwide sources from the international birthdate through 30 June 2015. Of these 11145 events, 8617 (77.3%) were non-serious and 2528 (22.7%) events were serious. Of the 3373 cases, 423 (12.5%) were fatal.

The most commonly reported fatal events were plasma cell myeloma (159 events), disease progression (82 events), and “death” (81 events).

The sponsor received a total of 2569 events in 632 cases from worldwide sources that were initially received during the interval period of 13 January 2015 through 30 January 2015. Of the 2569 events, 1895 were non-serious and 674 were serious. Of the 632 cases, 76 (12%) were fatal.

The most commonly reported fatal events were “death” (45 events, additional events reported in these cases included cardiac disorders, infections, progressive disease, cerebral hemorrhage, and renal failure) and disease progression (12 events).

After a comprehensive review of the Clinical and Safety databases (including analysis of postmarketing safety reports cumulative through 26 May 2015), gastrointestinal perforation, pericardial effusion and pericarditis were added as new ADRs.

Consideration of Long-term Safety of Carfilzomib

To assess long-term safety of study treatment, the subject incidence of overall adverse events and serious adverse events were evaluated during sequential dosing periods of months 1 to 6, 7 to 12, 13 to 18, 19 to 24, as well as after month 24, among subjects who received treatment in each period in Study 2011-003.

Based on the cumulative data in the ENDEAVOR 120-day Safety Update, subjects consistently received more treatment in the Cd arm compared with the Vd arm:

- > 6 months: Cd 324 subjects (70.0%) and Vd 221 subjects (48.5%)
- > 12 months: Cd 212 subjects (45.8%) and Vd 103 subjects (22.6%)
- > 18 months: Cd 99 subjects (21.4%) and Vd 39 subjects (8.6%)
- > 24 months: Cd 24 subjects (5.2%) and Vd 6 subjects (1.3%)

The percentage of subjects who had an adverse event during a treatment period generally decreased with increasing length of time on treatment in both arms. The percentage of subjects who had a serious adverse event also decreased with increasing length of time on treatment in both arms (with the exception of Vd at 13 to 18 months).

There was no trend towards increased subject incidence within the Cd and Vd arms of any individual serious adverse event between the early and later treatment periods, nor was there an increased difference in subject incidence of any individual serious adverse event between the 2 arms in the later treatment periods through month 24.

The number of subjects who received treatment > month 24 was low (Cd: 24 subjects; Vd: 6 subjects).

2.6. Discussion on clinical safety

Safety data of the current application is mainly based on results from the Phase 3 Study 2011-003 (ENDEAVOUR), in relapsed Multiple Myeloma patients in which Cd (n=463) was compared with Vd (n=456).

Overall, the carfilzomib safety database includes safety data from the ENDEAVOR study up to the data cut-off date of 30th June 2015, an update of selected ongoing and completed studies as well as the postmarketing experience with carfilzomib.

Following initial doses of carfilzomib at 20 mg/m^2, the dose was increased to 27 mg/m^2 in study PX 171 009 and to 56 mg/m2 in study 2011 003. A cross-study comparison of the adverse reactions occurring in the Kyprolis and dexamethasone (Kd) arm of study 2011 003 vs the Kyprolis, lenalidomide and

dexamethasone (KRd) arm of study PX 171 009 suggest that there may be a potential dose relationship for the following adverse reactions: cardiac failure (Kd 8.2%, KRd 6.4%), dyspnoea (Kd 30.9%, KRd 22.7%), hypertension (Kd 25.9%, KRd 15.8%), and pulmonary hypertension (Kd 1.3%, KRd 0.8%).

In ENDEAVOR study, more subjects in the Cd arm (25.1%, 116 subjects) compared with the Vd arm (11.4%, 52 subjects) remained on treatment. The median duration of Carfilzomib treatment was 21 weeks longer in the Cd arm (48.0 weeks and 12.0 cycles) than in the Vd arm (27.0 weeks and 8.0 cycles).

A total of 919 (98.9%) subjects (463 in the Cd arm, 456 in the Vd arm) who received at least 1 dose of randomized treatment were included in the safety analysis.

Subjects with at least 1 treatment-emergent AE was pretty similar between arms (99%). The most frequently reported events, were anemia (40.8%), diarrhea (33.5%), pyrexia (31.5%), fatigue (31.1%) and dyspnea (30.5%). Adverse events that occurred with a ⩾ 5% higher subject incidence in the Cd arm relative to the Vd arm were anemia, peripheral edema, upper respiratory tract infection, cough, pyrexia, dyspnea, headache, bronchitis, hypertension, vomiting, muscle spasms, increased blood creatinine and decreased lymphocyte count.

