24 September 2015
EMA/670306/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kyprolis

International non-proprietary name: Carfilzomib

Procedure No. EMEA/H/C/003790/0000

Note

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
ANC	absolute neutrophil count
AS	Active substance
ASM	Active Substance Manufacturer
AST	aspartate aminotransferase
AUC	area under the plasma curve
AV	atrioventricular
BCS	Biopharmaceutics Classification System
BSA	body surface area
CBR	clinical benefit rate
CD	cyclodextrin
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human use
CI	confidence interval
C-L	caspase-like
CL	clearance
Cmax	maximum concentration
CPP	Critical process parameter
CQA	Critical Quality Attribute
CR	complete response
CRP	C-reactive protein
CSR	clinical study report
CT-L	chymotrypsin-like
CYP3A4/5	cytochrome P450 3A4/5
D	high-dose dexamethasone (40 mg PO on Days 1–4, 9–12, and 17–20 of each 28-day cycle)
d	low-dose dexamethasone (40 mg PO on Days 1, 8, 15, and 22 of each 28-day cycle)
DCR	disease control rate
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
DoE	Design of experiments
DOR	duration of response
DOX/Doxil	liposomal doxorubicin
DSC	Differential Scanning Calorimetry
EBMT	European Group for Blood and Marrow Transplantation
EC	Ethics Committee
EC	European Commission
ECG	electrocardiogram
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EP	European Pharmacopoeia
ESMO	European Society for Medical Oncology
EU	European Union
EWP	Efficacy Working Party
FDA	Food and Drug Administration
GC(-MS)	Gas Chromatography (-mass spectrometry)
GCP	Good Clinical Practice
GI	gastrointestinal
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HPCD	hydroxypropyl beta-cyclodextrin
HPLC -PDA)	High performance liquid chromatography (photo diode array)
HR	hazard ratio

HRQL health-related quality of life
HtrA2 pro-survival protease in neurons
HUS hemolytic uremic syndrome
IBD international birth date
ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-OES Inductively coupled plasma optical emission spectrometry
IDMC Independent Data Monitoring Committee
IMiD immunomodulatory drug
IMWG International Multiple Myeloma Working Group
IPC In-process control
IR Infrared
IRC Independent Review Committee
ISS International Staging System
IU International Units
IV intravenous
K-M Kaplan-Meier
KRd Kyprolis (carfilzomib), Revlimid (lenalidomide), and low-dose dexamethasone
LC-MS Liquid chromatography mass spectrometry
LDPE Low density polyethylene
LoD Limit of Detection
LOQ Limit of Quantitation
MAA Marketing Authorisation Application
MDD maximum daily dose
MECL1 multicatalytic endopeptidase complex-like 1
MedDRA Medical Dictionary for Regulatory Activities
mg milligram
MI myocardial infarction
ml or mL millilitre
MM multiple myeloma
MMRM mixed model for repeated measures
MPD maximum planned dose
M-protein monoclonal protein
MS Mass Spectrometry
MTD maximum tolerated dose
NA not applicable OR not available
ND Not detected
NE not estimable
NMR Nuclear Magnetic Resonance
NR not reported OR non-response
NYHA New York Heart Association
ONX Onyx defined grouping OR specified search strategy
ORCA Onyx Response Computation Assessment
ORR overall response rate
OS overall survival
PAR Proven Acceptable Range
PD progressive disease
PE Polyethylene
PFS progression-free survival
P-gp P-glycoprotein
Ph. Eur. European Pharmacopoeia
PI Prescribing Information
PIL Patient Information Leaflet
PK pharmacokinetic
PR partial response
PRES posterior reversible encephalopathy syndrome
PT preferred term
QbD Quality by design
QC Quality Control

QLQ-C30 Quality of Life Questionnaire Core Module
QLQ-MY20 Quality of Life Questionnaire for Multiple Myeloma
QoL Quality of Life
QOS Quality Overall Summary
QP Qualified person
QRS measured from the beginning of the Q wave to the termination of the S wave, representing the time for ventricular depolarization
QTc corrected QT interval
QTcF corrected QT (interval) Fridericia's correction
QTc-PK corrected QT interval-pharmacokinetic
QTPP Quality target product profile
QWP Quality Working Party
R Revlimid (lenalidomide)
R/R relapsed/refractory
RD Revlimid (lenalidomide) with high-dose dexamethasone
Rd Revlimid (lenalidomide) with low-dose dexamethasone
RH Relative Humidity
SAE serious adverse event
SBECD sulfobutylether beta-cyclodextrin
sCR stringent complete response
SCT stem cell transplant
SM Staring material
SmPC Summary of Product Characteristics
SMQB Standardized MedDRA Queries, broad (scope)
SMQN Standardized MedDRA Query, narrow (scope)
SOC System Organ Class
SPA Special Protocol Assessment
T Thalomid (thalidomide)
t½ terminal half-life
TD Thalomid (thalidomide) and high-dose dexamethasone
TLS tumor lysis syndrome
TSE Transmissible Spongiform Encephalopathy
TTC Threshold of toxicological concern
TTP time to progression or thrombotic thrombocytopenic purpura
TTR time to response
USP United States Pharmacopoeia
USP/NF United States Pharmacopoeia/National Formulary
UV Ultraviolet
Vd Velcade (bortezomib) and low-dose dexamethasone
VRd Velcade (bortezomib), Revlimid (lenalidomide), low-dose dexamethasone
VTD Velcade (bortezomib), Thalomid (thalidomide), and dexamethasone
WFI water for injection
XR(P)D X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Amgen Europe B.V. submitted on 22 January 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Kyprolis, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 May 2013.

Kyprolis was designated as an orphan medicinal product EU/3/08/548 on 03 June 2008. Kyprolis was designated as an orphan medicinal product in the following indication: treatment of multiple myeloma.

The applicant applied for the following indication: 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.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Kyprolis as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that carfilzomib was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) 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 applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

New active Substance status

The applicant requested the active substance carfilzomib contained in the above medicinal product to be

considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 29 May 2009, 17 November 2011, 21 November 2011, 15 December 2011 and 18 October 2012. The Protocol Assistance pertained to non-clinical and clinical aspects of the dossier.

Licensing status

Kyprolis has been given a Marketing Authorisation in United States of America on 20 July 2012, Argentina on 24 February 2014, Israel on 08 January 2014 and Mexico on 24 October 2014.

1.2. Steps taken for the assessment of the product

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

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

- The application was received by the EMA on 22 January 2015.
- Accelerated Assessment procedure was agreed-upon by CHMP on 18 December 2014.
- The procedure started on 26 February 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 25 May 2015 . The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 26 May 2015 .
- The PRAC assessment overview was adopted by PRAC on 02 June 2015
- During the meeting on 22-25 June 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 June 2015 .
- The applicant submitted the responses to the CHMP consolidated List of Questions on 25 August 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 16 September 2015
- The PRAC RMP advice and assessment overview was adopted by PRAC on 16 September 2015
- The CHMP adopted a report on similarity of Kyprolis with Thalidomide Celgene, Revlimid, Imnovid and Farydak on 24 September.
- During the meeting on 24 September 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Kyprolis.

2. Scientific discussion

2.1. Introduction

Problem statement

Multiple myeloma (MM) is an incurable disease and accounts for 1% of all cancers and around 10% of all haematological malignancies. The incidence in Europe is 4.5–6.0/100 000/year; the mortality is 4.1/100 000/year (ESMO guidelines 2013). MM is also slightly more frequent in men than in women (approximately 1.4:1). MM is a disease of older adults. The median age at diagnosis is 66 years; only 10 and 2 per cent of patients are younger than 50 and 40 years, respectively (Kyle et al., 2003; Bladé et al., 1998).

MM is a malignant plasma cell proliferation that occurs within a spectrum of diseases that includes monoclonal gammopathy of undetermined significance, primary amyloidosis, non-secretory myeloma, and solitary plasmacytoma. The clinical presentation is characterized by anaemia, bone disease, impaired renal function, hypercalcaemia, recurrent infections, and hyperviscosity (Myeloma Working Group [IMWG], BJH, 2003).

The disease has a typical course characterised by a chronic phase lasting several years, and an aggressive terminal phase.According to the ESMO clinical guidelines (2013), the diagnosis is based on the detection of the monoclonal component (M protein) in serum or urine, of bone marrow plasma cell infiltration (aspiration and/or biopsy), and on the evidence of end-organ damage caused by the proliferative disorder (CRAB criteria: hypercalcaemia, renal insufficiency, anaemia, or bone lesions). The International Staging System (ISS) identifies three stages according to the combination of β2-microglobulin and of albumin (Greipp et al., 2005). In addition, cytogenetics evaluated by FISH is a major prognostic factor: recurrent genetic abnormalities like t(4;14), deletion(17p), chromosome 1 abnormalities, and t(14;16) are associated with a poorer outcome (Sawyer et al., 2011).

Therapies for myeloma currently consist of the following main classes of agents: proteasome and histone deacetylase inhibitors (bortezomib and panobinostat, respectively), immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide), corticosteroids, alkylators, anthracyclines, nitrosoureas (to a lesser extent), plus high-dose chemotherapy and autologous or allogeneic haematopoietic stem cell transplantation (ASCT) for those who are eligible. These agents are combined in clinical practice in an attempt to prolong remission. Specifically, bortezomib has been combined with dexamethasone (VD) + thalidomide (VTD) or lenalidomide (VRD) for induction in young patients, and thalidomide associated with melphalan and dexamethasone (MTD) was used as induction regimen in elderly /frail patients; The second/third lines treatment varies according to the duration of the previous response and the drugs already given (ESMO guidelines, 2013). Response rates decrease with every successive relapse (defined by the IMWG as previously treated myeloma patients who, after a period of being off-therapy, require salvage therapy): 58% at 1st relapse to 15% at 4th relapse. The prognosis is poor with an expected survival of < 1 year for relapsed and refractory disease (defined as relapse of disease in patients who achieve minor response or better, and then either become non-responsive while on salvage therapy, or progress within 60 days of last therapy) as compared to an expected survival of ~ 3 years with relapsed myeloma (Anderson et al. 2008; van de Donk et al. 2011; Kumar et al. 2012; Durie et al. 2012).

About the product

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 applicant requested the approval for the following indication: "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" which was recommended by the CHMP.

Kyprolis is administered intravenously (IV) as a 10 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/m^2 (maximum dose 44 mg) in cycle 1 on days 1 and 2. If tolerated, the dose should be increased to 27 mg/m^2 (maximum dose 60 mg) on day 8 of cycle 1. Treatment may be continued until disease progression or until unacceptable toxicity occurs. Treatment with Kyprolis combined with lenalidomide and dexamethasone for longer than 18 cycles should be based on an individual benefit-risk assessment.

The dose is calculated using the patient's baseline body surface area (BSA). Patients with a body surface area greater than 2.2 m^2 should receive a dose based upon a body surface area of 2.2 m^2. Dose adjustments do not need to be made for weight changes of less than or equal to 20%. From cycle 13, the day 8 and 9 doses of Kyprolis are omitted.

In combination with Kyprolis, lenalidomide is administered as 25 mg orally on days 1–21 and dexamethasone is administered as 40 mg orally or intravenously on days 1, 8, 15, and 22 of the 28 day cycles. Appropriate dose reduction for the starting dose of lenalidomide should be considered according to the recommendations in the current lenalidomide summary of product characteristics, for example for patients with baseline renal impairment. Dexamethasone should be administered 30 minutes to 4 hours before Kyprolis (SmPC, section 4.2).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a sterile lyophilized powder for solution for infusion containing 60 mg/vial of carfilzomib as active substance.

Other ingredients are: Betadex sulfobutyl ether sodium, anhydrous citric acid and sodium hydroxide, as described in section 6.1 of the SmPC.

Kyprolis powder for solution for infusion is available in 50 ml Type I clear glass vial, closed with fluoropolymer laminated elastomeric stopper and aluminium seal with plastic flip off cap, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of the active substance carfilzomib is (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide, corresponding to the molecular formula $C_{40}H_{57}N_5O_7$ and has a relative molecular mass 719.9 g/mol. The active substance has the following structure (fig. 1):

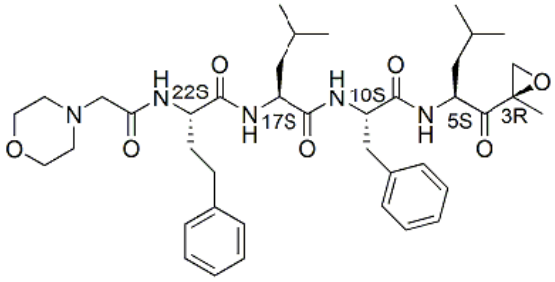


Figure 1. Molecular structure of carfilzomib

The structure of the active substance has been confirmed by ^{1}H and ^{13}C NMR, IR, UV-Vis, elemental analysis and mass spectrometry all of which support the chemical structure. Single crystal X-ray diffraction and amino acid analysis of an intermediate confirmed the absolute stereochemistry of the 5 chiral centres in the active substance.

Carfilzomib appears as a white to off-white, slightly hygroscopic, crystalline powder. It is practically insoluble in water, sparingly soluble in acetonitrile and soluble in ethanol (100%). Its aqueous solubility is pH dependent and is higher at low pH values and its pKa is 5.14 and partition coefficient is 3.77.

Carfilzomib contains five chiral centres [22S, 17S, 10S, 5S, 3R]. Chiral purity is controlled at the level of starting materials contributing to carfilzomib's chiral centres. The manufacturing process yield consistently the same crystal form. No evidence of polymorphs or pseudo-polymorphs has been observed during process development.

Manufacture, characterisation and process controls

Carfilzomib is synthesized in a 11-step convergent process, split between three manufacturing sites, from four well-defined starting materials (SMs) with acceptable specifications. Two variants of the process have been presented. The SMs have been defined following a CHMP request so that the critical stereochemistry defining steps are under regulatory control. The originally proposed SMs are considered as intermediates in the current synthesis. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products and reagents have been presented.

Following the redefinition of the SMs, at the request of CHMP in review, some of the methods used for SMs release and analysis of two of the newly defined intermediates) had not been formally fully validated. It is noted that formal verification and validation where necessary for the methods described above have been initiated. The applicant commits to report confirmation of verification and validation of these methods to the Agency by the end of 1Q 2016 (see 2.2.6 Recommendation(s) for future quality development). Based on the

currently presented information, the methods, as currently performed, are considered adequate to provide assurance of quality of active substance especially taking into account the extensive validation of methods used at the key control points at relevant intermediates, and the successful routine manufacture of carfilzomib meeting the proposed finished active substance specification.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were characterised and were well discussed with regards to their origin. Carfilzomib itself is an anticancer drug and as such ICH M7 does not apply. However, a conservative approach has been taken and an evaluation of the actual and potential structurally related impurities in carfilzomib was performed. Carfilzomib's epoxide group is identified as a structure alert for genotoxicity. However experimental genotoxicity studies showed no evidence of mutagenic activity. Therefore, the impurities that contain the epoxide group in the same position and chemical environment as in carfilzomib can also be considered non-mutagenic, as it is assumed that these impurities would act by the same genotoxic mode of action and would have the same molecular target as carfilzomib. Those of the impurities that showed a genotoxic structural alert other than the epoxide structure have been either toxicologically qualified or otherwise justified and are appropriately controlled in the active substance specification. Overall the presented information and discussion are considered satisfactory.

The active substance is packaged in a low-density polyethylene (LDPE) bags and stored in a secondary container.

The primary packaging material complies with the comply with the EU Regulation on Plastic Materials and Articles Intended to Come into Contact with Food (Reg. 10/2011) for plastic in contact with food and also with Monographs 3.1.3 of the European Pharmacopeia (Ph. Eur.).

Specification

The active substance specification includes tests and limits for appearance (visual), solubility (visual), specific optical rotation (Ph. Eur.), identification (IR, HPLC), assay (HPLC), impurities (HPLC), water content (Ph. Eur.), residual solvents (GC), trifluoroacetic acid content (LC-MS), palladium (ICP-OES), sulphated ash (Ph. Eur.), genotoxic impurities , microbial limit test (Ph. Eur.) and bacterial endotoxins (Ph. Eur.). The active substance specification and acceptance criteria are shown in table 1 below.

The omission of testing for polymorphism has been justified based on developmental data and considering the pharmaceutical form of Kyprolis. The limit for genotoxic impurities content is established according to Guideline on the Limits of Genotoxic Impurities (EMEA/CHMP/QWP/251344/2006 and ICH M7) and in fact the proposed limit is 20% of the TTC limit.

The proposed limits for impurities have been set considering the maximum daily dose (60 mg) and are in compliance with the note for Guidance ICH S9 and ICHQ3A(R2), or have been toxicologically qualified (see section 2.3.4).

The analytical methods used have been adequately described and non-compendial methods appropriately have been validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards of active substance and impurities has been presented.

Batch analysis results are provided for 25 batches of carfilzomib manufactured using both process variants and one batch of active substance manufactured using a combination of the two variants. These 25 batches were of varying batch sizes ranging from pilot to commercial scale and have been used in clinical development, process validation and stability. In addition batch results of seven batches manufactured using earlier processes used only in development have also been provided; these later batches were used during

clinical and non-clinical studies. All results comply with the proposed specifications. The presented results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

Stability data on three pilot and nine production scale batches of active substance manufactured at the proposed sites using both process variants and stored in packaging intended for marketing for up to 36 months at 5°C ± 3°C (long-term condition), for up to six months at 25°C ± 2°C/60% ± 5% RH (accelerated condition) were provided. Stability studies were conducted according to the ICH guidelines. The samples were tested for all parameters included in the release specification. In addition to these, polymorphism has been tested by XRD and DSC during stability studies of pilot batches in long term conditions. The other analytical methods used were the same as for release and were stability indicating. The stability results for all batches have met all acceptance criteria at all time-points both at the long-term and accelerated condition. No significant changes were observed.

Photo stability

A photo stability study was conducted using one pilot size batch in accordance with ICH Q1B. All samples were tested for appearance, assay, identification, impurities, and water content. There was no change in appearance, identification, or water content for any samples under all conditions tested. The exposed drug substance exhibited increased levels and numbers of impurities showing a clear indication of photo-degradation which has not been observed in release or stability testing of carfilzomib. However, the UV and fluorescent light exposure in the ICH photostability and light stress forced degradation studies is significantly higher than the exposure normally encountered during routine manufacturing. Based on the photostability studies, carfilzomib active substance is considered stable to light in the commercial packaging configuration, and protection from light is not required during production.

Forced Degradation Studies

Forced degradation was conducted in solid form (heat, light conditions) and in solution (light, acidic, alkali and oxidative conditions) to provide information about degradation products. Various degrees of degradation have been observed depending on the stress condition. The analytical methods were shown to be stability indicating.

Based on the stability results submitted the proposed retest period, storage conditions and the proposed container are acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Kyprolis is a sterile lyophilized powder for solution for infusion. It is provided in a single-use vial. Prior to use each vial is reconstituted with 29 ml of sterile water for injection (WFI) (not supplied) to provide a deliverable dose of up to 60 mg Carfilzomib as a 2 mg/ml solution. The reconstituted solution may be diluted with 5% dextrose solution.