The percentage of AEs grade 3 was higher in the Cd arm (78.8% vs 69.3 Vd vs Cd respectively). AEs grade ≥3 more frequently reported in the Cd vs Vd were anemia (10% vs 16%), hypertension (3% vs 13%), lymphocyte count decreased (2% vs 6%), dyspnea (2% vs 6%), lymphopenia (3% vs 5%), hypophosphatemia (1% vs 3%), pyrexia (1% vs 3%), bronchitis (1% vs 3%), and cardiac failure (1% vs 2%) (Vd vs Cd, respectively).

Regarding infections, the prolonged exposure to low-dose dexamethasone in study population may play a role in the increased risk of such events.

The incidence of SAEs was 54.9% in the Cd arm and 38.4% in the Vd arm. In all subjects, pneumonia was the most commonly reported treatment-emergent SAE (Cd 7.8%, Vd 8.8%). Serious adverse events that occurred more frequently (i.e., a difference of ⩾ 1% of subjects) in the Cd arm when compared with the Vd arm were dysphonia, pyrexia, pulmonary embolism, cardiac failure, bronchopneumonia, bronchitis, and plasmacytoma.

A total of 75 subjects (27.4%) in the Cd arm and 90 patients (31.6%) in the Vd arm had died at the time of data cut-off. Infections and cardiac adverse events were the most frequent fatal adverse events in the Cd arm within 30 days after the last dose.

The rate of discontinuation due to AEs was similar for Cd and Vd in each analysis of treatment discontinuation, with 25.3% in the Cd arm and 23.7% in the Vd arm discontinuing any treatment. The most common adverse events (⩾ 1%) that led to discontinuation of carfilzomib were cardiac failure (Cd 1.5%, Vd 0) and asthenia (Cd: 1.1%, Vd 0.4%).

Anemia, neutropenia, and thrombocytopenia are known class effects of proteasome inhibitors and immunomodulatory drugs. The cumulative subject incidence of thrombocytopenia was 31.7% (12.1% ≥ grade 3) in the Cd arm and 26.1% (14.5% ≥ grade 3) in the Vd arm, the cumulative subject incidence of neutropenia was 21.8% (15.3% ≥ grade 3) in the Cd arm and 16.4% (8.6% ≥ grade 3) in the Vd arm and the cumulative subject incidence of anemia was 41.7% (15.8% ≥ grade 3) in the Cd arm and 28.1% (10.1% ≥ grade 3) in the Vd arm.

The cumulative subject incidence if cardiac Arrhythmias was 17.3% (2.8% ≥ grade 3) in the Cd arm and 10.1% (4.4% ≥ grade 3) in the Vd arm. Torsades de pointes-QT prolongation (SMQB) occurred

in 1.9% of subjects in the Cd arm compared with 5.0% of subjects in the Vd arm. In the Cd arm, 1.1% of subjects had events that were Grade 3 or higher versus 3.1% of subjects in the Vd arm. For both treatment groups, the most common event, of any grade, was syncope (1.1% Cd arm, 3.7% Vd arm).

Cardiac Failure, the cumulative subject incidence was 8.6% (5.2% ≥ grade 3) in the Cd arm and 3.3% (2.0% ≥ grade 3) in the Vd arm. Cardiomyopathy, the cumulative subject incidence was 3.5% (1.9% ≥ grade 3) in the Cd arm and 1.3% (0.4% ≥ grade 3) in the Vd arm. Ischemic Heart Disease, the cumulative subject incidence was 3.0% (1.7% ≥ grade 3) in the Cd arm and 2.0% (1.5% ≥ grade 3) in the Vd arm.

The cumulative subject incidence of gastrointestinal events was 59.8% (9.7% ≥ grade 3) in Cd arm and 65.1% (14.3% ≥ grade 3) in the Vd arm.

Increased ALT, AST, gamma-glutamyltransferase, cholestasis, hyperbilirubinemia, and hepatic failure were previously identified as ADRs of carfilzomib. The cumulative subject incidence of Hepatic Failure, Fibrosis and Cirrhosis in ENDEAVOR trial was 2.6% (1.3% ≥ grade 3) in the Cd arm compare to 1.1% (0.2% ≥ grade 3) in the Vd arm.