During the development a study was performed to confirm the extractable volume of parenteral preparations in accordance to Ph.Eur. 2.9.17. Based on this study each vial is filled with adequate volume to allow withdrawal of 30 ml volume of reconstituted solution at 2 mg/ml to provide 60 mg carfilzomib.

Carfilzomib active substance is a non-polar ionisable weak base, is practically insoluble in water. The epoxide group of carfilzomib degrades over time in aqueous solution therefore, dosage form development focused on identification of compositions that could provide adequate stability of carfilzomib while enhancing the solubility necessary for the required therapeutic dose.

Over the course of clinical development a lyophilized carfilzomib formulation was selected as it provides a convenient clinical dosing preparation. In addition in order to ensure stability, a major objective of the formulation development program was to target a concentration of carfilzomib of 2 mg/ml or higher.

The aqueous solubility of carfilzomib is pH dependent however the desired carfilzomib concentration could not be achieved by pH-control. Moreover, low pH conditions were found to promote degradation and are thus unsuitable for clinical administration. The selected pH range for the commercial product has been sufficiently justified.

To achieve an acceptable solubility, well-established methods for solubilisation of hydrophobic pharmaceuticals, such as organic co-solvents, surfactants and modified cyclodextrin excipients, were evaluated. Initial experiments indicated that cyclodextrins (CDs) were more suitable than the other tested means of solubilisation. Sulfobutylether beta-cyclodextrin (SBECD) was selected because it provided carfilzomib with the necessary aqueous solubility without precipitation upon dilution, and further studies were conducted to select the cyclodextrin type, cyclodextrin concentration, carfilzomib/SBECD ratio and determine the optimal pH for a cyclodextrin formulation.

SBECD enhances carfilzomib solubility, provides isotonicity and acts as a bulking agent in the lyophilized cake. SBECD has been used widely as an excipient in parenteral preparations for over 10 years; in Europe marketed products including SBECD include Vfend (voriconazole) and Abilify (aripiprazole) injection. Therefore it is not considered as a novel excipient. The molecular structure of SBECD is shown below (fig.2).

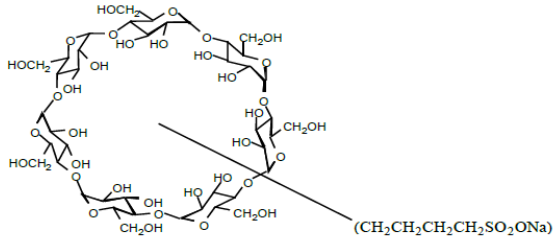


Figure 2. Molecular structure of SBECD

In the absence of a Ph. Eur. monograph it is considered acceptable that SBCED meets the NF requirements. With regards to SBECD purity, levels of the unreacted starting material, beta cyclodextrin and levels of the genotoxic agent 1,4-butane sultone re controlled in the excipient specification. Considering the therapeutic indication, and patient population, the proposed limit for 1,4-butane sultone is appropriate for control given the amount of SBECD dosed and the potential dosing duration, as per ICH M7 (Genotoxic Impurities).

Compatibility of the reconstituted product with the components of typical infusion systems (syringe and infusion sets) was evaluated. It can be concluded that light exposure is not a relevant factor to be considered and that the reconstituted solution was shown to be compatible with infusion systems tested and for at least as long as the duration of administration.

In addition the compatibility of reconstituted solution with 5% dextrose in 50 ml infusion bags was studied. The data provided support the information included in SPC Section 6.3 regarding the in-use shelf-life and storage conditions of the reconstituted solution.

Also based on the data of the compatibility study with 0.9% sodium chloride, in which a degradation product is generated, it is recommended to avoid the use of diluents or IV infusion bags containing chloride, such as 0.9% sodium chloride (section 6.2 of SmPC). However, it has been adequately justified that flushing the intravenous administration line with normal saline (or 5% glucose injection) immediately before and after Kyprolis administration, as mentioned in section 4.2 of SmPC, is not a concern taking into account the rate of degradation and the infusion time

An overview and history of the manufacturing process development, equipment and packaging from the early development stage through the commercial scale was provided. The process development is well summarized and sufficiently documented. The commercial manufacturing process for carfilzomib drug product was developed at laboratory scale and verified at pilot and commercial scales. The process steps and critical process parameters (CPPs) identified as having an impact on the product quality have been evaluated by conducting process characterisation studies.

Based on results from leachable studies it has been justified and accepted that control of leachables is not required. Carfilzomib is a tetrapeptide epoxyketone. High temperature terminal sterilisation is not feasible for peptides therefore sterile filtration and aseptic processing are applied to achieve product sterility. The selected sterilisation method (sterilisation by filtration) has been adequately justified.

During development of the lyophilisation cycle, the optimal carfilzomib solution concentration, the freezing temperature to achieve solidification, the primary drying temperature and duration to maintain the frozen formulation under its glass transition temperature and to reach a complete sublimation below the collapse temperature and the secondary drying temperature and duration to remove the bound water or adsorbed water were studied.

In addition a robustness study was carried out to evaluate the impact of variation from set points of shelf temperatures and chamber pressures on the lyophilised drug product. The lyophilisation process is considered critical. The same lyophilisation cycle was used at both proposed manufacturing sites. The data from laboratory scale and commercial scale demonstrate that the lyophilisation cycle to be used in commercial production is robust.

Carfilzomib product/process specific media fill tests have been successfully performed at both sites. Holding times have been defined at each site.

The operating principles of the equipment and the unit operations are the same at both proposed sites. Any minor differences related to batch size or manufacturer preferences does not impact product quality. Carfilzomib drug product is packaged in a single-use, 50 ml Type I clear glass vial with a 20 mm fluoropolymer laminated elastomeric stopper (chlorobutyl rubber) and an aluminium seal with a plastic flip-off cap.

Manufacture of the product and process controls

The product is manufacture comprises the following main steps: component preparation, compounding, sterile filtration, aseptic filling, lyophilisation, capping, inspection and bulk packaging. There are two proposed manufacturers. The process has been described in sufficient detailed for both sites. A criticality assessment was performed for each unit operation involved in the drug product manufacturing process. The assessment was used to define the critical process controls implemented during production to monitor and to ensure in-process material and finished drug product conforms to the respective specification. In-process control limits

and acceptable operating ranges have been established. Minor differences in the manufacturing process between the two sites were represented and are considered acceptable.

In accordance with Annex II to the guideline on process validation the aseptic manufacturing process by sterile filtration in combination with a lyophilisation process is considered a non-standard manufacturing process.The commercial manufacturing process was successfully validated at the first manufacturing site on with three consecutive commercial scale batches and on the second site with three consecutive batches manufactured on each production line. All validation batches met predetermined acceptance criteria demonstrating the consistency and the state of control of the process.

Product specification

The finished product release and shelf life specifications (table 3) include appropriate tests and limits for this kind of dosage form including appearance (visual), reconstitution time, pH of reconstituted solution (Ph. Eur.), osmolality (Ph. Eur.), identification (HPLC, HPLC- PDA/UV), assay (HPLC), uniformity of dosage units (Ph. Eur.), related substances (HPLC), water content (Ph. Eur.), particulate matter (Ph. Eur.), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

The proposed limits for a number of impurities at release and shelf-life exceed the limit of qualification defined in the ICH Q3B, considering the MDD defined in the SmPC. However the proposed limits are considered qualified in general toxicology and/or genotoxicity studies. In addition, taking into account that carfilzomib is intended to treat patients with advanced cancer, no additional testing is required for impurities qualification (See section 2.3.4).

The reconstitution time limit has been set in order to provide adequate time for the foam to dissipate and to allow a visual examination to check for particulate matter and to verify carfilzomib has dissolved before dose administration. Instructions for reconstitution are provided in section 6.6 of SmPC.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards of active substance and impurities has been presented.

Batch analyses results are provided for 27 batches including batches used in pivotal clinical studies as well as primary stability batches and full scale validation batches. Batches were manufactured at different sites including the commercial ones. All batches meet the proposed specification limits and confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on 16 commercial scale batches stored in the intended for marketing packaging and manufactured by both the proposed production sites and using active substance manufactured by both process variants. Results were provided from samples of finished product and for reconstituted solution (following 24 hours storage at ambient temperature) after storage for up to 36 months under long term conditions (5°C ± 3°C), for 6 months under accelerated conditions (25°C ±2°C /60% ± 5%RH). In addition for another three smaller scale batches, results were provided from samples of finished product and for reconstituted solution (following 24 hours storage at ambient temperature) after storage for up to 36 months under long term conditions (5°C ± 3°C), for 6 months under accelerated conditions (25°C ±2°C /60% ± 5%RH).

The stability attributes tested were: appearance, pH, reconstitution time, assay, related substances, water content, particulate matter, sterility. Sterility testing is performed at release and container closure integrity testing is performed at all other stability study time points. Acceptance criteria and analytical methods are those used for release, except for container closure integrity test (dye ingress test) for which satisfactory description and validation has been provided. The stability indicating character of the HPLC methods used for assay and related substances has been demonstrated through forced degradation studies. In long-term storage condition, a slight decrease of the assay is observed over time with a consistent increase in impurity levels; however the stability results for all batches have met all acceptance criteria for the shelf-life specification at the long-term storage condition of 5°C ± 3°C for test intervals up to 36 months. At the accelerated condition of 25°C/60%RH, the same trend is observed but out of specification result was observed for one impurity.

The stability results were consistent between batches manufactured at the two proposed sites and between batches manufactured at different process scales and on different manufacturing lines at each site.

In-use stability study

Stability of the solution after reconstitution was assessed after 24 hours of storage at ambient conditions to simulate in-use conditions. Samples were taken from the long-term stability studies after 3, 6, 12, 24, 36 months storage. All reconstituted solution test results meet the shelf-life specification acceptance criteria. The SmPC recommendations in section 6.3 are in line with the in use stability results.

Photostability study

Photostability of Kyprolis has been assessed as per ICH Q1B "Guideline Photostability Testing of New Drug Substances and Product" on 2 development batches representative of the commercial product. Unprotected vials exposed to light stress exhibited increased levels of related substances as well as decrease of the assay, with out of specification results whereas dark controls and vials protected in the cardboard box had comparable results within the specifications. Further to this study, the specific labelling recommendation "Retain in original package to protect from light" is included in section 6.4 of SmPC.

Stress degradation studies

Stress testing studies (forced degradation) were conducted on the lyophilized product and in solution at high temperature, light, acidic, basic and oxidative conditions. The studies showed that potential degradation products can be separated and quantified by the analytical method. The degradation products observed during long-term and accelerated storage were consistent with the acid-mediated degradation pathway observed from the forced degradation studies.

Temperature excursion study

A temperature excursion study was performed to evaluate the impact on temperature excursions that may occur during shipping, handling and/or dispensing and the results established safe time for temperature excursions.

Based on the overall submitted stability results, the proposed shelf life of 3 years (36 months), with the recommended storage conditions *"Store in a refrigerator (2℃ – 8℃)", "Store in the original carton in order to protect from light"* and *"Do not freeze"* are acceptable.

Adventitious agents

No materials of animal or human origin are directly used in the manufacture of the excipients used in Kyprolis.

In the manufacture of the excipient SBECD, an enzyme is used as a starting material. This enzyme is of microbial origin but is produced in a fermentation medium containing bovine casein hydrosylate, which in turn is manufactured from bovine milk. The cattle, which provide the milk, originate from countries designated free from BSE. These cattle are certified healthy and both the animals and the milk itself are fit for human consumption. The milk source meets the requirements for control of transmissible spongiform encephalopathy. The Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products (EMEA/410/01) states "In the light of the current scientific knowledge and irrespective of the geographical origin, bovine milk is unlikely to present any risk of TSE contamination". Therefore the TSE risk associated is negligible.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance has been presented in a satisfactory manner. The proposed synthetic route and the overall control strategy for the active substance are acceptable. The formulation development has been sufficiently explained. SBECD plays a key role in the chosen formulation, enhancing carfilzomib solubility. This excipient is used in other products marketed in the EU and, consequently, it is not considered to be a novel excipient. The finished product manufacturing process is described in sufficient detail and the controls in place are considered adequate to ensure the quality of the product. The choice of the sterilization method has been sufficiently justified and supported by data. Kyprolis is manufactured by aseptic processing which is considered as a non-standard process and therefore full process validation data have been provided confirming that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The proposed finished product specification has been justified and is acceptable. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant should submit validation and verification outstanding methods for starting material release and the newly defined intermediates, by the end of 1Q 2016.

2.3. Non-clinical aspects

2.3.1. Introduction

The pivotal *in vivo* non clinical studies were conducted using IV administration. Non-clinical studies were conducted in relevant animal models, consistent with ICH guidelines. The main studies were conducted in compliance with GLP.

EMA Scientific Advice was sought to confirm the acceptability of the nonclinical program with respect to the nonclinical and clinical assessment of QTc evaluation.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Carfilzomib and bortezomib were tested *in vitro* against the CT-L, C-L (also known as post-glutamyl peptide hydrolase PGPH) and T-L activities of the human 20S proteasome complex by enzymatic assays with fluorescence detection (study TR-0004-171). Carfilzomib and bortezomib were equipotent against CT-L activity. Both carfilzomib and bortezomib were time-dependent inhibitors with kinact/Ki values > 30000. Carfilzomib was > 300-fold more potent for the CT-L activity than either C-L or T-L activities, while bortezomib resulted in potent inhibition of C-L activity (IC50 = 75 nM).

A study (TR-0031-171) was conducted to evaluate the effects of a brief (1-hour) exposure to carfilzomib on proteasome inhibition and apoptosis in human tumour cell lines, including its effects on ubiquitinated protein levels, cleavage of caspase 3 and effects on plasma membrane integrity. The human tumour cell lines used were human adenocarcinoma (HT-29), human T-lymphoblast (Molt4) and human myeloma (plasmacytoma, RPMI-8226). In this study, exposure to carfilzomib led to accumulation of ubiquitinated proteins within 4 hours, indicating proteasome inhibition. By 24 hours both Molt4 and RPMI-8226 cells showed significant caspase 3 activation and apoptosis, whereas HT-29 cells entered cell cycle arrest immediately (24 hours) after exposure to carfilzomib, with apoptosis becoming evident at later (72-hours) time points.

In study TR-0032-171, carfilzomib maintained its cytotoxic potential in bortezomib-resistant cells. In HT-29 cells resistant to 100 and 200 nM bortezomib there was a 17- and 18-fold resistance to bortezomib, respectively, whereas the resistance to carfilzomib was no more than 3-fold. In cells conditioned to 300 nM bortezomib, there was a 114-fold increase in resistance compared to 4.3-fold resistance to carfilzomib.

Carfilzomib induced a dose- and time-dependent inhibition of proliferation, ultimately leading to apoptosis. Programmed cell death was associated with activation of c-Jun-N-terminal kinase, mitochondrial membrane depolarization, release of cytochrome c, and activation of both intrinsic and extrinsic caspase pathways. This agent also inhibited proliferation and activated apoptosis in patient-derived MM cells and neoplastic cells from patients with other hematologic malignancies. Importantly, carfilzomib showed increased efficacy compared with bortezomib and was active against bortezomib-resistant MM cell lines and samples from patients with clinical bortezomib resistance. Carfilzomib also overcame resistance to other conventional agents and acted synergistically with dexamethasone to enhance cell death (Kuhn et al, 2007).

In comparison to bortezomib, PR-171 exhibits equal potency but greater selectivity for the chymotrypsin-like activity of the proteasome. In cell culture, PR-171 is more cytotoxic than bortezomib following brief

treatments that mimic the in vivo pharmacokinetics of both molecules. Hematologic tumour cells exhibit the greatest sensitivity to brief exposure, whereas solid tumour cells and non-transformed cell types are less sensitive to such treatments. Cellular consequences of PR-171 treatment include the accumulation of proteasome substrates and induction of cell cycle arrest and/or apoptosis (Demo et al, 2007).

A study in rats was conducted to determine the PD of carfilzomib (TR-0027-171). Proteasome activity recovered with similar kinetics following either a single or QDx2 dose administration in rats. Recovery was complete within 48 hours of final dose administration for bone marrow and liver and was near complete in adrenal gland at this time point. No recovery of proteasome activity was detected in whole blood during the course of study. Both single and QDx2 dose administrations were well tolerated in this study.

Two *in vivo* studies were conducted to determine the PD of carfilzomib in male Sprague Dawley rats after a single dose or the fifth of 5 daily doses (TR-0021-171). After both single and QDx5 administration, dose-dependent inhibition in proteasome activity was observed in all tissues examined, with the exception of brain, where there was no inhibition of proteasome activity. After five daily doses ofPR-171, proteasome inhibition increased in whole blood, PBMCs, heart and lung, where a statistically significant increase in proteasome inhibition was noted. Recovery occurred in all tissues, except whole blood, with a t1/2 of ~ 24 hours. Recovery was complete in all tissues 9 days after the final dose.

Proteasome inhibition was observed in whole blood, adrenal glands, bone marrow, liver and PBMC in Sprague Dawley rats (TR-0015-171). No proteasome inhibition was detected in brain. Dose dependent inhibition of proteasome activity in whole blood 1 hour after the first dose was observed. Partial to complete recovery of proteasome activity was seen within 24 hours of dosing in adrenal gland, liver and PBMCs. No recovery of proteasome activity was observed within 24 hours of dosing in whole blood (erythrocytes) or bone marrow.

Carfilzomib mediated an anti-tumor response in HT-29 bearing BNX mice when administered QDx2 at 5 mg/kg (TR-0037-171). Bortezomib administered BIW with a 72 hour rest between doses was unable to inhibit tumour growth. Carfilzomib treatment was well tolerated and did not induce changes in clinical signs or loss of body weight.

Carfilzomib, at a dose of 1 mg/kg in rats, resulted in equivalent inhibition of the chymotrypsin-like activity of the 20S proteasome when delivered as an IV bolus injection or an infusion of either 5 or 30 minutes in length (TR-0089-171). No major inhibition of the caspase-like or trypsin-like activities of the proteasome was detected with carfilzomib administration at a dose of 1 mg/kg in rats.

Greater than 80% proteasome inhibition was observed in whole blood and PBMCs one hour after IV bolus administration of PR-171 to male Cynomolgus monkeys at 1.0, 1.15, 2.0 and 4.0 mg/kg (TR-0011-171). At these near-complete levels of proteasome inhibition, there was no dose-dependency in the pharmacodynamic response to PR-171. Recovery in proteasome activity occurred slowly in the erythrocyte compartment, where no new protein synthesis occurs. More rapid recovery in proteasome activity was observed in PBMCs, consistent with the observation that nucleated cells are capable of rapid proteasome synthesis following inhibition of proteasome activity in vitro. Daily administration (QD x 5) at the well-tolerated dose of 1.0 mg/kg QD x 5 showed>90% inhibition of proteasome activity in whole blood when tested one hour after dosing on Days 1, 3 and 4.

A single dose pharmacodynamic study was conducted in female cynomolgus monkeys (TR-0046-171). PD response for IV-administered orally available tripeptide epoxyketone analog to carfilzomib (PR-58825) in blood was slower than the PD response to carfilzomib for some of the cohorts. Animals treated orally with 10 mg/kg showed partial inhibition of proteasome activity in the adrenal gland, bone marrow, lung, and inguinal lymph node which was not statistically significant. Oral administration of 20 mg/kg PR-58825 significantly

inhibited the proteasome activity in all tissues except the adrenal gland and brain. IV administration of PR-58825 induced proteasome inhibition in all tissues. PR-58825 penetrated the blood brain barrier when administered IV. IV treatment of animals with carfilzomib induced proteasome inhibition in all tissues except for brain and liver.

Greater than 80% proteasome inhibition in whole blood was achieved after one dose in doses ranging from 0.5 – 2 mg/kg carfilzomib (TR-00218-171). Recovery in whole blood was incomplete due to the irreversible mechanism of action of carfilzomib. Approximately 50% proteasome inhibition was observed in heart tissue 24 hours after the last dose. Proteasome activity recovered completely during the 9 day non-dosing period.

As a part of a safety pharmacology study in cynomolgus monkeys, the PD of carfilzomib was determined by measurement of proteasome CT-L activity in whole blood (TR-0024-171). Inhibition of proteasome activity measured in whole blood is presumed to be relatively unchanged over the first 25 hours following irreversible inhibition. Erythrocytes are not capable of de novo synthesis of proteasome, and slow recovery is seen over several days in whole blood, presumably due to replacement of erythrocytes. The levels of proteasome inhibition in whole blood were similar to the ones detected in the the 4-week repeat dose intravenous toxicity study of carfilzomib in monkeys.

Secondary pharmacodynamic studies

The inhibitory activities of carfilzomib and bortezomib were studied against a panel of 21 proteases representing each major class of non-proteasomal proteases (study TR-0002-171). The criteria for significant inhibition was >50% compared to control. At 10 µM, carfilzomib did not result in significant inhibition of any protease tested. Human pancreatic chymotrypsin was inhibited by 38%, while all other enzymes tested were inhibited by ≤11%. In contrast, bortezomib at the same concentration inhibited cathepsin G (found in neutrophils), chymase (mast cells and skeletal muscle) and human pancreatic chymotrypsin by ≥90% as well as renin, angiotensin converting enzyme (ACE) and human leukocyte elastase by more than 25%.

Carfilzomib was tested for the ability to inhibit 67 receptors and 16 non-proteasomal enzymes. Significant inhibition was defined as ≥50% (study TR-0003-171). In this study, carfilzomib inhibited the tachykinin receptors NK1 and NK2 receptors by 61% and 120% respectively and the sodium channel (site2) by 51%. In addition, binding to a few receptors (CCKA, D3, σ, V1a and Cl- channel) was inhibited by 30-50%. In follow-up experiments, IC50 values for carfilzomib interactions with the NK1 and NK2 receptors were established at 22 and 0.7 µM, respectively. In an *in vitro* arterial contraction model, carfilzomib acted as an antagonist of the NK2 receptor with IC50 values >100 higher than that for proteasome inhibition.

Safety pharmacology programme

An *in vitro* study (TR-0088-171), evaluated the effects of carfilzomib on the hERG channel (a surrogate for Ikr, the rapidly activating, delayed rectifier cardiac potassium current) expressed in human embryonic kidney cells. In a preliminary concentration range assay, 2.2 µM carfilzomib produced a 54.2% inhibition of the hERG potassium current. Based on this result, additional concentrations of 0.7 and .15 µM were selected to evaluate the concentration-response relationship. Carfilzomib inhibited hERG potassium current by 6.9% at 0.7 µM, 12.7% at 1.5 µM and 54.2% at 2.2 µM. The IC50 was 2.1 µM. Under identical conditions, the positive control (60 nM terfenadine) inhibited hERG potassium current by 85.4% (n=2).

Study TR-0023-171 was conducted to assess the potential cardiovascular, respiratory and central nervous system effects of carfilzomib when administered IV as a single dose (1, 2, 3 mg/kg, 2 animals/sex/dose) to

conscious telemetered cynomolgus monkeys. Extensive inhibition of whole blood proteasome activity was found following a single IV injection of carfilzomib at dosage levels of 1, 2, and 3 mg/kg. There were no treatment-related respiratory or primary neurologic effects at any dosage level. Both high-dose males were euthanized due to cardiovascular findings and to physical signs in one of the animals. Premature ventricular contractions and decreased blood pressure were found in 1 high-dose male, and the other high-dose male had increased ST segments and T wave amplitudes, decreases in PR, QRS, and QT intervals, physical signs consistent with the poor condition of the animal, decreased blood pressure, increased heart rate, increased serum troponin T levels, and macroscopic lesions in the heart. QTc prolongations were not observed. There were no cardiovascular findings in males or females at 1 and 2 mg/kg and in females at 3 mg/kg. Irritation at the injection sites resulted in the early termination of 2 females at 2 mg/kg and 1 female at 1 mg/kg. The NOAEL for the study was 1 mg/kg. The NOAEL for cardiovascular effects was 2 mg/kg. The NOAEL for respiratory and neurobehavioral effects was 3 mg/kg.

Pharmacodynamic drug interactions

At concentrations up to 10 µM, carfilzomib did not inhibit CYP1A2, 2C9, 2C19 and 2D6. For CYP3A4, the IC50 value was 3 and 3.7 µM, respectively, using 7-benzyloxy-4-trifluoromethylcoumarin and dibenzyl fluorescein as the substrate (TR-0034-171).

Carfilzomib administration also had no notable effect on hepatic total CYP content. The activities of CYP1A and 2D appeared to be essentially unaffected by carfilzomib administration (TR-0042-171). CYP2C activity on Day 18 at 2 mg/kg decreased to 45 and 53% of controls in males and females, respectively. In males, on Day 19, a dose-dependent decrease occurred in CYP2C activity (51, 15 and 6% of controls at 2, 4 and 6 mg/kg, respectively); in females, a notable increase was noted (approximately 3-fold over the vehicle control at 2 and 4 mg/kg). No treatment-related changes in CYP3A activity were noted on Day 18 in male or female rats. On Day 19, a notable dose-dependent decrease in CYP3A activity occurred in male rats (67, 41 and 16% of controls at 2, 4, 6 mg/kg, respectively), whereas only a slight non dose-related decrease occurred in females (values were 65, 73 and 73% of controls at 2, 4 and 6 mg/kg, respectively).

The effects of Carfilzomib on hepatic microsomal protein, hepatic microsomal total cytochrome P450 content and activities of selected cytochrome P450 enzymes was assessed in in male and female Cynomolgus monkeys (TR-0043-171). No significant changes in CYP2C or 3A activity were observed on Day 19 or 28. On Day 28, CYP1A activity was decreased in males and females across all groups without clear dose dependency, whereas in samples taken on Day 19 no significant changes in CYP1A activity were seen.

Carfilzomib did not markedly affect male CYP1A, female CYP2C and male or female CYP3A enzyme expression at the concentrations examined (TR-0197-171). In contrast, carfilzomib may decrease female CYP1A and increase male CYP2C enzyme expression. Additionally, a dose-dependent decrease in total hepatic CYP content was observed in female monkeys treated with carfilzomib.

Study (TR-0087-171) was conducted to investigate whether carfilzomib is a substrate and/or an inhibitor of P-gp using the Caco-2 bidirectional permeability assay. The ability of carfilzomib to serve as a P-gp substrate was assessed at the dosing concentrations of 0.1, 1 and 3 µM, whereas the ability of carfilzomib to inhibit P-gp activity was assessed at the highest soluble concentration of 3 µM. The efflux ratio of carfilzomib ranged from 6.3 to 28.6 at carfilzomib concentrations up to 3 µM. The efflux ratio of carfilzomib at 0.1 µM was reduced from 12.5 to 1.4 and from 28.6 to 3.8 in the presence of known P-gp inhibitors 10 µM cyclosporine A and ketoconazole, respectively. In the assessment of carfilzomib as an inhibitor of P-gp, carfilzomib at 3 µM inhibited the efflux transport of digoxin by 25% in the Caco-2 system while the known P-gp inhibitors,

cyclosporine A and ketoconazole at 10 µM, eliminated the efflux transport of digoxin completely. Given the very short T½ of carfilzomib *in vivo*, it is unlikely that even marginal inhibition would last >1 hour.

The permeability and efflux potential of carfilzomib was assessed in a Caco-2 monolayer system (at 0.3, 1 and 3 µM) and cell line CPT-B1 (at 1 µM), a proprietary cell line with reduced expression levels of human BCRP (TR-0625-171). The efflux ratios of carfilzomib in Caco-2 cells were 5.76, 8.84 and 9.34 at concentration of 0.3, 1 and 3 µM, respectively; the efflux ratio was 31.3 in CPT-B1 cells at 1 µM. The relative efflux ratio (Caco-2/CPT-B1) was 0.283, smaller than the predefine criteria of 2 to qualify as a BCRP substrate, showing that reduced BCRP level did not lead to a decrease in the efflux of carfilzomib. Therefore, carfilzomib is not classified as a BCRP substrate.In the assessment of inhibition potential of BCRP, known BCRP inhibitor Ko143 decreased the efflux ratio of cladribine from 15.9 to 1.23, achieving essentially a complete inhibition of BCRP activity in CPT-P1 cells (a proprietary cell line with reduced expression levels of human P-gp). Carfilzomib at 3 µM changed the efflux ratio of cardribine from 15.9 to 12.5, corresponding to 22.9% inhibition of BCRP activity.

2.3.3. Pharmacokinetics

The PK properties of carfilzomib were evaluated in mice, rats and monkeys, the same species used for pharmacology and toxicology studies. Following a single IV bolus administration in mice, rats and monkeys, the plasma concentration of carfilzomib rapidly declined in a biphasic manner, with T½ generally lower than 20 minutes. The systemic plasma clearance was similar or higher than the reported hepatic blood flow for each species, indicating that extrahepatic elimination was the predominant clearance pathway. In rats, the PK profiles were similar with IV bolus administration using frozen or lyophilized drug products.

Following a 30 minutes IV infusion to rats at 8 mg/kg, the Cmax (1.55 µM) was achieved within 15 minutes of infusion. This value is close to the steady state plasma concentration (Css = 1.25 µM) predicted from the clearance value obtained in the IV bolus administration. Compared to the IV bolus administration at the same dose, the Cmax was 28-fold lower, whereas the AUC, CL and T½ values were comparable. In addition, the level of proteasome inhibition achieved with IV bolus and 30-minute infusion were identical.

Carfilzomib showed high plasma protein binding *in vitro*, and has rapid and wide tissue distribution upon IV administration *in vivo*. The highest levels of radiolabel were found in liver, muscle, skin and small intestine. At 0.5 and 24 hours after dosing, the tissue to plasma concentration of radioactivity in brain and spinal cord was less than 2, suggesting minimal to no penetration of the blood brain barrier, although carfilzomib has not been studied in animals with a compromised blood brain barrier.

Carfilzomib was rapidly metabolized *in vitro* when incubated in liver microsomes supplemented with cofactor NADPH, indicating it is a substrate of CYP450 enzymes. However, additional *in vitro* and *in vivo* studies showed that the major pathways for metabolic elimination of carfilzomib were peptide cleavage and epoxide hydrolysis. In rat blood and tissue homogenates, carfilzomib rapidly disappeared and 2 metabolites (M14 and M15) resulting from hydrolysis at peptide bonds rapidly formed. When incubated with hepatocytes, the diol of carfilzomib (metabolite M16) was the predominant metabolite, supporting the importance of epoxide hydrolysis. In a study conducted in plasma samples from rats and monkeys and in rat bile and urine samples, metabolites M14 and M16 were the major metabolites. The role of CYP450 was further assessed in this study, showing that the presence of CYP450 inhibitors had minimal effect on the rate of carfilzomib disappearance, and indicating that CYP450 enzymes do not play an important role in the metabolic elimination of carfilzomib. Major metabolites in humans lack a reactive pharmacophore, so they do not have activity as proteasome inhibitors.

Following a single IV administration of 3H-carfilzomib to rats, radioactivity was eliminated slowly such that excretion was not complete by 168 hours post dosing. Urinary and fecal excretion accounted for a mean of 14.1 and 18% of the administered dose, with and overall recovery of 79.3%. In addition, after a single IV dose of carfilzomib to bile-duct-cannulated rats, carfilzomib was mainly excreted in bile and urine in the form of metabolites with less than 1% of the dose excreted intact as parent compound. The mean total recovery in the form of carfilzomib and metabolites within 24 hours post dose was 56.5% of the dose.

The inhibitory effect of carfilzomib on CYP450 enzymes (1A2, 2C8, 2C9, 2C19, 2D6, 3A4/5) was evaluated *in vitro* using human liver microsomes. In this study carfilzomib showed modest direct and time-dependent inhibition of CYP3A4/5 activity. The time-dependent inhibition was NADPH-dependent and resistant to dilution, suggesting that carfilzomib is an irreversible or quasi-irreversible inhibitor of CYP3A4/5.

The ability of carfilzomib to induce CYP1A2 and 3A4 was evaluated in cultured human hepatocytes, showing no induction of the enzymatic activity. No or minimal induction in CYP activity was noted in liver samples taken from rats and monkeys after repeated dose administration for 6 and 9 months, respectively.

Carfilzomib is primarily metabolized via peptidase and epoxide hydrolase activities. Therefore, CYP450-mediated mechanisms play a minor role in the overall metabolism of carfilzomib. In addition, a metabolism study (TR-0212-171) showed that metabolism rate of carfilzomib in human hepatocytes was not affected by known CYP450 inhibitors.

Carfilzomib showed minimal inhibitory effects on P-gp in a Caco-2 monolayer system but was found to be a P-gp substrate. However, carfilzomib is not classified as a BCRP substrate and the inhibitory effect of carfilzomib on BCRP was minimal. Given that carfilzomib is IV administered and has a short half-life, the PK of carfilzomib is unlikely to be affected by P-gp or BCRP inhibitors or inducers *in vivo*.

The *in vitro* studies evaluating the possible inhibitory activity of carfilzomib on some transporters known to be involved in clinically relevant in vivo drug interactions (OATP1B1, OATP1B3, OAT1, OAT3, OCT2, BSEP) showed that for OATP1B1, inhibition by carfilzomib has been shown with an IC50=2,01µM.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity studies are summarised in Table 4.

Table 1. Summary of single-dose toxicity studies conducted with carfilzomib

Study reference/GLP compliance	Species (number, sex)	Route of administration Doses (mg/kg)	MTD (mg/kg/day)	Major findings
Single dose toxicology and PD studies of PR-171 in rats: determination of MTD *TR-0006-171* Study PDR-012 and PDR-015 No GLP	Rat SD, M	IV 0.5,1,1.5,3,4.5,7,9	~8	**At ≥9 mg/kg** 2 /9 rats died 24 to 48 h post dose **At 4.5 et 7 mg/kg**, for PDR-012 ↑ reticulocytes effect on albumin and phosphorus levels **At ≥7mg/kg,** proteasome inhibition in blood and tissues (≥90%)
DRF toxicity study of PR-171 in male Cynomolgus monkeys *TR-0008-171* Study SNBL.048.03 No GLP	Cynomolgus monkeys (2-3/group)	Single IV (1,1.16,2,4) + daily IV dose (1 mg/kg) for 5 days		**At 1 mg/kg**: **1 animal dead 2 days post dose** (fluid in the thoracic and pericardial cavities, congestion of the liver and kidneys, discoloration of the GI mucosa, degenerative changes in the myocardium) **At 2 mg/kg:** emesis **At 4 mg/kg: 1 animal dead 2 days after dosing** (fluid in the thoracic and pericardial cavities, congestion of the liver and kidneys, discoloration of the GI mucosa, hemorrhage and necrosis in the GI tract, **degenerative changes in the myocardium**). In surviving animals, emesis, ↑ urea nitrogen and creatinine, ↓ platelets and serum albumin. **QD5 (1 mg/kg):** well tolerated, No treatment-related changes Half-life =7.2 min
Single dose PK/PD and toxicology studies of PR-171 in male SD rats: Determination of MTD *TR-0010-171* Study PDR-014 No GLP	Rat SD, M (15/group)	Single IV (10, 15, 25)	Not determined	**At 10 mg/kg:** 2/12 animal died within 24h after dosing, surviving animals presented BW loss and renal and hepatic toxicity **At ≥15 mg/kg: all animal died**
Pharmacodynamics and toxicity of carfilzomib in rats: effect of infusion delivery *TR-0356-171* No GLP	Rat SD, M (3-10/group)	IV bolus (8 mg/kg) and IV infusion (10 or 30 min) (8,10,12)	30-min infusion: 8 mg/kg Bolus: <8 mg/kg	**At 8 mg/kg (bolus): mortality (14/32 animals**). In surviving animals, ↑ BUN and creatinine 24h post-dose.↑ ALT. effect on stomach, liver, adrenals, intestines, kidneys and lungs **At 8 mg/kg (30-min infusion):** no mortality, ↓ BUN and ↑creatinine 24h post-dose. Effect on stomach and liver **At 8 mg/kg (10-min infusion):** ↓ mortality (1/8) **At 10 and 12mg/kg (30-min-infusion):** mortality (1/6 and 4/6 animals) No difference in terms of proteasome inhibition after bolus or infusion administration Infusion of carfilzomib resulted in reduced toxicity in rats.

Repeat dose toxicity

Repeat-dose, GLP-compliant, IV toxicity studies in rats of 1- and 6-months duration were conducted (TR-0014-171; TR-0072-171).

In the 1-month study, carfilzomib was administered as an IV bolus at dosage levels of 0.5, 1, 2, 4, and 6 mg/kg (3–36 mg/m^2) for 2 treatment cycles (each cycle consisting of 5 consecutive daily doses followed by a 9-day rest), followed by a 2-week recovery period, equivalent to the dosing schedule of the clinical trial PX-171-001. In the 6-month study, carfilzomib was administered IV (bolus) at dosage levels of 1, 2, and 4 mg/kg (6–24 mg/m2) for 3 and 6 cycles of treatment (each 28-day cycle had dosing on Days 1, 2, 8, 9, 15, and 16; equivalent to the dose schedule used in all other clinical trials) with an 8-week recovery period. In the 1-month study, mortality was found at dosage levels ≥ 1 mg/kg, and the cause of death was considered cardiac failure (cardiomyopathy). With the change in dosing regimen used in the 6-month study (dosing twice weekly rather than for 5 consecutive days), there was no mortality at 1 mg/kg, but mortality was found at ≥ 2 mg/kg (≥ 12 mg/m^2). The cause of death for most of these animals was cardiovascular in nature (cardiac fibrosis or cardiac failure), but some deaths were considered due to gastrointestinal haemorrhage/necrosis or renal tubular necrosis. In the chronic (6-month) study, decreases in body weight gain in males at all dosage levels and decreases in food consumption in males at all dosage levels and females at ≥ 2 mg/kg were greatest on the days immediately following dosing, with recovery during the 12-day non-dosing periods at the end of each cycle. A variety of clinical pathology findings, particularly at the middle (2 mg/kg) and high (4 mg/kg) dose levels, were consistent with stimulated erythropoiesis, acute phase reactions, stress, target organ toxicity, or declining physical condition of the animals. Platelet levels were decreased at the terminal sacrifice (taken 24 hours after the last dose) but not at the interim or recovery sacrifices, which were 12 and 47 days after dosing, respectively. Histomorphological changes noted in more than 1 animal/sex were found in the kidney (chronic progressive nephropathy), liver (periportal vacuolation), spleen (decreased marginal zone cellularity), and mesenteric lymph nodes (increased mast cells). Exposure to carfilzomib and its 3 major metabolites (M14, M15, and M16) was generally dose-proportional in males and females. There were no gender-related differences in exposure to carfilzomib or its metabolites. Proteasome activity in whole blood was inhibited by > 85% at all dosage levels after the first dose and by > 90% after the first doses of Cycles 3 and 6. Minimal recovery in proteasome activity was found after the 12-day washout periods at all dosage levels, consistent with the irreversible mechanism of action of carfilzomib and the inability of erythrocytes to synthesize new proteasomes. The STD10 in the chronic rat study was determined to be 2 mg/kg (12 mg/m^2) based upon the death of 3 animals (1 with uncertain relationship to treatment) at this dose and mortality of > 10% in the 4 mg/kg dose group. The no observed adverse effects level (NOAEL) was determined to be 1 mg/kg. The plasma carfilzomib Cmax and AUClast values (5 minutes as first blood sample time point) in males (females) on Day 142 at the STD10 of 2 mg/kg were 519 ± 57 (466 ± 67) ng/mL and 10,215 (9281) ng·min/mL, respectively.