Bronchopneumonia and respiratory infections, urinary tract infections, and preferred terms of sepsis and viral infections were previously identified as ADRs for carfilzomib. Lung infection has been included as a new uncommon AE associated to use of carfilzomib Furthermore rhinitis has been newly identified adverse reaction (SmPC, section 4.8).

Despite peripheral neuropathy is a known adverse event of proteasome inhibitors, cases of grade 2 and higher peripheral neuropathy were reported in 6% of patients with relapsed multiple myeloma in the Kd arm, compared with 32% in the Vd arm.

The cumulative subject incidence was 20.1% (2.4% ≥ grade 3) in the Cd arm and 52.6% (8.6% ≥ grade 3) in the Vd arm. The most common adverse events were peripheral neuropathy (Cd 9.9%, Vd 27.4%), peripheral sensory neuropathy (Cd 5.8%, Vd 15.1%), and neuralgia (Cd 2.2%, Vd 15.4%).The cumulative subject incidence of Interstitial Lung Disease was 1.5% (1.3% ≥ grade 3) in the Cd arm and 0.7% (0.4% ≥ grade 3) in the Vd arm.

The cumulative subject incidence of Renal Adverse Events was 8.9% (4.8% ≥ grade 3) in the Cd arm and 5.9% (3.3% ≥ grade 3) in the Vd arm.

Cases of venous thromboembolic events, including deep vein thrombosis and pulmonary embolism with fatal outcomes, have been reported in patients who received Kyprolis. The overall incidence of venous thromboembolic events was higher in the Kyprolis arms of two phase 3 studies. In study PX 171 009 the incidence of venous thromboembolic events was 15.3% in the KRd arm and 9.0% in the Rd arm. Grade ≥ 3 venous thromboembolic events were reported in 5.6% of patients in the KRd arm and 3.9% of patients in the Rd arm. In study 2011 003 the incidence of venous thromboembolic events was 10.6% in the Kd arm and 3.1% in the bortezomib plus dexamethasone (Vd) arm. Grade ≥ 3 venous thromboembolic events were reported in 3.0% of patients in the Kd arm and 1.5% of patients in the Vd arm (SmPC sections 4.4 and 4.8) Venous thromboembolic events has been classified as an identified risk in the Risk Management plan.

2.6.1. Conclusions on clinical safety

Overall, in the ENDEAVOR trial, safety data were largely consistent with the known safety profile of carfilzomib with rhinitis and lung infection being new adverse reactions observed in patients treated for MM. Toxicity was generally manageable.PSUR cycle

The PSUR cycle remains unchanged.

2.7. Risk management plan

The CHMP received the following PRAC Advice on the submitted RMP:

The PRAC considered that the RMP version 5.1 (dated 25 April 2016) could be acceptable if the MAH implements the changes to the RMP as described in the PRAC advice dated 13 May 2016.

The CHMP endorsed this advice without changes.

The MAH implemented the changes in the RMP as requested by PRAC and CHMP.

The CHMP endorsed the RMP version 5.2 (dated 20 May 2016).

The PRAC and CHMP also endorsed RMP version 6.0 (dated 23 May 2016), combining the RMP versions 4.3 (dated 27 April 2016) and 5.2, approved within variations II-001/G and II-004/G (positive CHMP opinion received on 28 April 2016), respectively, with the following contents.

Safety concerns

Table 35 – Summary of the safety concerns

Important identified risks	• Cardiac toxicity (cardiac failure, myocardial ischemia, myocardial infarction & cardiac arrest) • Pulmonary toxicities • Pulmonary hypertension • Dyspnea • Hypertension including hypertensive crises • Acute renal failure • Tumor lysis syndrome • Infusion reactions • Hemorrhage and thrombocytopenia • Venous thromboembolic events • Hepatic toxicity • Thrombotic microangiopathy • Posterior reversible encephalopathy syndrome (PRES) • Febrile neutropenia
Important potential risks	• Herpes zoster infections

	• Reproductive and developmental toxicity
Missing information	• Use in patients with hepatic impairment • Use in patients with clinically significant cardiovascular disease including recent myocardial infarction (within the last 4 months), New York Heart Association (NYHA) Class III or IV cardiac failure, uncontrolled angina, and uncontrolled arrhythmias • Use in pregnant or breastfeeding women