The potential toxicity and PD profile of carfilzomib after 2 daily IV injections of 2 mg/kg (24 mg/m^2) was evaluated in a GLP-compliant study in cynomolgus monkeys (TR-0157-171). IV administration of carfilzomib resulted in > 90% inhibition of proteasome activity in whole blood after the first dose. Decreased erythroid mass on Days 4 and 5 and decreased reticulocyte counts on Day 4 were followed by recovery of the reticulocyte counts by Day 7 and mild erythroid hyper cellularity on Day 7, indicative of responsive bone marrow. Decreased platelet counts on Days 2 to 4 were fully recovered by Day 7 and were not associated with megakaryocyte changes in the bone marrow. Mild to moderate increases on Day 2 in serum urea, associated with mild increases in serum creatinine and increased urine specific gravity, were consistent with pre-renal azotaemia and were fully recovered by Day 3. Decreases in serum albumin were associated with increases in plasma fibrinogen and serum C-reactive protein (CRP), and this constellation of findings was

consistent with an acute-phase reaction; full recovery was found by Day 7. Increased serum troponin I values were transient in 3 animals that did not have microscopic evidence of myocardial toxicity and were persistent in 1 animal that also had increases in serum AST and ALT and myocardial lesions (degeneration and vascular congestion).

Repeat-dose, GLP-compliant, IV toxicity studies in cynomolgus monkeys of 1 and 9 months duration were conducted (TR-0017-171; TR-0073-171). In the 1-month study, carfilzomib was administered IV (bolus) at dosage levels of 0.5, 1, and 2 mg/kg (6-24 mg/m^2) for 2 treatment cycles (each cycle consisting of 5 consecutive daily doses followed by a 9-day rest). In the 9-month study, carfilzomib was administered IV (bolus) at dosage levels of 0.5, 1, and 2 mg/kg (6–24 mg/m^2) for 9 cycles of treatment (each cycle consisted of 2 consecutive days of dosing per week for 3 weeks, followed by a 12-day rest), with an 8-week recovery period. In the 1-month study, with daily dosing for 5 consecutive days, a dosage level of 2 mg/kg (24 mg/m^2) resulted in the premature death in 6 of 10 monkeys during the first cycle of administration; the cause of death was cardiac toxicity (inflammation, haemorrhage, necrosis, oedema) and/or pulmonary haemorrhage and oedema. In the 9-month study, the same dosage levels were used as in the 1-month study, but the dosing regimen was reduced from 5 to 2 consecutive daily doses weekly (i.e., the current regimen being submitted for approval). With the reduction in dosing frequency, mortality still occurred at 2 mg/kg (24 mg/m^2), but the incidence was decreased to 2 of 12 animals at Days 132 and 157. Proteasome inhibition at this dose level was $\geq$ 85%. The cause of death in the monkeys on the 9-month study was multiorgan toxicity, including cardiac inflammation, pulmonary inflammation and oedema, renal dysfunction, or, in 1 female, declining physical condition, associated with severe no regenerative anaemia associated with decreased bone marrow cellularity, severe hypoalbuminemia associated with subcutaneous swelling, and moderate increases in liver enzymes, particularly ALT and alkaline phosphatase (ALP), associated with marked diffuse hepatocellular glycogen accumulation in the liver. Decreases in erythroid parameters (RBC, haemoglobin, and haematocrit) at all dosage levels, characterized by recovery during non-treatment periods and associated with increased reticulocyte counts, were consistent with a regenerative anaemia. Similarly, decreased platelet counts just after drug administration, associated with increased platelet counts at the end of cycles (after a 12-day nondosing period), at 2 mg. The plasma clearance appeared to increase as carfilzomib dose increased. As a consequence, both Cmax and AUClast values of carfilzomib increased less than dose proportionally. The data from the TK investigations showed that exposure did not change following repeat-dose administration and was similar between genders. Inhibition of proteasome activity in whole blood was > 80% after the first dose and > 90% in Cycles 3, 6, and 9 at all dosage levels, with little recovery during the non-dosing periods, consistent with the irreversible mechanism of action of carfilzomib and the inability of erythrocytes to synthesize new proteasomes. The HNSTD was considered to be 0.5 mg/kg (6 mg/m^2) and was associated with > 80% proteasome inhibition in the blood after the first dose. Similar proteasome inhibition (80% to 90% is achieved with doses of 20 to 27 mg/m^2 in humans). The plasma carfilzomib Cmax and AUClast values (5 minutes as first blood sample time point) in males (females) on Day 225 at the HNSTD of 0.5 mg/kg were 43.1 ± 4.6 (47.5 ± 9.4) ng/mL and 804 ± 99 (886 ± 148) ng·min/mL, respectively.

Genotoxicity

A summary of genotoxicity studies is presented in Table 5.

Table 2. Summary of genotoxicity studies

Type of test/ Study reference /GLP status	Test system	Product/ Concentrations range/ Metabolising system	Main findings
Bacterial Reverse Mutation test TR-0069-171 Study OTE0001 GLP	*S. typhi* TA1535, TA1537,TA98 and TA100 *E. coli* WP2 uvrA (pKM101)	Carfilzomib 5 – 5000 µg/plate +/- S9 mix	No signs of toxicity No evidence of mutagenic potential **Negative**
Bacterial Reverse Mutation test TR-0425-171 Study HUB0133 GLP	*S. typhi* TA1535, TA1537,TA98 and TA100 *E. coli* WP2 uvrA (pKM101)	Carfilzomib spiked with impurities: 1.5 – 5000 µg/plate +/- S9 mix	No signs of toxicity No evidence of mutagenic potential **Negative**
In vitro mammalian chromosome aberration test in human lymphocytes TR-0070-171 Study OTE0002 GLP	Human lymphocytes cultured *in vitro*	Carfilzomib Absence of S9, 3-hour treatment: 0.078-0.313 µg/ml Presence of S9, 3-hour treatment: 0.625-2.5 µg/ml Absence of S9, 21-hour treatment: 0.0156-0.0625 µg/ml Presence of S9, 3-hour treatment: 2.5-5.5 µg/ml	Increase in chromosomal aberration at concentrations ≥0.0625 µg/ml without S9 and ≥2.5 µg/ml with metabolic activation **Positive**
In vitro mammalian chromosome aberration test in human lymphocytes TR-0426-171 Study HUD0131 GLP	Human lymphocytes cultured *in vitro*	Carfilzomib spiked with impurities: Absence of S9, 3-hour treatment: 0.04,0.08 and 0.12 µg/ml Presence of S9, 3-hour treatment: 1,2 and 3 µg/ml	Significant increase in chromosomal aberration at all concentrations without S9 Significant increase in chromosomal aberration at 3 µg/ml with metabolic activation **Positive**
Mouse micronucleus test TR-0071-171 GLP	M and F CD-1 mice (6/sex/dose)	Carfilzomib IV administration (twice, 24h apart) 1.25-5 mg/kg/day in M 0.31-1.25 mg/kg/day in F Positive control gp:Mitomycin C.	Treatment related mortality at 5 mg/kg (M) No bone marrow cell toxicity No increase of micronucleated polychromatic erythrocytes up to 2.5 and 1.25 mg/kg/day in M and F **Negative**
Mouse *in vivo* micronucleus test TR-0422-171 HUD0132 GLP	M and F CD-1 mice (6/sex/dose)	Carfilzomib heat-stressed and spiked with impurities: IV administration (twice, 24h apart) 0.625-2.5 mg/kg/day Positive control gp:Mitomycin C.	No bone marrow cell toxicity No increase of micronucleated polychromatic erythrocytes **Negative**

Carcinogenicity

No studies were submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

A summary of reproductive and developmental studies is presented in Table 6.

Table 3. Summary of reproductive and developmental studies

Study type/ Study reference / GLP	Species; Number/ sex/group	Dose (mg/ kg/day) Dosing period Route	NOAEL (mg/kg/ day) & AUC	Major findings
Preliminary intravenous embryo-fetal toxicity study in rats Tr-0074-171 Study 07-4332 No GLP	Timed-mated female SD rat 8/group	IV once daily 0.5,1,2 from GD 6 to 17	2 mg/kg: high dose recommended for the definitive study	**Dams:** No mortality **At 2 mg/kg**: ↓ BW and BW gain, and food consumption Deficit in adjusted maternal BW gain **At 1 mg/kg**: ↓ BW and food consumption Deficit in adjusted maternal BW gain **At 0.5 mg/kg**: ↓ BW gain No findings at maternal necropsy **Fetuses:** **Up to 2 mg/kg:** No effect on pre or post-implantation loss, placenta or fetal weight, no external malformations at any doses
Carfilzomib: An intravenous embryo-fetal toxicity study in rats Tr-0075-171 Study 07-4333 GLP	Time-mated female SD CD rats (22/group)	IV once daily 0.5, 1, 2 from GD 6 to 17	NOAEL (maternal) =0.5 NOAEL (embryo-foetal) =2	**Dams:** **At 2 mg/kg**: 2 dams dead (fluid in the thorax, enlarged heart) ↓activity, piloerection, hunched appearance, labored breathing ↓ BW and BW gain, and food consumption Deficit in adjusted maternal BW gain **At 1 mg/kg**: Piloerection, hunched appearance Small and transient ↓ BW, BW gain and food consumption **At 0.5 mg/kg**: Transient ↓ BW gain and food consumption **Fetuses:** **Up to 2mg/kg:** No effect on pre and post implantation loss, on placental or fetal weights, on incidence of malformations Proteasome inhibition >60% at all dose levels in whole blood
Carfilzomib: Preliminary intravenous embryofetal toxicity study in rabbits (non GLP) TR-0123-171 Study 07-4334 No GLP	Presumed pregnant female rabbit 8/group	IV once daily 0.2; 0.4;0.8 from GD 6 to 19	NOAEL (maternal and embryo-foetal) =0.4	**Dams:** **At 0.8 mg/kg/day**: 1 animal dead ↓ BW and BW gain, and food consumption At necropsy of the decedent:: red fluid in the thoracic and pericardial cavities, edematous pericardium, enlarged lymph node, edematous thymus **At 0.4 mg/kg**: Slight ↓ BW gain and food consumption **Fetuses:** **At 0.8 mg/kg/day**: Surviving rabbits: Post-implantation loss (60%), fetal toxicity, ↓ fetal BW

Toxicokinetic data

The results of the comparison of maximum plasma drug concentrations and systemic exposures between animals and humans are presented in Table 7.

Table 4. Comparison of maximum plasma drug concentrations and systemic exposures between animals and humans

Species	Dose	Parameter	Carfilzomib	M14	M15	M16
Rat	2 mg/kg[b] (12 mg/m^2)	C_{max} (ng/mL)	519(466)	432 (479)	196 (132)	282 (273)
		AUC_{last} (ng·min/mL)	10215 (9281)	18218 (16960)	3903 (2283)	4003 (3426)
Monkey	0.5 mg/kg[c] (6 mg/m^2)	C_{max} (ng/mL)	43.1 (47.5)	113 (98.9)	35.1 (26.0)	276 (207)
		AUC_{last} (ng·min/mL)	804 (886)	4943 (3957)	1216 (778)	4020 (2882)
Human	20(27)[d] mg/m^2	C_{max} (ng/mL)	3060 ± 1791 (4564 ± 1784)	ND	ND	ND
		AUC_{last} (ng·min/mL)	18722 ± 10971 (23322 ± 5942)	ND	ND	ND
	15(20)[e] mg/m^2	C_{max} (ng/mL)	2546 ± 1406 (4247 ± 1598)	92.2 ± 18.9 (136 ± 30)	14.8 ± 3.5 (19.7 ± 6.3)	151 ± 36 (209 ± 78)
		AUC_{last} (ng·min/mL)	13181 ± 7000 (21342 ± 3992)	16500 ± 5844 (33690 ± 5329)	1510 ± 435 (2327 ± 936)	4011 ± 1136 (6136 ± 2804)

AUC_{last} = area under the curve from the dosing time to the last measurable concentration;
Cmax = maximum plasma concentration; ND = not determined; ng = nanogram; TK = toxicokinetic(s).

a. Average values from the last day of TK blood sample collection from chronic toxicity studies.
b. Severely toxic dose to 10% of animals (STD10). Males (Females).
c. Highest non-severely toxic dose (HNSTD). Males (Females).
d. Source: TR-0475-171. Values (arithmetic mean ± standard deviation) from PX-171-007 on Cycle 1 Day 1(20 mg/m^2) and Cycle 1 Day 16 (27 mg/m^2).
e. Source: TR-0479-171. Values (arithmetic mean ± standard deviation) from PX-171-005 on Cycle 1 Day 1(15 mg/m^2) and Cycle 2 Day 15 (20 mg/m^2).

Local Tolerance

Dedicated studies of local tolerance have not been submitted (see discussion on non-clinical aspects).

Other toxicity studies

The impurity profiles of carfilzomib batches used in toxicology studies are provided in quality section.

A standard genotoxicity battery to support qualification of carfilzomib impurities per ICH guidelines Q3A and Q3B was performed. Further studies in the chromosome aberration test in human lymphocytes and the mouse micronucleus were carried out using carfilzomib spiked or not with impurities: There were no unexpected findings and no mutagenic risk at the levels tested related to the impurity profile of carfilzomib. It should be noted thatone impurity is both a potential drug substance impurity and drug product degradant, is also a major metabolite of carfilzomib in rats, monkeys, and humans.

A structure-based in silico programwas performed to assess the structure-activity relationship (SAR) for carfilzomib and the identified degradation products Only one degradation product observed in carfilzomib drug product has a structural alert for genotoxicity and this impurity is both a drug substance impurity and a drug product degradation product. The impurity showed a mutagenic structural alert for alkylating agent resulting from the alkyl chloride group. This impurity has been evaluated in experimental *in vitro* and *in vivo*

genotoxicity studies and the results showed no evidence of mutagenic activity. This impurity is controlled by the drug product specifications.

One study (TR-0424-171) was conducted in mice in order to assess the toxicity of carfilzomib and bortezomib in mice receiving a sublethal challenge with lipopolysaccharide (LPS) and to profile the plasma levels of cytokines in mice receiving carfilzomib, LPS, or the combination. Carfilzomib at 3 and 5 mg/kg pre or post LPS challenge resulted in 100% mortality. Same dosing without challenge did not result in mortality. Combination of carfilzomib at 3 or 5 mg/kg or bortezomib and LPS resulted in 3 – 10 fold increases in serum urea, creatinine, liver transaminase and creatine kinase levels, similar findings to carfilzomib at 10 mg/kg with. Carfilzomib administration at 5 and/or 10 mg/kg resulted in a mild elevation (10-100 fold less than LPS alone) of the cytokines granulocyte-macrophage colony stimulation factor (GM-CSF), interleukin-1α (IL-1α) and the chemokines KC (keratinocyte-derived chemokine 1, a mouse ortholog of CXCL1/IL-8), and interferon-inducible protein 10 (IP-10). No significant increase in the cytokines tumour necrosis factor α (TNF-α), IL-1β, interferon-γ (IFN-γ), or IL-6 were induced by carfilzomib. Carfilzomib administered 1 hr prior to LPS resulted in a significant increase of the release of RANTES, MCP-1, IL-6, IL-1β, IFN-γ, and IL-17 measured 6 or 12 hr after endotoxin challenge.

2.3.5. Ecotoxicity/environmental risk assessment

The Applicant has submitted an ERA based on the guideline on "Environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00).

The logKow for carfilzomib has been determined analytically by titration to be to 3.77, which is below the threshold of 4.5. Therefore a PBT assessment was not deemed necessary.

The PEC surfacewater has been calculated using a refined Fpen value which was based on carfilzomib's orphan designation. The value obtained was 0.000825 µg/L, which is below the action threshold of 0.01 µg/L and, therefore, a phase II assessment was not required.

Table 5. Summary of main study results

Substance (INN/Invented Name): Carfilzomib (Kyprolis)			
CAS-number (if available): 868540-17-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Titration	3.77	Potential PBT (**N**)
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.000825	µg/L	> 0.01 threshold (**N**)

Carfilzomib PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

2.3.6. Discussion on non-clinical aspects

In the *in vitro* studies, carfilzomib showed to be a potent, selective and irreversible inhibitor of the chymotrypsin-like (CT-L) activity of purified human 20S proteasome and was 50- to 300-fold selective over the other proteasome catalytic activities caspase-like (C-L) and trypsin-like (T-L). *In vivo*, carfilzomib showed more potent cytotoxic activity against both haematological and solid tumour cell lines than C-L inhibitor bortezomib, with haematological tumour cell lines being most sensitive to such treatments. Continuous exposure to carfilzomib was associated with more potent cytotoxic and pro-apoptotic activity as compared to brief exposure in different tumour cells. In addition, carfilzomib was cytotoxic to bortezomib-resistant cells.

The PD of carfilzomib was determined *in vivo* in rats and monkeys by measurement of CT-L proteasome activity in tissue extracts, showing a dose-dependent proteasome inhibition 1 hour after administration in all tissues examined except the brain. Recovery of proteasome activity in tissues had a t½ of approximately 24 hours, while in whole-blood samples (enucleated erythrocytes), recovery was slower, likely due to the inability of mature erythrocytes to synthesize new proteasomes and the relatively slow rates of red blood cell turnover. This slow turnover of RBCs together with the irreversible inhibitory activity of carfilzomib is also likely the reason of cumulative proteasome inhibition. The kinetics of recovery from proteasome inhibition after multiple doses was similar to that after a single dose. Administration of carfilzomib as a 30-minute infusion resulted in similar levels of proteasome inhibition as an IV bolus administration, suggesting that the PD response is a function of the total dose and not maximum concentration, as expected for an irreversible inhibitor.