Pharmacovigilance plan

Table 36 – Ongoing and Planned Studies in the Post-authorization Pharmacovigilance Plan

Study / Activity **Type, title and category (1-3)**	**Objectives**	**Safety Concerns Addressed**	**Status**	**Date for Submission of Interim or Final Reports**
CFZ001 An Open-Label, Single Arm, Phase 1 Study of the Pharmacokinetics and Safety of Carfilzomib in Subjects with Relapsed Multiple Myeloma and End-stage Renal Disease Category 3	Primary: To assess the influence of End-stage Renal Disease (ESRD) on area under the curve (both area under the curve, from time 0 to the last concentration measured [$AUC_{0\text{-last}}$] and area under the curve, from time 0 extrapolated to infinity [$AUC_{0\text{-inf}}$]) of carfilzomib 56 mg/m^2 at Cycle 2 Day 1 (C2D1) in subjects with relapsed multiple myeloma.	Carfilzomib exposure (pharmacokinetics) in patients with renal impairment, including those with renal failure, in patients receiving a higher dose (56 mg/m^2) of carfilzomib	Ongoing	Final clinical study report (CSR) Q2 2016 (planned)
CFZ002 An Open-Label, Single-Arm, Phase 1 Study of the Pharmacokinetics and Safety of Carfilzomib in Subjects with Advanced Malignancies and Varying Degrees of Hepatic Impairment. Category 3	Primary: To assess the influence of hepatic impairment on area under the curve (both area under the curve, from time 0 to the last concentration measured [$AUC_{0\text{-last}}$] and area under the curve, from time 0 extrapolated to infinity [$AUC_{0\text{-inf}}$]) of carfilzomib at Cycle 1 Day 16 (C1D16) in subjects with relapsed or progressive advanced malignancies.	Hepatic toxicity Use in patients with hepatic impairment	Ongoing	Final CSR Q2 2016 (planned)

Risk minimisation measures

Table 37 – Summary Table of the Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Cardiac toxicity (cardiac failure, myocardial ischemia, myocardial infarction & cardiac arrest)	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the package leaflet (PL): • Warnings and precautions • Possible side effects	None
Pulmonary toxicities	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the package leaflet (PL): • Warnings and precautions • Possible side effects	None
Pulmonary hypertension	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the package leaflet (PL): • Warnings and precautions • Possible side effects	None
Dyspnea	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the package leaflet (PL): • Warnings and precautions • Possible side effects	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Hypertension including hypertensive crises	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the package leaflet (PL): • Warnings and precautions • Possible side effects	None
Acute renal failure	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the package leaflet (PL): • Warnings and precautions • Possible side effects	None
Tumor lysis syndrome	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the package leaflet (PL): • Warnings and precautions • Possible side effects	None
Infusion reactions	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the package leaflet (PL): • Warnings and precautions • Possible side effects	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Thrombocytopenia	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the package leaflet (PL): • Warnings and precautions • Possible side effects	None
Venous thromboembolic events (VTE)	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.6, Fertility, pregnancy and lactation • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PL: • Warnings and precautions • Possible side effects	None
Hepatic toxicity	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the package leaflet (PL): • Warnings and precautions • Possible side effects	None
Thrombotic microangiopathy	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the package leaflet (PL): • Warnings and precautions • Possible side effects	None
Posterior reversible encephalopathy syndrome (PRES)	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the package leaflet (PL): • Warnings and precautions • Possible side effects	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Febrile neutropenia	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the package leaflet (PL): • Possible side effects	None
Important Potential Risks		
Herpes zoster infections	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration	None
Reproductive and developmental toxicity	Relevant text is provided in the following sections of the SmPC: • Section 4.6, Fertility, pregnancy and lactation • Section 5.3, Preclinical safety data Relevant text is provided in the following sections of the package leaflet (PL): • Pregnancy and breast-feeding	None
Missing Information		
Use in patients with hepatic impairment	Relevant text is provided in the following sections of the SmPC: • Section 4.8, Undesirable effects • Section 5.2, Pharmacokinetic properties	None
Use in patients with clinically significant cardiovascular disease including recent myocardial infarction (within the last 4 months), NYHA Class III or IV cardiac failure, uncontrolled angina and uncontrolled arrhythmias	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects	None
Use in pregnant or breastfeeding women	Relevant text is provided in the following sections of the SmPC: • Section 4.6, Fertility, pregnancy and lactation • Section 5.3, Preclinical safety data Relevant text is provided in the following sections of the package leaflet (PL): • Pregnancy and breast-feeding	None

2.8. Update of the Product information

As a consequence of this new indication and the grouped type II variation, sections 4.1, 4.2, 4.8, 5.1, 5.2, and 6.6 of the SmPC have been updated. The Package Leaflet and the RMP (final version 6.0) has been updated accordingly.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

No critical amendments of the product information have been proposed and a user consultation is not considered needed.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Study 2011-003 (ENDEAVOUR) has provided convincing evidence of clinical efficacy of carfilzomib in combination with dexamethasone alone in terms of the primary endpoint PFS, compared to bortezomib plus dexamethasone, in adult patients with multiple myeloma who have received at least one prior therapy with HR = 0.533 ($p < 0.0001$), based on 414 (79%) IRC-confirmed PFS events occurred (52% and 37% of events in Vd and Cd respectively).

The robustness of the PFS effect is supported by sensitivity analyses (investigator, ORCA, next treatment, interim analysis and missing assessment) and by general consistency within subgroups including subgroups of special interest as prior bortezomib treatment (PFS HR 0.56 95%CI [0.436, 0.728]), prior lenalidomide (PFS HR 0.69 95%CI [0.516, 0.918]) and prior Imid and bortezomib (PFS HR 0.64 95%CI [0.473, 0.861]). . The secondary endpoints including response rate by IRC, the treatment with Cd provides a higher response (62.6% [58.0, 67.0] vs 76.9% [72.8, 80.7] Vd vs Cd respectively) and a deeper response (CR: 20 [4.3%] vs 50 [10.8%]; VGPR 104 [22.4%] vs 194 [41.8%]). The median duration of the response (both by IRC and investigator) was also significantly superior in the Cd arm (10.4 months [9.3, 13.8] in Vd vs 21.3 months [21.3, NE] in Cd; IRC) (8.6 months [7.5, 10.2] in Vd vs 12.9 months [10.2, 15.8] in Cd; Investigator). The median TTP according to IRC was longer in the Cd arm (22.2 months [95% CI: 17.7, NE]) than in the Vd arm (10.1 months [95% CI: 8.8, 11.7]).

Regarding the clinical benefit rate and disease control rate by IRC, both support the superiority of the combination of carfilzomib ad dexamethasone (CBR: 81.9% vs 73.8% Cd vs Vd respectively) (DCR: 90.5% vs 85.2%).

Uncertainty in the knowledge about the beneficial effects

Based on the results of the first interim analysis a positive trend for Cd vs Vd (HR = 0.786; 95% CI: 0.575, 1.075; p = 0.065) was observed for OS. This positive trend has been unchanged in a post hoc analysis carried out with 322 events (65% of total events required; HR 0.805 95%CI: 0.646, 1.003). Despite the fact that Cd is pointing out a clear trend in OS benefit, the data are not definitive. Additional

follow-up will further quantify the OS benefit of Cd over Vd (see discussion on clinical efficacy).

Regarding the subgroup of patients who received bortezomib in the line just prior to randomization and had an interval relapse free of 6-12 months, there were not substantial differences between treatments (median PFS duration 6.5 months; 95% CI: 1.1, 17.5 in the Vd arm and 7.2 months (1.5, NE) in the Cd arm with HR=0.963; 95% CI: 0.32, 2.899) Nevertheless, the sample size of this subgroup is really low so as to draw conclusions about that. Of note, the ORR was 75% (6/8 subjects) in the Vd arm, and 42% (5/12 subjects) in the Cd arm. In those with an interval relapse >12 months, the benefit of Cd seems consistently higher than in those subjects treated with Vd

In those patients refractory to any prior lenalidomide treatment the delay in the progression is less clear (PFS HR 0.80 95%CI [0.573, 1.110]) even though there seem to be a higher response in those treated with Cd than those treated with Vd (61.9% vs 54.9%).

Risks

Unfavourable effects

A total of 919 (98.9%) subjects (463 in the Cd arm, 456 in the Vd arm) who received at least 1 dose of randomized treatment were included in the safety analysis.

Subjects with at least 1 treatment-emergent AE was pretty similar between arms (99%). The most frequently reported events, were anemia (40.8%), diarrhea (33.5%), pyrexia (31.5%), fatigue (31.1%) and dyspnea (30.5%). Adverse events that occurred with a $\geqslant$ 5% higher subject incidence in the Cd arm relative to the Vd arm were anemia, peripheral edema, upper respiratory tract infection, cough, pyrexia, dyspnea, headache, bronchitis, hypertension, vomiting, muscle spasms, increased blood creatinine and decreased lymphocyte count.