With regards to safety pharmacology, carfilzomib inhibited the hERG current at all tested concentrations from 0.7µM, with an estimated IC50 of 2.1 µM. An *in vivo*, cardiovascular toxicity was detected with premature ventricular contractions, decreased blood pressure, increased ST segments and T wave amplitude, decreases in PR, QRS and QT intervals, increased heart rate and serum troponin T levels and macroscopic lesions in the heart . However, no QTc prolongations were observed *in vivo*. In addition, there were lack of ECG findings in Cynomolgus monkey and rat however the animal exposure was lower than human exposure. Taken together, despite hERG inhibition, the non-clinical data suggest no specific pro-arrhythmic potential for carfilzomib. A combined safety pharmacology study has been conducted with carfilzomib in telemetered monkey after IV administration. No effect was observed on CNS or respiratory parameters at dose up to 3 mg/kg. However, carfilzomib induced cardiovascular toxicity after IV administration at 3 mg/kg (36 mg/m^2) in monkey. At 1 and 2 mg/kg, carfilzomib seems to be better tolerated. In view of the effect of myocardium observed during repeat-dose toxicity studies, the cardiovascular findings in monkey were likely due to myocardial toxicity (see discussion on clinical safety).

In vitro, carfilzomib inhibits OATP1B1 with an IC50=2,01 µM whereas it is unknown whether carfilzomib may or not inhibit other transporters OATP1B3,OAT1, OAT3, OCT2 and BSEP, at systemic level. Nonetheless, considering the fast elimination of carfilzomib, notably 5 minutes after starting infusion, the risk of clinically relevant interactions with substrates of these transporters is probably low (SmPC section 4.5).

Carfilzomib is a P glycoprotein (P gp) but not a BCRP substrate. However, given that Kyprolis is administrated intravenously and is extensively metabolised, the pharmacokinetic profile of carfilzomib is unlikely to be affected by P gp or BCRP inhibitors or inducers. In vitro, at concentrations (3 µM) lower than those expected at therapeutic doses, carfilzomib inhibits the efflux transport of digoxin, a P gp substrate, by 25%. Caution

should be observed when carfilzomib is combined with substrates of P gp (e.g. digoxin, colchicine) (SmPC section 4.5).

The ability of carfilzomib to induce CYP1A2 and 3A4 was evaluated in cultured human hepatocytes, showing no induction of the enzymatic activity. No or minimal induction in CYP activity was noted in liver samples taken from rats and monkeys after repeated dose administration for 6 and 9 months, respectively.

In addition, despite that some metabolites (M14, M15, M16) have high exposures in human plasma, no information regarding its possible CYP inhibition or induction has been submitted by the Applicant. According to the Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1) the potential inhibitory and induction effects of metabolites on CYP should be considered. M14, M15 and M16 are Phase I metabolites with an AUC both larger than one fourth of the AUC of the parent drug and larger than 10% of the drug related exposure; therefore *in vitro* testing of their activity on CYP is warranted. These studies are ongoing and the applicant was recommended to submit the final results.

The PK properties of carfilzomib were evaluated in mice, rats and monkeys. Following a single IV bolus administration the plasma concentration of carfilzomib rapidly declined in a biphasic manner, with T½ generally lower than 20 minutes. The systemic plasma clearance was similar or higher than the reported hepatic blood flow for each species, indicating that extrahepatic elimination was the predominant clearance pathway. These studies suggested that the PD effect of carfilzomib depends on the total dose administered and not the Cmax.

Carfilzomib showed high plasma protein binding *in vitro*, and has rapid and wide tissue distribution upon IV administration in vivo. Minimal to no penetration of the blood brain barrier was detected. Carfilzomib was rapidly metabolized *in vitro* when incubated in liver microsomes, indicating it is a substrate of CYP450 enzymes. However, additional *in vitro* and *in vivo* studies showed that the major pathways for metabolic elimination of carfilzomib were peptide cleavage and epoxide hydrolysis, with three major metabolites common to animals and humans. Following a single IV administration of 3H-carfilzomib to rats, radioactivity was eliminated slowly such that excretion was not complete by 168 hours post dosing.

In vitro studies indicated that carfilzomib did not induce human CYP3A4 in cultured fresh human hepatocytes. A clinical trial using oral midazolam as a CYP3A probe demonstrated that the pharmacokinetics of midazolam were unaffected by concomitant carfilzomib administration, indicating that carfilzomib is not expected to inhibit the metabolism of CYP3A4/5 substrates and is not a CYP3A4 inducer in human subjects. However, it is unknown whether carfilzomib is an inducer of CYP1A2, 2C8, 2C9, 2C19 and 2B6 at therapeutic concentrations. Caution should be observed when carfilzomib is combined with medicinal products that are substrates of these enzymes, such as oral contraceptives. Effective measures to avoid pregnancy should be taken, an alternative method of effective contraception should be used if the patient is using oral contraceptives (SmPC section 4.5).

Monkeys administered a single bolus intravenous dose of carfilzomib at 3 mg/kg (which corresponds to 36 mg/m2 and is similar to the recommended dose in humans of 27 mg/m^2 based on BSA) experienced hypotension, increased heart rate, and increased serum levels of troponin T. The repeated bolus intravenous administration of carfilzomib at $\geq$ 2 mg/kg/dose in rats and 2 mg/kg/dose in monkeys using dosing schedules similar to those used clinically resulted in mortalities that were due to toxicities occurring in the cardiovascular (cardiac failure, cardiac fibrosis, pericardial fluid accumulation, cardiac haemorrhage/degeneration), gastrointestinal (necrosis/haemorrhage), renal (glomerulonephropathy, tubular necrosis, dysfunction), and pulmonary (haemorrhage/inflammation) systems. The dose of 2 mg/kg/dose in rats is approximately half the recommended dose in humans of 27 mg/m2 based on BSA. The highest non-

severely toxic dose of 0.5 mg/kg in monkeys resulted in interstitial inflammation in the kidney along with slight glomerulopathy and slight heart inflammation. Those findings were reported at 6 mg/m2 which are below the recommended dose in humans of 27 mg/m^2 (SmPC section 5.3).

Carfilzomib was clastogenic in the *in vitro* chromosomal aberration test in peripheral blood lymphocytes. Carfilzomib was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) test and was not clastogenic in the *in vivo* mouse bone marrow micronucleus assay (SmPC section 5.3).

Fertility studies with carfilzomib have not been conducted. No effects on reproductive tissues were noted during 28-day repeat-dose rat and monkey toxicity studies or in 6-month rat and 9-month monkey chronic toxicity studies. Carfilzomib caused embryo-foetal toxicity in pregnant rabbits at doses that were lower than in patients receiving the recommended dose. Carfilzomib administered to pregnant rats during the period of organogenesis was not teratogenic at doses up to 2 mg/kg/day , although carfilzomib exposure in animals was below the exposure achieved in humans (SmPC section 4.6).

Kyprolis is not recommended during pregnancy and in women and men of childbearing reproductive potential not using effective contraception. Female patients of child bearing potential (and/or their partners) must use effective contraception measures during and for one month following treatment. It cannot be excluded that the efficacy of oral contraceptives may be reduced during carfilzomib treatment (s. In addition, due to an increased risk of venous thromboembolic events associated with carfilzomib, females should avoid the use of hormonal contraceptives that are associated with a risk of thrombosis during treatment with carfilzomib. If a patient is currently using oral contraceptives or a hormonal method of contraception that is associated with a risk of thrombosis, the patient should switch to an alternative method of effective contraception (SmPC section 4.6).

Based on its mechanism of action and findings in animals, Kyprolis can cause foetal harm when administered to a pregnant woman. Kyprolis should not be used during pregnancy unless the clinical condition of the woman requires treatment with Kyprolis. If Kyprolis is used during pregnancy, or if the patient becomes pregnant while taking this drug medicinal product, the patient should be apprised of the potential hazard to the foetus (SmPC section 4.6).

It is unknown whether carfilzomib or its metabolites are excreted in human milk. Based on its pharmacological properties, a risk to the suckling child cannot be excluded. Consequently, as a precautionary measure, breast feeding is contra indicated during and for at least 2 days after treatment with Kyprolis (SmPC section 4.6).

The local tolerance of carfilzomib has been evaluated within the repeat-dose toxicity studies. Macro and microscopic analysis of the injection site were performed during repeat-dose toxicity studies in rat and monkey. Minimal to moderate inflammation, oedema and haemorrhage were reported are observed at the injection site in some monkeys. Those findings suggest that IV injected carfilzomib was slightly irritant.

With regards of the Environmental Risk Assessment of the product the LogKOW value has been provided but no data has been included in the dossier on how this calculation was performed. The study on which logKOW was calculated was forwarded but the detailed methods for the calculation is lacking. The applicant was recommended to perform an adequate OECD 107 report which allows assessing the Log Kow according to current guidance.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical documentation submitted was considered adequate and acceptable. The relevant information has been included in the SmPC (sections 4.4, 4.5, 4.6, 5.1 and 5.3).

2.4. Clinical aspects

2.4.1. Introduction

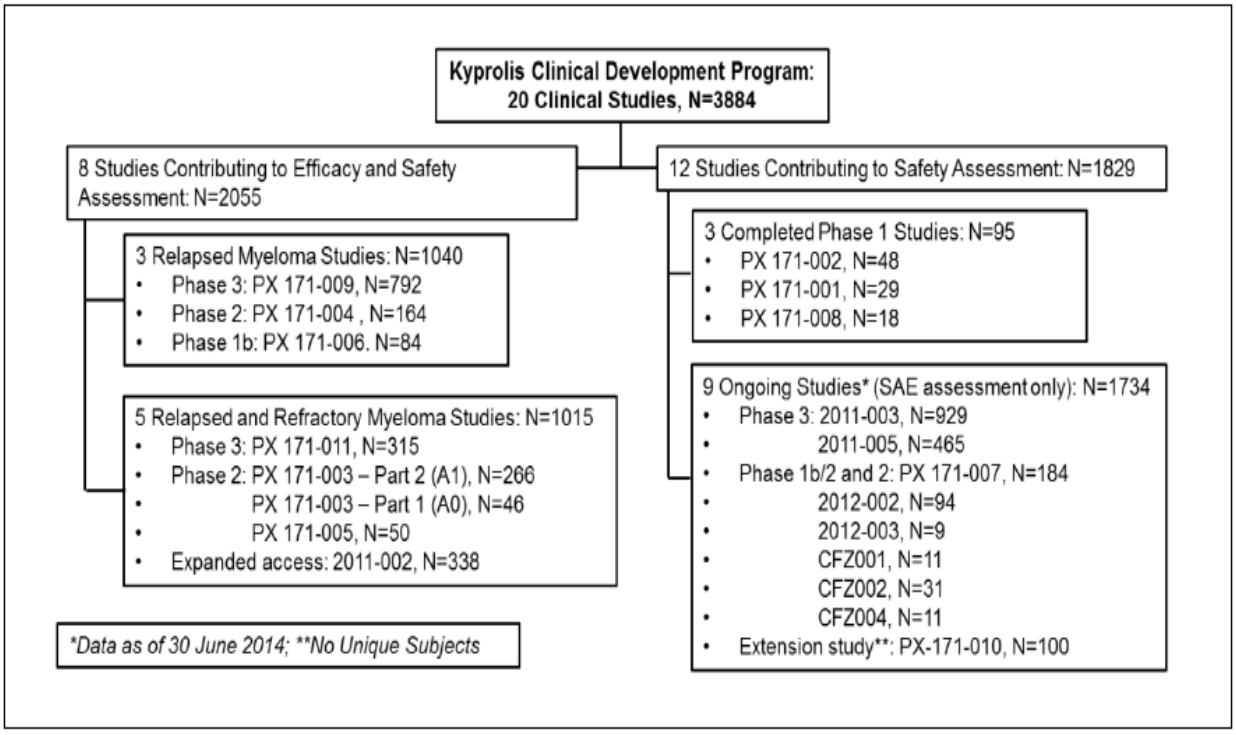
GCP

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



2.4.2. Pharmacokinetics

Pharmacokinetics (PK) of IV administration of carfilzomib has been studied in 483 subjects, across multiple Phase 1b/2 and Phase 3 trials. Carfilzomib PK has been characterized from a dose range of 15 to 70 mg/m^2.

An overview and summary of PK parameters is provided in Table 9, Table 10, and Table 11.

Table 6. PK parameters of Carfilzomib at Day 1 Cycle 1 in Studies PX-171-001 and PX-171-002

PK Parameters Cycle 1	PX-171-001	PX-171-002	
	20 mg/m^2 (n = 4)	20 mg/m^2 (n = 8)	27 mg/m^2 (n = 5)
$AUC_{0\text{-last}}$[a] (ng·min/mL)	5494 ± 4471	4911 ± 3495	3409 ± 3964
$AUC_{0\text{-last}}$[ab] (ng·h/mL)	91.6 ± 74.5	81.9 ± 58.3	56.8 ± 66.1
$AUC_{0\text{-inf}}$ (ng·min/mL)	5500 ± 4472	4942 ± 3497	3417 ± 3962
C_{max} (ng/mL)	683 ± 599	528 ± 406	406 ± 517
T_{max} (minutes)	6 ± 1	7 ± 2	6 ± 2
$t_{½}$ (minutes)	23 ±10	39.4 ± 28.8	26.8 ± 4.7
CL (L/h)	792 ± 642	660 ± 354	4476 ± 6540
V_{ss} (L)[b]	96.6 ± 95.6	108.4 ± 71.2	1538.9 ± 2861.8

AUC = area under concentration–time curve; $AUC_{0\text{-last}}$ = AUC to last measureable time point; $AUC_{0\text{-inf}}$ = AUC extrapolated to infinity; CL = plasma clearance; C_{max} = maximum observed concentration; PK = pharmacokinetics; StD = standard deviation; T_{max} = time of maximum observed concentration; $t_{½}$ = elimination half-life; V_{ss} = volume of distribution at steady state.
Note: Data shown as arithmetic mean ± StD.
[a] Last sampling time point after carfilzomib administration was 4 hours.
[b] Values expressed as a different unit are derived from original report for cross-study comparison

Table 7. PK parameters after single dosing of Carlfizomib in Studies PX-171-005 and PX-171-007

PK Parameters Cycle 1	PX-171-005 15 mg/m^2 (n = 8)	PX-171-007 (2–10 min IV infusion) Solid Tumor 20 mg/m^2 (n = 30)	PX-171-007 (30 min IV infusion) Multiple Myeloma 20 mg/m^2 (n = 30)
$AUC_{0\text{-last}}$ (h·ng/mL)	187 (75.3)	251 (92.0)	269 (54.3)
$AUC_{0\text{-inf}}$ (h·ng/mL)	233 (51.6)[a]	223 (104)[b]	273 (55.3)[c]
C_{max} (ng/mL)	2077 (91.4)	2390 (104)	722 (62.1)
T_{max} (h)	0.0417 (0.0333, 0.117)	0.0500 (0, 0.167)	0.250 (0.0833–0.750)
$t_{½}$ (h)	0.398 (0.375, 0.626)[a]	0.444 (0.152, 2.20)[b]	0.888 (0.411–1.57)[c]
CL (L/h)	151 ± 79.3[a]	263 ± 398[b]	164 (89.6)[c]
V_{area} (L)	104 ± 81.9[a]	223 ± 328[b]	-
V_{SS} (L)	—	27.7 ± 48.6[b]	21.8 (24.6)[d]

AUC = area under concentration–time curve; $AUC_{0\text{-last}}$ = AUC to last measureable time point; $AUC_{0\text{-inf}}$ = AUC extrapolated to infinity; CL = plasma clearance; C_{max} = maximum observed concentration; CV = coefficient of variation; h = hour(s); StD = standard deviation; $t_{½}$ = elimination half-life; T_{max} = time of maximum observed concentration; V_{area} = apparent volume of distribution; V_{ss} = volume of distribution at steady state.
Notes: $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, CL and V_{ss} (PX-171-007, 30 min IV infusion) geometric mean (geometric CV%) presented; T_{max} and $t_{½}$ median (minimum, maximum) presented; arithmetic mean ± StD presented for all other parameters, unless otherwise stated.
[a] n=6
[b] n=23
[c] n=28
[d] n=27

Table 8. Comparison of PK parameters of Carfilzomib for subjects with multiple myeloma (PX-171-005 and PX-171-007)

Plasma PK Parameters	15 mg/m^2 2–10 min infusion (n = 8)	20 mg/m^2 2–10 min infusion (n = 6)	27 mg/m^2 30 min infusion (n = 1)	36 mg/m^2 30 min infusion (n = 3)	45 mg/m^2 30 min infusion (n = 4)	56 mg/m^2 30 min infusion (n = 12)
$AUC_{0\text{-last}}$ (h·ng/mL)	187 (75.3)	350 (20.7)	488 (NA)	702 (72.4)	740 (24.8)	948 (34.0)
$AUC_{0\text{-inf}}$ (h·ng/mL)	233 (51.6)[a]	340 (21.3)[b]	489 (NA)	483 (0.5)[c]	740 (24.8)	917 (24.4)[d]
C_{max} (ng/mL)	2077 (91.4)	4026 (36.2)	1290 (NA)	1792 (73.4)	1758 (25.8)	2079 (43.9)
$t_{½}$ (h)	0.398	0.579	0.973 (NA)	1.22	1.02	0.815
	(0.375, 0.626)[a]	(0.284, 2.50)[b]		(1.07–1.36)[c]	(0.967–1.09)	(0.666–1.92)[d]

AUC = area under concentration–time curve; $AUC_{0\text{-inf}}$ = AUC extrapolated to infinity; $AUC_{0\text{-last}}$ = AUC to last measureable time point; C_{max} = maximum observed concentration; CV = coefficient of variation; PK = pharmacokinetic(s); $t_{½}$ = elimination half-life.

Notes: $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}: geometric mean (geometric CV%) presented; $t_{½}$ median (minimum, maximum) presented.

a. n = 6
b. n = 5
c. n = 1
d. n = 10

Absorption

The Cmax and AUC following a 2- to 10-minute intravenous infusion of 27 mg/m^2 was 4232 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 mg/m^2, there was a dose-dependent increase in exposure (SmPC section 5.2).

Distribution

The mean steady-state volume of distribution of a 20 mg/m2 dose of carfilzomib was 28 L. When tested in vitro, the binding of carfilzomib to human plasma proteins averaged 97% over the concentration range of 0.4 to 4 micromolar (SmPC section 5.2).

Elimination

Carfilzomib was rapidly and extensively metabolised. The predominant metabolites measured in human plasma and urine, and generated in vitro by human hepatocytes, were peptide fragments and the diol of carfilzomib, suggesting that peptidase cleavage and epoxide hydrolysis were the principal pathways of metabolism. Cytochrome P450 mediated mechanisms played a minor role in overall carfilzomib metabolism. The metabolites have no known biologic activity (SmPC section 5.2).

Following intravenous administration of doses ≥ 15 mg/m^2, carfilzomib was rapidly cleared from the systemic circulation with a half-life of ≤ 1 hour on day 1 of cycle 1. The systemic clearance ranged from 151 to 263 L/hour, and exceeded hepatic blood flow, suggesting that carfilzomib was largely cleared extrahepatically. Carfilzomib is eliminated primarily via metabolism with subsequent excretion of its metabolites in urine (SmPC section 5.2).

Dose proportionality - Time dependency

Dose-proportionality of Carfilzomib during Study PX-171-007 was evaluated using a Power Model. A linear relationship was evaluated between the natural log-transformed (ln-transformed) PK parameters $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} and the ln-transformed dose on Days 1 and 16 of Cycles 1, 3, and 5. Results are shown in Table 12.

Table 9. Dose Proportionality Assessment of Carfilzomib in solid tomur (2-10 minutes IV perfusion) – Days 1 and 16 Combined (Study PX-171-007)

PK Parameter	Intercept	Slope	95% CI	p-value for Slope = 1
C_{max} (ng/mL)	3.494	1.204	(0.74, 1.67)	0.3877
AUC_{last} (hr·ng/mL)	0.933	1.277	(0.86, 1.69)	0.188
AUC_{inf} (hr·ng/mL)	0.132	1.475	(0.97, 1.98)	0.0628

Dose levels:
20 mg/m^2 (20 mg/m^2 for all doses).
27 mg/m^2 (20 mg/m^2 on Day 1 and Day 2, then 27 mg/m^2 on Days 8, 9, 15, and 16).
36 mg/m^2 (20 mg/m^2 on Day 1 and Day 2, then 36 mg/m^2 on Days 8, 9, 15, and 16).

In the final population PK analysis, the interindividual variability (IIV) for each parameter, expressed as percent coefficient of variation (%CV), was 60% for CL, 119% for V1, and 49% for V2.

Special populations

Two population PK analyses were conducted: an interim analysis (Studies PX-171-003 – Part1 (A0)/ PX-171-003 – Part 2 (A1), PX-171-004, PX-171-005, PX-171-006 and PX-171-007) and a final analysis to incorporate PK data from subjects in Phase 3 PX-171-009 study. Exposure metrics derived from the final model are consistent with the non-compartmental analysis of carfilzomib PK.

Among the covariates tested in the population PK analyses [interim analysis: age, weight, height, body mass index, sex, race , CrCl, dexamethasone use (dose level per day as continuous variables or categorical y/n variables), lenalidomide dose (continuous variable), degree of renal impairment (mild/moderate/severe), treatment cycle and disease type (solid tumor yes/no); final analysis: CrCl, body weight, BSA, age, race, sex, and disease type (multiple myeloma *versus* solid tumor)], only CrCL was identified as statistically significant covariate in the interim analysis and BSA in the final analysis.

Renal Impairment

In case of CrCl, an effect of CrCl on central compartment carfilzomib CL was observed: in subjects with severe renal impairment (CrCl < 30 mL/min), CL was reduced by approximately 20% with a large degree of overlap from the typical value for subjects with full renal function.

In relation with BSA, it corresponds to a 13% decrease in CL in a subject with the lowest BSA of 1.37 m^2 and a 19% increase in a subject with the highest BSA of 2.82 m^2 relative to those with the median BSA value of 1.9 m^2. Additionally, carfilzomib dose was calculated using the subject's actual body surface area at baseline and subjects with a body surface area greater than 2.2 m^2 received a dose based upon a body surface area of 2.2 m^2.

A special population study (PX-171-005) was conducted in 50 multiple myeloma subjects with various degrees of renal impairment (normal, mild, moderate, severe and chronic dialysis), receiving an initial dose of 15 mg/m^2, which could be escalated to 20 mg/m^2 starting in Cycle 2 if 15 mg/m^2 was well tolerated in Cycle 1. No apparent differences in carfilzomib CL, AUC, and Cmax between subjects with normal and those with varying levels of renal functional impairment following single- or repeat-dose administration has been detected (results shown in Table 13).

Table 10. Summary of PK Parameters of Carfilzomib in Plasma after 20 mg/m^2 IV Injection (Day 15 of Cycle 2)

Plasma PK Parameters	Normal Renal Function (N=6)	Mild Impairment (N=7)	Moderate Impairment (N=3)	Severe Impairment (N=2)	Chronic Dialysis (N=4)
AUC_{last} (hr·ng/mL)	350 (20.7)	237 (48.5)	283 (67.8)	456 (93.8)	337 (28.2)
AUC_{inf} (hr·ng/mL)[a]	340 (21.3)	246 (52.4)	NC	474 (87.1)	374 (44.4)
AUC_{extr} (%)[a]	0.351 ± 0.574	0.338 ± 0.359	NC	3.68 ± 4.13	0.165 ± 0.0399
C_{max} (ng/mL)	4026 (36.2)	2679 (67.0)	2401 (114)	3499 (134)	3384 (29.8)
t_{max} (hr)	0.0333 (0.0167, 0.167)	0.0500 (0.00, 0.117)	0.0500 (0.0500, 0.117)	0.0833 (0.0833, 0.0833)	0.0333 (0.0333, 0.0500)
$t_{1/2}$ (hr)[a]	0.579 (0.284, 2.50)	0.568 (0.486, 3.02)	NC	6.57 (3.97, 9.16)	0.732 (0.570 ,0.893)
CL (L/hr)[a]	123 ± 28.4	160 ± 99.1	NC	81.7 ± 47.1	100 ± 25.0
V_{area} (L)[a]	164 ± 140	247 ± 204	NC	898 ± 878	102 ± 6.66
λ_z (1/hr)[a]	1.20 ± 0.790	0.955 ± 0.527	NC	0.125 ± 0.0698	0.996 ± 0.311
MRT_{inf} (hr)[a]	0.102 ± 0.130	0.0902 ± 0.0682	NC	2.22 ± 2.86	0.0712 ± 0.00719

AUC_{last}, AUC_{inf} and C_{max}: geometric mean (geometric CV%) presented; t_{max} and $t_{1/2}$ median (minimum, maximum) presented; arithmetic mean ± SD presented for all parameters unless otherwise stated.
NC = value cannot be calculated
[a] N=5 (Normal); N=6 (Mild); N=0 (Moderate); N=2 (Chronic Dialysis)

In addition, a second renal impairment study (CFZ001) was conducted meanly to characterize the pharmacokinetics (PK) and safety of carfilzomib 56 mg/m^2 using a 30-minute infusion in patients with ESRD. In this study lenalidomide has not been administered together carfilzomib. The results are presented in Table 14.

Table 11. Summary of Plasma Carfilzomib PK Parameters Following IV dministration of 27 mg/m^2 Carfilzomib on Day 16 of Cycle 1, and of 6 mg/m^2 Carfilzomib on Day 1 of Cycle 2 in Multiple Myeloma Subjects 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)
$AUC_{0\text{-last}}$ (hr·ng/mL)	344 (24.8)	444 (37.2)	563 (41.9)	712 (162)
$AUC_{0\text{-}\infty}$ (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)
$t_{1/2}$ (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_{∞} (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)

Notes: geometric mean (geometric CV%) is presented for all parameters, unless otherwise stated; tmax median (minimum–maximum) is presented.
[a] n = 11; [b] n = 5.

Hepatic Impairment

A hepatic impairment study (Study CFZ002) is currently ongoing to examine the PK of carfilzomib at higher doses (up to 56 mg/m^2) in subjects with hepatic impairment. The preliminary results are presented in Table 15.

Table 12. Summary of Plasma Carfilzomib PK Parameters Following IV Administration of Carfilzomib in Subjects with Advanced Malignancies Categorized by Dose and Hepatic Function

PK Parameters	27 mg/m^2			56 mg/m^2		
	Normal N = 10	Mild N = 14	Moderate N = 5	Normal N = 8	Mild N = 8	Moderate N = 1
AUC_{last} (ng·hr/mL)	378 (40.8)	546 (39.2)	446 (42.1)	760 (99.9)	1107 (73.7)	733
$AUC_{0\text{-}\infty}$ (ng·hr/mL)	348 (35.4)[a]	529 (40.3)[b]	457 (48.9)[d]	604 (98.3)[e]	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)[d]	0.508 (54.7)[e]	0.621 (47.7)	0.489
CL (L/hr)	157 (32.5)[a]	86.8 (48.6)[c]	117 (50.8)	136 (105.4)	92.0 (77.2)	123
$MRT_{0\text{-}\infty}$ (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)[c]	19.6 (45.6)	24.8 (188.0)	14.8 (51.9)	12.9

Pharmacokinetic interaction studies

In study PX-171-008, the PK of midazolam, a sensitive CYP3A was evaluated after single and repeat dosing of carfilzomib at 27 mg/m^2. Results are shown in Table 16.

Table 13. Summary of PK Parameters for Midazolam (Study PX-171-008)

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.

Pharmacokinetics using human biomaterials

2.4.3. Pharmacodynamics

Mechanism of action

No clinical studies addressing the mechanism of action were submitted.

Primary and Secondary pharmacology

Intravenous carfilzomib administration resulted in suppression of proteasome chymotrypsin-like (CT-L) activity when measured in blood 1 hour after the first dose. Doses of ≥ 15 mg/m^2 consistently induced an (≥ 80%) inhibition of the CT-L activity of the proteasome. In addition, carfilzomib administration resulted in inhibition of the latent membrane protein 2 (LMP2) and multicatalytic endopeptidase complex-like 1 (MECL1) subunits of the immunoproteasome ranging from 26% to 32% and 41% to 49%, respectively, at 20 mg/m^2.

Little to no inhibition of the other subunits of the constitutive proteasome (Beta1 and Beta2) was seen following an initial dose of carfilzomib. This suggested that the majority of the activity was intact in tissues that predominantly express this form of the proteasome (eg, liver, kidney, and heart). However, data from Cycle 2 showed a trend to fast increase the inhibition of the Beta1 and Beta2 subunits of the constitutive proteasome with subsequent cycles (Table 17). No data are available about further subsequent cycles.

Table 14. Proteasome Inhibition at Carfilzomib 15, 20, 27, 35 and 45 mg/m^2

			Relative (%) Inhibition ± SEM (No. Samples Analyzed)							
			Whole Blood				PBMC			
Dose: mg/m^2	**Study**	**Day**	**CT-L**	**Beta5**	**Beta2**	**Beta1**	**CT-L**	**LMP7**	**LMP2**	**MECL1**
15	**PX-171-001**	**Cycle 1** Day 1	75.2 ± 2.5 (n = 6)	ND			74.5 ± 10.9 (n = 6)	ND		
15	**PX-171-002**		81.3 ± 1.3 (n = 3)	ND			73.4 ± 5.7 (n = 3)	ND		
15 Study Renal Impairment	**PX-171-005**		80.7 ± 1.3 (n = 23)	66.3 ± 2.3 (n = 13)	1.2 ± 3.0 (n = 13)	-20.9 ± 10.3 (n = 13)	83.6 ± 1.9 (n = 23)	77.7 ± 4.9 (n = 10)	29.0 ± 10.1 (n = 10)	46.9 ± 5.9 (n = 10)
15 NormalRenal Impairment			80.2 ± 1.6 (n = 6)	66.0 ± 2.0 (n = 6)	1.5 ± 4.5 (n = 6)	-8.3 ± 5.6 (n = 6)	82.1 ± 3.2 (n = 6)	80.5 ± 3.9 (n = 6)	26.8 ± 8.6 (n = 6)	46.1 ± 8.6 (n = 6)
15 + L10 mg D40 mg	**PX-171-006**		81.3 ± 2.7 (n = 5)	69.2 ± 4.0 (n = 5)	7.9 ± 5.9 (n = 5)	-2.7 ± 5.6 (n = 5)	88.5 ± 5.0 (n = 4)	84.7 ± 1.9 (n = 4)	42.4 ± 19.2 (n = 4)	42.3 ± 6.2 (n = 4)
15 + L15 mg D40 mg			82.1 ± 0.2 (n = 3)	74.3 ± 6.8 (n = 3)	10.9 ± 4.7 (n = 3)	5.7 ± 5.5 (n = 3)	82.7 ± 9.0 (n = 2)	82.1 ± 4.8 (n = 2)	40.5 ± 8.7 (n = 2)	52.2 ± 9.8 (n = 2)
15 NormalRenal Impairment	**PX-171-005**	**Cycle 2** Day 1	92.5 ± 3.1 (n = 6)	93.3 ± 0.3 (n = 6)	50.8 ± 0.6 (n = 6)	25 ± 4.3 (n = 6)	92.2 ± 3.0 (n = 6)	80.5 ± 4.3 (n = 5)	0.4 ± 24.2 (n = 5)	52.0 ± 10.6 (n = 5)
15 + L10 mg D40 mg	**PX-171-006**		94.9 ± 1.0 (n = 4)	92.1 ± 1.1 (n = 4)	46± 4.8 (n = 4)	19.5 ± 1.2 (n = 4)	94.1 ± 2.2 (n = 3)	77.7 ± 12.9 (n = 3)	30.4 ± 25.1 (n = 3)	34.3 ± 30.4 (n = 3)
15 + L15 mg D40 mg			92.6 ± 5.2 (n = 2)	96.0 ± 0.7 (n = 2)	58.2± 2.5 (n = 2)	39.8 ± 4.2 (n = 2)	86.1 ± 1.6 (n = 2)	74.2 ± 8.2 (n = 2)	27.8 ± 10.0 (n = 2)	47.8± 11.3 (n = 2)
20	**PX-171-001**	**Cycle 1** Day 1	77.7 ± 0.8 (n = 5)	ND			82.4 ± 2.2 (n = 5)	ND		
20	**PX-171-002**		82.6 ± 1.6 (n = 8)	ND			80.1 ± 3.9 (n = 8)	ND		
20/27 + L25 mg D40 mg	**PX-171-006**		88.0 ± 1.3 (n = 8)	ND	ND	ND	83.1 ± 3.4 (n = 8)	ND	ND	ND
20	**PX-171-007**		84.1 ± 1.3 (n = 21)	74.4 ± 1.4 (n = 20)	17.4 ± 2.4 (n = 21)	4.8 ± 3.4 (n = 21)	82.1 ± 1.5 (n = 19)	83.2 ± 1.6 (n = 19)	29.2 ± 3.9 (n = 19)	45.4 ± 4.4 (n = 19)
20 ST Phase 1b			79.2 ± 1.1 (n = 9)	70.2 ± 1.5 (n = 9)	13.9 ± 1.9 (n = 9)	-0.1 ± 5.7 (n = 9)	82.7 ± 1.3 (n = 9)	82.7 (n = 9)	25.8 (n = 9)	41.0 (n = 9)
20 ST Phase 2			87.9 ± 1.2 (n = 12)	77.9 ± 1.5 (n = 11)	20.1 ± 3.9 (n = 12)	9.6 ± 4.2 (n = 12)	81.5 ± 1.3 (n = 10)	83.6 ± (n = 10)	32.0 ± (n = 10)	49.4 ± (n = 10)
20 MM - 30 min infusion			69.1 ± 8.6 (n = 6)	72.9 ± 4.0 (n = 4)	-2.9 ± 2.2 (n = 4)	-14.4 ± 5.2 (n = 4)	85.0 ± 3.4 (n = 5)	86.3 ± 1.8 (n = 3)	30.2 ± 9.4 (n = 3)	50.3 ± 6.1 (n = 3)
20/20 ST Phase 1b	**PX-171-007**	**Cycle 2** Day 1	90.4 (n = 3)	94.7 (n = 3)	65.6 (n = 3)	50.6 (n = 3)	84.0 ± 0.8 (n = 3)	89.4 ± 3.8 (n = 3)	23.0 ± 27.4 (n = 3)	46.0 ± 4.2 (n = 3)
27	**PX-171-002**	**Cycle 1** Day 1	82.8 ± 1.1 (n = 6)	ND			82.9 ± 2.1 (n = 5)	ND		
27 + L25 mg D40 mg	**PX-171-006**	**Cycle 2** Day 1	83.5 ± 16.0 (n = 2)	ND	ND	ND	76.8 ± 12.6 (n = 7)	ND	ND	ND
20/27 ST Phase 1b	**PX-171-007**		90.7 (n = 3)	96.3 (n = 3)	75.5 (n = 3)	54.4 (n = 3)	87.6 ± 2.3 (n = 3)	87.1 ± 1.3 (n = 3)	37.5 ± 7.0 (n = 3)	62.5 ± 2.6 (n = 3)

36 ST - 30 min infusion	**PX-171-007**	**Cycle 1** Day 1	73.5 ± 5.9 (n = 6)	81.0 ± 2.4 (n = 6)	7.2 ± 2.8 (n = 6)	-9.7 ± 5.2 (n = 5)	86.9 ± 3.7 (n = 5)	89.9 ± 1.2 (n = 3)	33.6 ± 8.1 (n = 5)	54.3 ± 5.5 (n = 5)
20/36 ST Phase 1b	**PX-171-007**	**Cycle 2** Day 1	91.0 (n = 3)	96.7 (n = 3)	84.8 (n = 3)	68.3 (n = 3)	94.1 ± 0.6 (n = 3)	92.0 ± 3.6 (n = 3)	57.6 ± 2.3 (n = 3)	76.8 ± 2.4 (n = 3)
20/36 ST Phase 2			95.3 (n = 5)	93.7 (n = 11)	65.9 (n = 12)	49.9 (n = 12)	86.6 ± 2.7 (n = 10)	87.7 ± 1.3 (n = 10)	39.1 ± 6.7 (n = 10)	57.1 ± 4.3 (n = 10)
45 ST - 30 min infusion	**PX-171-007**	**Cycle 1** Day 1	89.3 ± 1.0 (n = 3)	83.9 ± 3.4 (n = 3)	20.8 ± 3.5 (n = 3)	-11.0 ± 0 (n = 1)	94.1 ± 1.2 (n = 3)	53.8 ± 2.6 (n = 3)	77.5 ± 6.6 (n = 3)	54.3 ± 5.5 (n = 5)

Source: For PX-171-001: Appendix 3 in TR-0118-171; for PX-171-002: Appendix C in TR-0427-171; for PX-171-005: Table 3 (subjects with normal renal function) in TR-0476-171; for PX-171-007: Tables 3 and 4A in TR-0478-171. For PX-171-006: TR-0477-171 Report.
CT-L = chymotrypsin-like; LMP = latent membrane protein; MECL1 = multicatalytic endopeptidase complex-like 1; NA = not applicable; ND = no data; PBMC = peripheral blood mononuclear cells; SEM = standard error of the mean L= lenalidomide D=dexamethasone.

Because carfilzomib is an irreversible inhibitor of the proteasome, there is no recovery of proteasome activity in enucleated erythrocytes. In contrast, PBMCs are capable of proteasome turnover, and thus recovering from carfilzomib-induced proteasome inhibition (Meiners 2003). However, minimal recovery in PBMC was noted on Cycle 1 Day 2, demonstrating that proteasome inhibition was prolonged (≥ 48 hours) following consecutive-day dosing. The full recovery was still not achieved after a 5-day nondosing period (Day 8, predose). Complete or near-complete recovery of proteasome activity was observed in PBMCs between cycles, and no change in proteasome content was noted in these cells.

The levels (> 80%) and durations (≥ 48 hours) of proteasome inhibition achieved with carfilzomib at 20 and 27 mg/m^2 in subjects were greater than that reported with bortezomib (Papandreou 2004; Orlowski 2002). In these studies, maximal inhibition of CT-L activity, measured using an enzymatic assay similar to the one performed in the studies described here, was ~65% with complete or near-complete recovery in 72 hours.