The percentage of AEs grade 3 was higher in the Cd arm (78.8% vs 69.3 Vd vs Cd respectively). AEs grade $\geq$3 more frequently reported in the Cd vs Vd were anemia (10% vs 16%), hypertension (3% vs 13%), lymphocyte count decreased (2% vs 6%), dyspnea (2% vs 6%), lymphopenia (3% vs 5%), hypophosphatemia (1% vs 3%), pyrexia (1% vs 3%), bronchitis (1% vs 3%), and cardiac failure (1% vs 2%) (Vd vs Cd, respectively).

Rhinitis and lung infection have been newly identified adverse events (SmPC) and have been added in the SmPC.

Uncertainty in the knowledge about the unfavourable effects

There are no important uncertainties in the knowledge of unfavourable effects.

Effects Table

Table 38: Effects Table for Kyprolis in patients with MM at relapse. ENDEAVOUR study (data cut-off: 10 Nov 2014)

Effect	Short Description	Unit	Treatment Cd	Control Vd	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS (IRC)	Delay in tumour progression without death	Median (months)	18.7	9.4	Sensitive analyses support the main result	Assessment report
OS (IRC)	Life expectancy	Median (months)	NE	24.4	Immaturity of data (1st IA)	
ORR (IRC)	proportion of subjects who achieved bestresponse (sCR, CR, VGPR, PR)	% of patients	76.9	62.9	Higher deep of response in Cd arm / Result not supported by investigator analysis	
CBR	proportion of subjects who achieved bestresponse (sCR, CR, VGPR, PR, MR)	% of patients	81.9	73.8	Result not supported by investigator analysis	
DCR	proportion of subjects in each study arm whoachieved a best response (sCR, CR, VGPR, PR, MR)	% of patients	90.5	85.2	Result not supported by investigator analysis	
Unfavourable Effects						
AEs (1)	Subjects with at least 1 AE	%	98.5	98.9		
AEs grade 3-4	Subjects with at least 1 AE grade 3-4	%	78.8	69.3		
SAEs (2)	Subjects with at least 1 SAE	%	59.4	38.4		
Deaths	Incidence of death	%	6.3	23.7		
AEs leading to discontinuation (3)	Incidence of	%	25.3	4.6		
Anemia	Incidence of	%	40.8	27.6		
Diarrhea	Incidence of	%	33.5	40.1		
Pyrexia	Incidence of	%	31.3	14.7		

Effect	Short Description	Unit	Treatment Cd	Control Vd	Uncertainties/ Strength of evidence	References
Fatigue	Incidence of	%	31.1	29.4		
Dyspnea	Incidence of	%	30.5	13.2		
Rhinitis	Incidence of	%	5.4	2.2		New in SmPC
lung infection	Incidence of	%	0.7	5.1		New in SmPC (SAEs ≥1% of Subjects)

Abbreviations: AE: adverse event; CBR: clinical benefit rate; Cd: carfilzomib+dexamethasone; CR: complete response; DCR: disease control rate; IA: interim analysis; IRC: independent review committee; MR: minimal response; NE: not estimated; PFS: Progression free survival; PR: partial response; ORR: overall response rate; SAE: serious adverse event; sCR: stringent complete response; SmPC: product information; VGPR: very good partial response; Vd: bortezomib+dexamethasone

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The use of the treatment combination carfilzomib and dexamethasone provides a longer PFS (18.7 months (95% CI: 15.6, NE) versus 9.4 months (95% CI: 8.4, 10.4) for bortezomib+dexamethasone, as a consequence of a higher antitumor activity. The ORR is higher and deeper than that obtained by Vd. This fact is in itself of clinical value, given that the regimen bortezomib and dexamethasone is one of the current regimens at relapse. Hence, a new available regimen better than Vd could mean a certain advantage. Moreover, when the results from the ENDEAVOUR study are indirectly compared to the available alternatives, only the triple combination KRd (carfilzomib-lenalidomide-dexamethasone) seems superior. So, in those patients not candidates to receive that triplet, a new alternative as Cd would be valuable.