QT Effects

In the linear mixed model, the effect of carfilzomib on cardiac repolarization using the QTcF interval and the concentration-QTc relationships seems to show no clear signal of any dose-related effect. The upper CI for predicted effect on QTcF and QTcB at Cmax based on the concentration-QTc model was 4.8 msec and 5.9 msec, respectively. However, the results of the ECG Central Tendency with the correction of Fredericia or Bazett in the individual studies and in the combination report showed that the upper bound of the two- side 90% CI (equal to one-side 95%) around the mean effect on QTc were over 10 msec at several time points (PX-171-005, PX-171-007). Results are reported in Table 18.

Table 15. Integrated Analysis of PX-171-005 and PX-171-007: Change From Baseline *Versus* the Plasma Concentration: Estimates From Linear Mixed Model[a] – QTc Fridericia and QTc Bazett (Electrocardiographic Population)

QT Parameter	Slope of Plasma Conc. Effect on Δ QTc	Standard Error of Slope of Plasma Conc. Effect on Δ QTc	p-value	Overall Model Fit	Carfilzomib	
					Predicted Δ QTc at Average Cmax 380.45 ng/mL	One-sided Upper 95% Confidence Bound of Predicted Δ QTc[b]
QTcF	-0.000385	0.001576	0.8070	< 0.0001	3.3232	4.7565
QTcB	-0.004384	0.001787	0.0146	< 0.0001	4.2558	5.9096

C_{max} = maximum concentration; QTc = corrected QT interval; QTcB = QTc interval using Bazett correction; QTcF = QTc interval using Fridericia's correction.
[a] Linear Mixed Model: plasma concentration as a fixed effect with subject included in the model as a random effect.
[b] Upper Bound = upper one-sided 95% linear mixed model-based confidence limit.

Exposure-response Analysis

Two exposure-response analysis for carfilzomib were conducted: exploratory exposure-response analysis (PX-171-003 – Part 2 (A1), PX-171-004, PX-171-005, PX-171-006, and PX-171-007) and updated exposure–response analysis, adding Phase 3 PX-171-009 study (ASPIRE).

In the exploratory Exposure-response analysis, a relationship between carfilzomib Cycle 1, Day 1 AUC and response category was identified, with higher AUC exposures seen in subjects with responses (minimal response [MR], partial response [PR], very good partial response [VGPR], and complete response [CR]) compared to those without response (stable disease [SD] or progressive disease [PD] or unknown). No relationship between safety endpoints and carfilzomib exposure metrics was evident at that time.

In the updated Exposure-response analysis from the PX-171-009 study using the 20/27 mg/m^2 dose regimen did not identify any apparent relationship between exposure and efficacy endpoints, including PFS (primary efficacy endpoint) and ORR/CBR. In a pooled analysis across 15- to 20/56-mg/m^2 dose levels statistically significant relationships between carfilzomib AUC.C1avg and response rates were identified by logistic regression. The multiple logistic regression analysis also identified several statistically significant covariate effects for ORR and CBR, including subjects refractory to bortezomib, baseline platelet count ≥ 150 (10^9/L), combination therapy with lenalidomide and dexamethasone, and race. The odds ratios relating to the other covariates generally describe larger effects than the one relating to PK exposure. In the pooled analysis for safety endpoints, no statistically significant relationships between either AUC or Cmax and increased AE incidence were found.

2.4.4. Discussion on clinical pharmacology

Carfilzomib and its metabolites parmacokinetics has been overall characterized from a dose range of 15 to 70 mg/m^2 with several PK studies with different population, regimens and doses of carfilzomib and two population PK analyses. PK parameters from the sparse PK sample studies (PX-171-003, PX-171-004, PX-171-006 and PX-171-009) seem to be in line with PK parameters from the intensive PK studies (PX-171-005 and PX-171

Population pharmacokinetic analyses indicate there are no effects of age or gender on the pharmacokinetics of carfilzomib.

Renal function status had no effect on the clearance or exposure of carfilzomib following single or repeat-dose administration at doses up to 20 mg/m^2 (SmPC section 5.2). No data of dose of 27 mg/m^2 have been provided in the study of subjects with renal impairment. Preliminary results of a second renal impairment study (CFZ001) have been submitted however, several limitations should be further discussed and justified in the final clinical report of study CFZ001. The final results of this study will be provided (see Risk Management Plan).

Administration of lenalidomide and dexamethasone has been included as covariates in the interim population PK analysis. Additionally, combination dosing with lenalidomide and dexamethasone did not seem to affect proteasome inhibition in PD estudies. However, data with concomitant use of lenalidomide and dexamethasone are limited. Lenalidomide is poorly metabolized and a majority of lenalidomide is eliminated through urinary excretion. Carfilzomib will be maineanly eliminated in urine as metabolite M14 or incorporated into normal biosynthetic pathways due to its peptidic nature and its irreversible bindings to its target. Interaction at renal level cannot be fully ruled out. Additionally, renal AEs have been observed with both drugs. In studies where lenalidomide were administered together carfilzomib (PX-171-006 and pivotal

PX-171-009) population were restricted to patients with a CrCl ≥ 50 ml/min, due to the recommendation of reduction for the starting dose of lenalidomide for patients with baseline renal impairment.

Appropriate dose reduction for the starting dose of lenalidomide in patients with baseline renal impairment should be considered according to the recommendations in the lenalidomide Summary of product characteristics. No starting dose adjustment for Kyprolis is required in patients with baseline mild, moderate, or severe renal impairment or patients on chronic dialysis. Since dialysis clearance of Kyprolis concentrations has not been studied, the medicinal product should be administered after the dialysis procedure. In phase 3 clinical studies the incidence of adverse events of acute renal failure was higher in subjects with lower baseline creatinine clearance than that among subjects with higher baseline creatinine clearance (SmPC section 4.2).

No dedicated pharmacokinetic studies have been completed in patients with hepatic impairment (SmPC section 5.2). A hepatic impairment study (Study CFZ002) is currently ongoing to examine the PK of carfilzomib at higher doses (up to 56 mg/m^2) in subjects with hepatic impairment. In light of preliminary results, no modification of the dose recommendation in subjects with hepatic impairment has been proposed. However, the final results of this study will be provided (see Risk Management Plan).

Regarding dexamethasone, carfilzomib is not expected to inhibit CYP3A4/5 or other CYP substrates and it is not an inducer of CYP3A4. Thus, carfilzomib as perpetrator is not expected to influence the exposure of dexamethasone. As victim, dexamethasone (as a weak to moderate inducer of CYP3A4) is not expected to affect carfilzomib exposure, since CYP-mediated pathways do not appear to play a significant role in the overall metabolism of carfilzomib.

The inhibition of Beta1 and Beta2 observed in cycle 2 of patient whole blood samples (which is primarily composed of red blood cells) does not reflect the inhibition levels in organ tissues that have the ability to synthesize new proteasome and recovery activity. The volume of whole blood required to assay Beta1 and Beta2 activity in tissues such as liver, kidney, and heart made this analysis impractical.

The potential for carfilzomib to induce CYP450 isoforms (1A2 and 3A4) in cultured fresh human hepatocytes was evaluated in study TR-0086-171.Carfilzomib was not an inducer of CYP1A2 or 3A4 at the concentrations tested (0.1, 0.5, 2.5 µM). Instead, carfilzomib caused a reduction in both CYP1A2 and 3A4 catalytic activity for all 3 donors in a concentration-dependent fashion. A concentration-dependent decrease in CYP3A4 mRNA expression was also observed when the hepatocytes were treated with carfilzomib, suggesting that the reduction of CYP3A4 activity may be partially attributable to CYP3A4 mRNA down-regulation. Treatment with carfilzomib at the concentrations tested did not cause cytotoxicity.

An evaluation of possible effects of carfilzomib on cardiac function was performed by analyzing, via central blind reading, triplicate ECG in 154 subjects with advanced malignancies, including multiple myeloma. The effect of carfilzomib on cardiac repolarization using the QT interval with Fridericia's correction (QTcF interval) and the analysis of concentration QTc relationships show no clear signal of any dose-related effect. The upper bound of one-sided 95% confidence interval (CI) for predicted effect on QTcF at Cmax was 4.8 msec. With Bazett's correction (QTcB interval), the upper bound of one-sided 95% confidence interval (CI) for predicted effect on QTcB at Cmax was 5.9 msec (SmPC section 5.1).

There have been cases of QT interval prolongation reported in clinical studies. An effect of Kyprolis on QT interval cannot be excluded (SmPC section 4.8).

The difference in the exposure-response results between the PX-171-009 study analysis and the pooled analysis could be due to the high clinical response (98/102 subjects included in analysis achieved at least a

PR) in PX-171-009, a relatively narrow range of plasma exposures achieved within PX-171-009 as a result of a single dose level evaluated (ie, 20/27 mg/m2), and the potential confounding effect in the pooled analysis of differences in subject characteristics and regimens across studies that tested different doses of carfilzomib.

Due to the high variability in exposure parameter, PBMC percent CT-L activity data may be a more sensitive predictor of efficacy and safety outcomes across these studies that carfilzomib exposure metrics alone. Additionally, the sparse sampling strategies utilized across some of the studies may have limited the precision of estimated carfilzomib exposure metrics. In any case, the potential confounding effect in these pooled analyses of differences in subject characteristics and regimens across studies that tested different doses of carfilzomib cannot be avoided; thus, these exposure response analyses are only considered as exploratory and supportive analyses.

2.4.5. Conclusions on clinical pharmacology

Carfilzomib and its metabolites pharmacokinetics have been reasonably well investigated in a dose range of 15 to 70 mg/m^2 with several PK studies with different population, regimens and doses of carfilzomib and population PK analyses. The studies submitted as part of the clinical pharmacology were considered acceptable to investigate the PK and PD aspects of carfilzomib.

2.5. Clinical efficacy

2.5.1. Dose response studies

PX-171-001 was an open-label, dose-escalation safety trial with the primary objective of charactering dose limiting toxicities (DLTs) and identifying the maximum tolerated dose (MTD) of calfilzomib given as an IV bolus over 2 min at doses from 1.2 to 20 mg/m^2 for 5 times per week in a 14-day cycle in subjects with previously treated hematologic malignancies including myeloma. All 29 treated subjects experienced 1 or more AEs. The most common AEs regardless of grade or causality were nausea, fatigue (each in 48.3% of subjects), and diarrhea (34.5%). Although no subject discontinued study due primarily to an AE, AEs contributed to treatment interruption or discontinuation in 4 cases. AEs indicative of neuropathy were not common, showed no dose relationship, and were all grade 1 or 2 in severity. Ten SAEs were reported among 6 subjects. Three of the 10 SAEs were considered possibly related to carfilzomib (febrile neutropenia, chills, and neutropenia). No subject died during treatment. At the 20 mg/m^2 dose level, 2 subjects experienced DLT: grade 4 thrombocytopenia and grade 3 febrile neutropenia and chills—all considered possibly related to carfilzomib. Consequently, 15 mg/m^2 was considered to be the MTD of carfilzomib when administered daily for 5 consecutive days.

The stepped-up dosing was then tested in PX-171-002, an open-label phase 1 study of escalating dose levels of carfilzomib administrated from 1.2 to 20mg/m^2 twice weekly (D1, 2, 8, 9, 15 and 16) for 3 weeks, followed by 1 week of rest in 28-day cycle. Up to 86 subjects with various haematologic malignancies were planned. The study was divided into a sequential dose escalation phase (Part 1), followed by a dose expansion period (Part 2) consisting of: A) a carfilzomib-only cohort and B) a carfilzomib-plus dexamethasone cohort.

During the escalation phase across carfilzomib dose levels, objective responses were observed at the higher carfilzomib doses: between 15 and 27 mg/m^2 in 5 of 27 evaluable subjects (4 PRs and 1 MR) and were seen

only in subjects with MM. Considering subjects with a PR, the response rate was 14.8% (95% CI: 4.2, 33.7). Including the MR, the overall objective response rate was 18.5%. Responses generally occurred early in treatment, with all 4 PRs documented during Cycle 1. Median PFS for the 27 evaluable subjects was 176.0 days (95% CI: 54.0, 239.0).Through the carfilzomib dose of 27 mg/m^2, the MTD was not reached in this trial. Hence, the minimally effective dose on this schedule appeared to be carfilzomib 15 mg/m^2 given in a regimen of once daily, twice per week, during 3 weeks in a 4-week cycle.

During the expansion period, 7 patients entered the dose expansion phase of Study PX-171-002 and treated with a starting dose of 20/27 mg/m^2; 4 were treated with a starting dose of 20/27 mg/m^2 with dexamethasone. No additional efficacy was observed with addition of low-dose dexamethasone (40 mg/week; 120 mg/28-day cycle), either upon examination of the patients who received carfilzomib + dexamethasone beginning with the first dose in Cycle 1 Day 1 or of the 1 patient with stable disease in whom dexamethasone was added on Cycle 3 Day 1. One patient out of 4 receiving carfilzomib + dexamethasone experienced a drug related SAE (hypoxia) as well as 3 AEs that were considered to be dose limiting toxicities (DLTs); these consisted of grade 3 elevations in alkaline phosphatase and liver transaminases (ALT and AST). No patient receiving single-agent carfilzomib experienced an adverse event (AE) considered to be a DLT.

On the basis of this trial, a dose of 20 mg/m^2 followed by a dose of 27 mg/m^2 ("the step up program") was recommended for future studies in patients with advanced hematologic malignancies to reduce adverse events associated with carfilzomib infusion.

The study PX-171-006 was the basis for the selected dosed of CRd in subjects with relapsed multiple myeloma. In this phase 1b dose-escalation study, both carfilzomib (15, 20 or 20/27mg/m^2) and lenalidomide (10, 15, 20 or 25mg/day) were escalated in sequential cohorts in combination with low-dose dexamethasone (40mg/week). Subjects received carfilzomib (15-27 mg/m^2) IV over 10 minutes on Days 1, 2, 8, 9, 15 and 16 of a 28-day cycle (Day 8 and 9 doses could have been omitted at the investigator's discretion for C13 and higher), along with lenalidomide (10-25 mg) and dexamethasone until progression or unacceptable toxicity. The primary endpoint was to evaluate safety and the MTD of carfilzomib with lenalidomide and dexamethasone. All subjects (100.0%) had at least 1 AE, the majority of which were Grade 1 and 2 in severity. At least one Grade 3 or higher AE was experienced in 95.2% subjects and 53.6% had at least 1 SAE. A total of 14 subjects (16.7%), including 10 subjects (19.2%) in the MPD group, discontinued treatment due to an AE, and 4 subjects (all in the MPD group) had at least 1 carfilzomib dose reduction due to an AE. Seventy-eight (92.9%) subjects experienced at least 1 treatment-related AE. A total of 3 subjects (3.6%) died on study; deaths were due to progressive disease (n = 2) and natural causes/underlying disease (n = 1). The MTDs of carfilzomib and lenalidomide were not reached in this study

2.5.2. Main study

Methods

PX-171-009 (ASPIRE Study)

This was a randomized, multicenter, phase 3 study comparing carfilzomib, lenalidomide, and dexamethasone vs. lenalidomide and dexamethasone in subjects with relapsed multiple myeloma.

Study Participants

Inclusion criteria

The study included adult subjects with symptomatic and measurable multiple myeloma, as defined by 1 or more of the following (assessed within 21 days prior to randomization): serum M-protein ≥ 0.5 g/dL; urine Bence-Jones protein ≥ 200 mg/24 hours; for subjects with immunoglobulin A (IgA) myeloma whose disease could be reliably measured only by serum quantitative immunoglobulin (qIgA), qIgA was ≥ 750 mg/dL (0.75 g/dL). Patients were required to have at least 1 prior treatment but no more than 3 protocol-defined multiple myeloma regimens, with documented relapsed or progressive disease on or after any regimen (subjects refractory to the most recent line of therapy were eligible), achieved a response to at least 1 prior regimen (defined as ≥ 25% decrease in M-protein or total protein in countries in which electrophoresis was not routinely available). The other main criteria included Eastern Cooperative Oncology Group (ECOG) performance status 0- 2 with life expectancy ≥ 3 months and the following laboratory values within 21 days prior to randomization: ALT ≤ 3.5 times the upper limit of normal (ULN) and serum direct bilirubin ≤ 2 mg/dL or 34 μmol/L; absolute neutrophil count (ANC) ≥ 1.0 × 10^9/L; haemoglobin ≥ 8 g/dL (80 g/L) (subjects may have been receiving red blood cell [RBC] transfusions in accordance with institutional guidelines); platelet count ≥ 50 × 10^9/L (≥ 30 × 10^9/L if myeloma involvement in the bone marrow was > 50%); creatinine clearance (CrCl) ≥ 50 mL/minute (either measured or calculated using a standard formula such as the Cockcroft and Gault formula).

Exclusion criteria

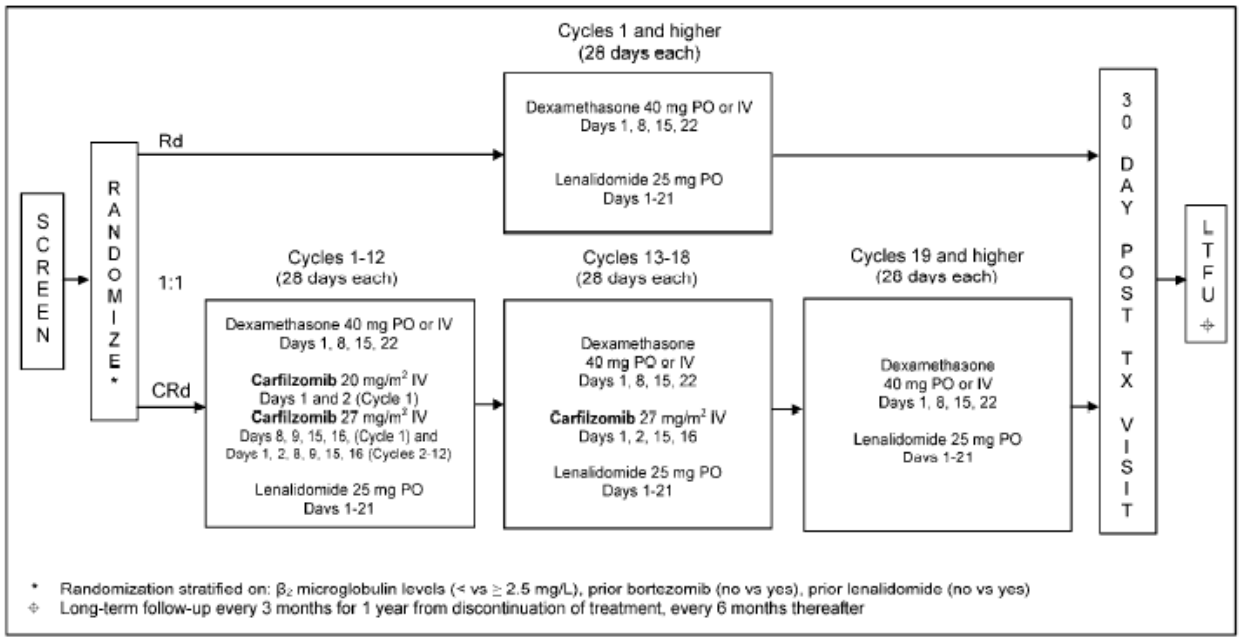
Subjects were excluded in case of progression during treatment (if previously treated with bortezomib alone or in combination); progression during the first 3 months of initiating treatment or at any time during treatment if the lenalidomide/dexamethasone combination was the subject's most recent line of therapy (if previously treated with a Rd combination); discontinuation of previous lenalidomide or dexamethasone due to intolerance; prior carfilzomib treatment; POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes); Waldenström Macroglobulinemia or immunoglobulin M (IgM) myeloma; Plasma cell leukaemia (> 2.0 × 10^9/L circulating plasma cells by standard differential); chemotherapy within 3 weeks prior to randomization or antibody therapy within 6 weeks prior to randomization; radiotherapy to multiple sites or immunotherapy/antibody therapy within 28 days prior to randomization; localized radiotherapy to a single site within 7 days prior to randomization; corticosteroid therapy at a dose equivalent to dexamethasone > 4 mg/day within 21 days prior to randomization; pregnant or lactating females; major surgery within 21 days prior to randomization; acute active infection requiring treatment systemic antibiotics, antivirals, or antifungals) within 14 days prior to randomization; known human immunodeficiency virus, active hepatitis B or C infections; myocardial infarction within 4 months prior to randomization, New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities, unless subject had a pacemaker; uncontrolled hypertension or uncontrolled diabetes within 14 days prior to randomization; other malignancy, including myelodysplastic syndrome (MDS), within the past 3 years (with the exception of adequately treated basal cell carcinoma, squamous cell skin cancer, thyroid cancer, carcinoma in situ of the cervix or breast, prostate cancer of Gleason Score 6 or less with stable prostate-specific antigen levels, cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder or benign tumors of the adrenal or pancreas); significant neuropathy (Grades 3- 4, or Grade 2 with pain) within 14 days prior to randomization; known history of allergy to Captisol (a cyclodextrin derivative used to solubilize carfilzomib);

contraindication to any of the required concomitant drugs or supportive treatments; ongoing graft *versus* host disease; pleural effusion requiring thoracentesis or ascites requiring paracentesis within 14 days prior to randomization; any other clinically significant medical disease or condition which, in the investigator's opinion, may have interfered with protocol adherence or a subject's ability to give informed consent.