Overall, there is a pattern of more frequent Grade 3/4 adverse events (78.8% vs 69.3 Vd vs Cd) and SAEs (54.9% vs 38.4 Vd vs Cd) in patients treated with Cd compared to those treated with Vd.

Rhinitis and lung infection are added as newly identified ADRs on the PI.

The rate of discontinuation due to AEs was similar for Cd and Vd in each analysis of treatment discontinuation, with 25.3% in the Cd arm and 23.7% in the Vd arm discontinuing any treatment. The most common adverse events (⩾ 1%) that led to discontinuation of carfilzomib were cardiac failure (Cd 1.5%, Vd 0) and asthenia (Cd: 1.1%, Vd 0.4%).

Benefit-risk balance

The efficacy of carfilzomib with dexamethasone alone in the target population is considered clinically relevant and, in the view of the safety profile, the benefits are considered to outweigh the combined risks and uncertainties. Therefore, the benefit-risk balance is considered positive.

Discussion on the Benefit-Risk Balance

At relapse, the choice of treatment in patients with MM depends on several factors, being the previous response and free relapse interval, two of the most important factors when it comes to deciding the best treatment alternative. Recently, the landscape of therapeutic armamentarium has been modified with the

introduction of several combinations (which includes either carfilzomib or panobinostat) even though, both lenalidomide and bortezomib are the basis for the decisions at relapse.

The introduction of a new combination of carfilzomib (a proteasome inhibitor) and dexamethasone would be valuable from the clinical point of view, since not all patients are candidates to receive a triple combination. There is no doubt that the use of carfilzomib along with dexamethasone provides a longer delay in the progression of MM than the combination of bortezomib and dexamethasone. This benefit in terms of PFS (regardless of the method of analysis) could be related to the deeper response of patients treated with Cd, which hopefully could be eventually translated into a longer survival. Certainly, the recent combination of carfilzomib-lenalidomide and dexamethasone appears to be a better choice for those patients who are fit for it, but a better alternative to Vd in terms of efficacy with an acceptable tolerability and toxicity (treatment discontinuations due to an AE were similar) would be of interest in the relapse setting.

The overall clinical benefit of the treatment has been demonstrated.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends by consensus the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include new indication for Kyprolis to be used with either lenalidomide and dexamethasone or dexamethasone alone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 6.0) is updated in accordance.
In addition, the Marketing authorisation holder (MAH) updated section 6.6 of the SmPC to include the option to administer Kyprolis in a 100 mL intravenous bag containing 5% glucose solution for injection in line with the extension of indication part of this variation.
Furthermore the MAH took the opportunity to include some editorial changes and harmonisations in the PI and to update the information of local representatives for Croatia and Cyprus.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include new indication for Kyprolis to be used with either lenalidomide and dexamethasone or dexamethasone alone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 6.0) is updated in accordance.

In addition, the Marketing authorisation holder (MAH) updated section 6.6 of the SmPC to include the option to administer Kyprolis in a 100 mL intravenous bag containing 5% glucose solution for injection in line with the extension of indication part of this variation.

Furthermore the MAH took the opportunity to include some editorial changes and harmonisations in the PI and to update the information of local representatives for Croatia and Cyprus.

Summary

Please refer to the published Assessment Report Kyprolis H-3790-II-01-G-AR.

REFERENCES

Jiang J, Kirk C, Muchamuel T, et al. The benefits of irreversibility: Infusion administration of carfilzomib results in potent proteasome inhibition and improved safety in animals. Cancer Res. 2011;71(8):2607. AACR Annual Meeting 2011. Abstract 2607.

Yang J, Wang Z, Fang Y, et al. Pharmacokinetics, pharmacodynamics, metabolism, distribution, and excretion of carfilzomib in rats. Drug Metab Dispos. 2011;39(10):1873–82.

Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005;352:2487–98.

Klein JP, Moeschberger ML. Survival Analysis: Techniques for Censored and Truncated Data. New York, NY: Springer-Verlag; 1997.

Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials. 1996;17(4):343–46.

Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983;70(3):659–63.

Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. Hoboken, NJ: John Wiley and Sons, Inc.; 1980.

DeMets DL and Lan G. The alpha spending function approach to interim data analyses. In: Thall PF (ed). Recent Advances in Clinical Trial Design and Analysis, Boston, Kluwer Academic Publishers, 1995:1–27.

Jennison C, Turnbull BW. Group Sequential Methods with Applications to Clinical Trials Boca Raton, FL: Chapman & Hall/CRC Press; 1999.