Treatments

An overview of dose, regimen and follow up for each treatment group is shown in Figure 1.

Figure 1. Study schema (Study PX-171-009)



ADFU = active disease follow-up; CRd = carfilzomib, Revlimid (lenalidomide), and dexamethasone; IV = intravenous(ly); LTFU = long term follow-up; PO = orally; Rd = Revlimid (lenalidomide)/dexamethasone; TX = treatment

Notes: Subjects who did not have disease progression upon discontinuation of all study treatments entered ADFU and were followed for disease status and survival until progression or death every 3 months for up to 1 year after treatment discontinuation and then entered long-term follow-up (LTFU) for survival every 6 months thereafter. Subjects with progression of myeloma upon discontinuation of all study treatments entered LTFU for survival and were followed every 3 months for 1 year and every 6 months thereafter.

Screening was performed within 21 days before randomization. After screening, eligibility determination, and randomization, study treatment was to commence within 5 days after randomization; delays beyond 5 days must have been confirmed with the medical monitor.

Subjects in both randomized study arms continued lenalidomide and dexamethasone until disease progression or unacceptable toxicity. For subjects in the CRd arm, carfilzomib was administered for up to a maximum of 18 cycles, after which subjects continued on lenalidomide and dexamethasone until disease progression or unacceptable toxicity.

Dose decrements for carfilzomib, lenalidomide, and dexamethasone are illustrated in Figure 2.

Figure 2. Dose Decrements for Carfilzomib, Lenalidomide, and Dexamethasone (Study PX-171-009)

Nominal Dose	Dose Decrements		
	Dose -1	Dose -2	Dose -3
20 mg/m^2 (CFZ)[a]	15 mg/m^2	11 mg/m^2	—
27 mg/m^2 (CFZ)[a]	20 mg/m^2	15 mg/m^2	11 mg/m^2
25 mg (LEN)[b]	15 mg	10 mg	5 mg
40 mg (DEX)[b]	20 mg	12 mg	—

— = not applicable; CFZ = carfilzomib; CRd = carfilzomib/Revlimid (lenalidomide)/dexamethasone arm; DEX = dexamethasone; LEN = lenalidomide; Rd = Revlimid (lenalidomide)/dexamethasone arm

[a] CRd arm only.

[b] Both study arms (CRd and Rd).

The following Concurrent Treatments, were not allowed: Chemotherapy (either approved or investigational) within 3 weeks prior to randomization or antibody therapy within 6 weeks prior to randomization; Radiotherapy to multiple sites or immunotherapy/antibody therapy within 28 days prior to randomization; localized radiotherapy to a single site within 7 days prior to randomization; Corticosteroid therapy at a dose equivalent to dexamethasone > 4 mg/day within 21 days prior to randomization.

Objectives

The primary objective of the pivotal study was to compare progression-free survival (PFS) in subjects with relapsed multiple myeloma receiving carfilzomib, lenalidomide, and dexamethasone (CRd) versus subjects receiving lenalidomide and dexamethasone (Rd).

The secondary objective was the comparison of the effect of CRd versus Rd on the following: overall survival (OS), overall response rate (ORR), disease control rate (DCR), duration of response (DOR), change over time in the Global Health Status/Quality of Life of the EORTC Quality of Life Core Module QLQ-C30 (QLQ-C30 GHS/QoL) and safety.

The Exploratory objective was to compare the two treatment arms in terms of Time to progression (TTP), Additional health-related quality of life (HRQL) subscales of EORTC QLQ-C30 and QLQ-MY20, Time to next treatment and Clinical benefit rate (CBR).

Outcomes/endpoints

The primary endpoint was PFS assessed by IRC, defined as the duration in months from the date of randomization to the date of confirmed progressive disease (PD) or death due to any cause, whichever was earlier, according to the International Myeloma Working Group - Uniform Response Criteria (IMWG-URC), reported in Table 19.

Table 16. Summary of International Myeloma Working Group Uniform Response Criteria (IMWG-URC)

Response Subcategory[1]	Multiple Myeloma Response Criteria
sCR[2]	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow and • Normal SFLC ratio and • Absence of clonal cells in bone marrow[3]
CR[2]	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow
VGPR[2,4]	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-component with urine M-component < 100 mg per 24 hours
PR[2,4]	• ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours • If present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Stable	Not meeting criteria for CR, VGPR, PR, or PD
PD[5]	Any one or more of the following: • Increase of ≥ 25% from lowest response value in: ○ serum M-component (absolute increase must be ≥ 0.5 g/dL) and/or ○ urine M-component (absolute increase must be ≥ 200 mg per 24 hours) and/or ○ Bone marrow plasma cell percentages (absolute % must be ≥ 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in size of existing bone lesions or soft tissue plasmacytomas.[6,7,8] Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) attributed solely to the plasma cell proliferative disorder

Source: Durie 2006

Secondary endpoints included overall survival (defined as duration in months from randomisation to death due to any cause), overall response rate (proportion of subjects who achieved a best response of sCR, CR, VGPR or PR according to IMWG-URC), duration of response (duration in months from the date of initial start of response [PR or better] to the earlier date of documented PD or death due to any cause [for ORR and DCR separately]) disease control rate (defined as the proportion of subjects who achieved a best response of sCR,CR, VGPR, PR, MR, or SD lasting ≥ 8 weeks [MR was determined using EBMT criteria]), duration of disease control (defined as the duration in months from randomization to the earlier date of start of PD or death due to any cause for subjects who achieved disease control), Change over time in EORTC QLQ-C30 Global Health Status/QoL scale and safety and tolerability as determined by assessments of treatment-emergent AEs, laboratory values, vital signs, and ECGs.

Exploratory endpoints included time to progression (defined as the duration in months from the date of randomization to the date of documented disease progression), clinical benefit rate (defined as the proportion of subjects who achieve a best response of sCR, CR, VGPR, or PR according to IMWG-URC, or MR, according to the EBMT criteria), time to next treatment (defined as the duration in months from the date of randomization to the date of initiating subsequent anti-myeloma therapy) and additional HRQL subscales of EORTC QLQ-C30 and QLQ-MY20.

Sample size

An estimated 526 PFS events were needed to provide 90% power to detect a hazard ratio of 0.75 (a 25% of risk reduction for the CRd regimen compared with the Rd regimen).

A median PFS of 11.2 months for the Rd arm was expected based on results from two Phase 3 studies of lenalidomide/dexamethasone in relapsed myeloma patients with a history of 1 to 3 prior therapies (Dimopoulos 2007; Weber 2007). The required number of PFS events was determined based on a 1-sided log-rank test with an overall type I error rate of 0.025 (which is equivalent to 0.05 for 2-sided tests) under the group sequential monitoring plan.

The original design had the planned sample size of 700 subjects to achieve the required PFS events in 36 months assuming 18 months of enrolment and additional 18 months of follow up. As a consequence of the 1st interim analysis the sample size was increased to approximately 780 subjects in order to decrease the time to reach the required number of events.

Randomisation

Patients were randomized to receive either CRd or Rd with a ratio of 1:1 and they were planned to start study treatment within 5 days of randomisation. Randomization was stratified based on:

1. β 2 microglobulin levels (< 2.5 mg/L vs. $\geq$ 2.5 mg/L)
2. Prior bortezomib versus no prior bortezomib
3. Prior lenalidomide versus no prior lenalidomide

Blinding (masking)

This was an open-label study.

Statistical methods

The response and progressive disease outcomes were determined by the local investigator and also by the IRC in a blinded manner periodically throughout the trial. The primary analysis of PFS was performed using the ITT population based on subjects' outcomes as determined by the IRC.

For subjects meeting one of situations as following, the primary analysis of PFS was right-censored according to the conventions described in Table 20.

Table 17. Date of Progression or Censoring for Progression-Free Survival

Situation	Date of Progression or Censoring	Outcome
No *post*-baseline disease assessment	Date of randomization	Censored
Non-protocol systemic anticancer treatment started before documentation of disease progression or death	Date of last disease assessment prior to start of non-protocol systemic anticancer treatment	Censored
Death or progression after more than one missed disease assessment (more specifically, more than 63 days after last disease assessment while the subject is on treatment or more than 140 days after last disease assessment if the subject has discontinued study treatment and is in active disease follow-up)[a]	Date of last disease assessment visit without documentation of disease progression that is before the first missed visit	Censored
Alive and without documentation of disease progression (including lost to follow-up without PD)	Date of last disease assessment	Censored
Death or disease progression between planned disease assessments	Date of death or first disease assessment showing disease progression, whichever occurs first	Progressed
Death before first disease assessment	Date of death	Progressed

[a] *63 days correspond to approximately 2 cycles plus a 7-day window and 140 days correspond to approximately one and a half visits during active disease follow-up period.

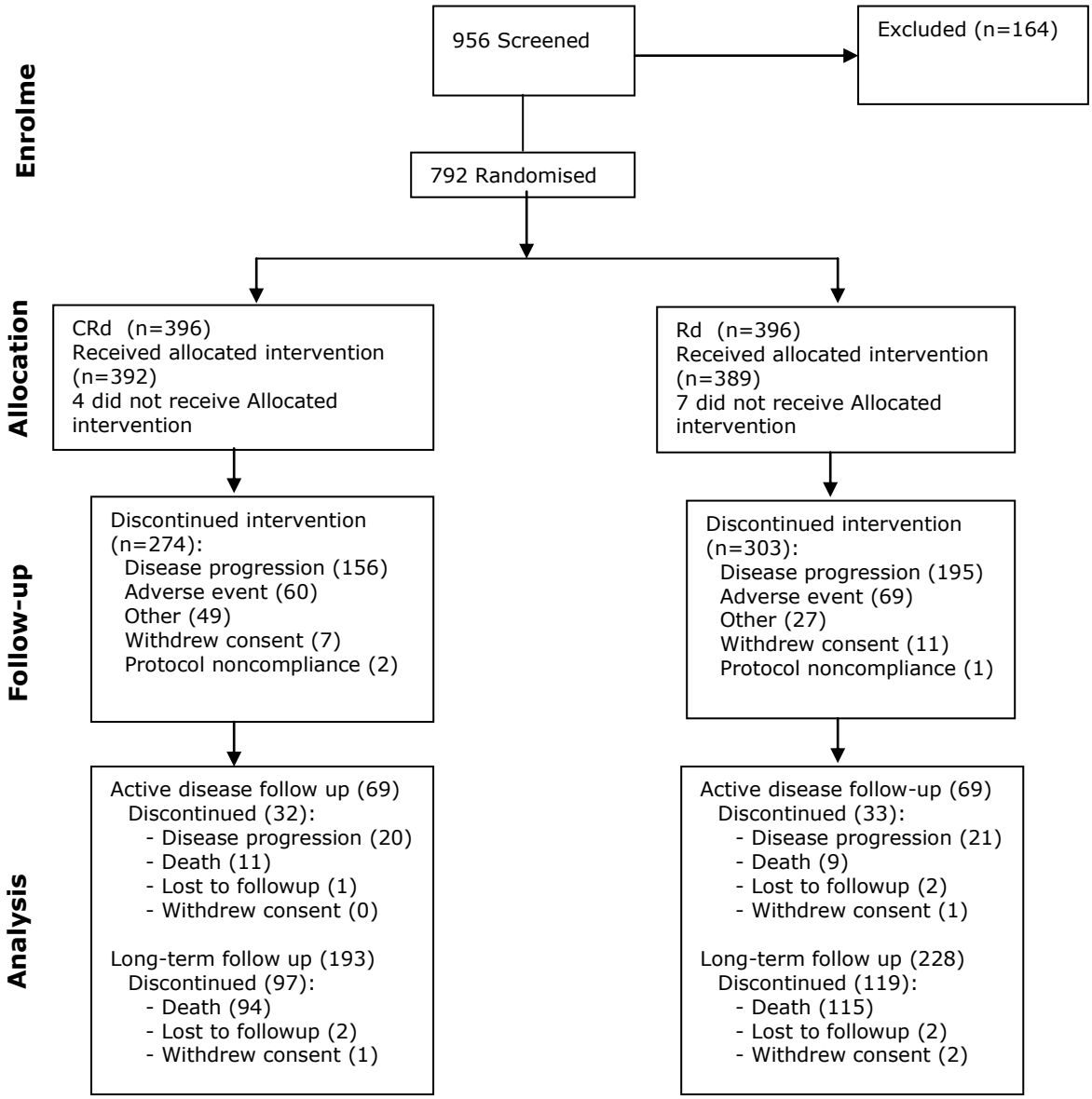
The PFS was assessed using following pre-specified sensitivity analyses:

- PFS assessed by local investigators
- PFS assessed by the Sponsor using a computer-based algorithm ORCA (Onyx Response Computational Assessment) in a central, independent and blinded manner.
- Un-stratified Analysis
- Analysis using interval censoring. The interval was constructed as follows: (1) if the PFS event is PD, then interval will be (date of last assessment before PD, date of the assessment indicating PD]; (2) if the PFS event is death, then interval will be [date of death, date of death]; and (3) if no PFS event is observed, then the interval will be (date of last assessment,].
- Initiation of non-protocol anti-cancer therapy treated as PFS Event. PFS was broadly defined as duration from randomization to documented disease progression, initiation of non-protocol anti-cancer therapy, or death, whichever occurs earlier.
- Initiation of non-protocol anti-cancer therapy treated as neither a PFS Event nor a Censoring Event. The data censoring rules are the same as those for the primary analysis of PFS except that the initiation of non-protocol anti-cancer therapy was excluded as a mechanism for censoring.
- Analysis based on Scheduled Assessment Dates instead of Actual Assessment Dates. The impact on the analysis of PFS due to potential systematic difference in disease assessments between treatment arms was assessed.
- Per-Protocol Analysis

Up to 3 analyses of PFS were planned: 2 interim analyses by the Independent Data Monitoring Committee (IDMC) and 1 final analysis. The first interim analysis was occurred in December 2011 only for administrative purposes for blinded re-evaluation of sample size and did not include a comparison between 2 arms. Based on the IDMC recommendation, the sample size was increase from 700 to 780 subjects in order to decrease the enrolment time. The total required number of PFS events 526 remained unchanged. The second interim analysis was planned when approximately 420 (80%) of 526 planned total events were observed, which provides 90% power to detect a target HR of 0.75. As of the 16 June 2014 data cut-off date, this pre-specified interim analysis was trigged on 431 IRC-assessed PFS events. The IDMC assessed the efficacy and safety results of this interim analysis and recommended stopping the study for efficacy, but to continue for safety and OS monitoring.

Results

Participant flow



Recruitment

The date of the first patient enrolled was 14 July 2010. During the period of 14 July 2010 and 16 June 2014 (data cut-off date), a total of 956 subjects with relapsed MM were screened. A total of 792 subjects were randomized from 129 sites in 20 countries located in Europe, North America and Israel.

Conduct of the study

An overview of the protocol amendments, all implemented prior to the data cut-off date, is reported in Table 21.

Table 18. Protocol Amendment History (Study PX-171-009)

Amendment Number	Version Date	Main Purpose(s) for the Protocol Amendment	Number of Subjects Enrolled[a]
Original	20 November 2009	Not applicable	0
1.0	05 February 2010	• Per FDA feedback, amended text to emphasize the importance of confirming progression by 2 measurements of serum or urine M-protein. Also permitted 10% additional enrollment to help achieve 526 progression events.	0
2.0	22 April 2010	• Updated lenalidomide REMS requirements: o Included requirement for RevAssist program (US participants) for access to lenalidomide. o Language was also added to describe the lenalidomide requirements for subjects in ex-US countries, including RevAid for access to lenalidomide in Canada and a Pregnancy Risk Minimization Plan for Celgene trials.	0
2.1	03 May 2010	Minor administrative amendment consisting of the following: • Adressed FDA request that OS be listed as the first secondary endpoint. • Reordered secondary endpoints. • Made changes to protocol synopsis, statistical methods, and efficacy analysis to clarify disease outcome grading by investigator to be consistent with text in body of the protocol.	235
3.0	04 March 2011	• The window provided for Inclusion Criterion 2 to demonstrate measurable disease by central laboratory analyses was increased from within 14 days prior to randomization to within 21 days prior to randomization to account for the challenge in logistics of trans-country sample shipment followed by analysis and review. • Additional changes included: o Refined the technique for measuring soft tissue plasmacytomas from a simple unidirectional to bidirectional measurements. o Defined the "measurability" of any given soft tissue plasmacytoma and amended progression criteria accordingly. o Clarified definition for females of childbearing potential (for all countries except Canada) and pregnancy test requirements. o Clarified that MR was defined per EBMT criteria. o Clarified inclusion criterion for measurement of serum IgA. o Clarified that, for PK assessment, lenalidomide should be taken a minimum of 2 hours (instead of 4 hours) after the carfilzomib dose.	557

Amendment Number	Version Date	Main Purpose(s) for the Protocol Amendment	Number of Subjects Enrolled[a]
4.0	19 December 2011	• Prespecified sample size adjustment from700 subjects to approximately 780 subjects following the first interim analysis review by an IDMC. • Additional changes included: o Clarified that, regardless of SPEP and UPEP results at screening, both tests were required to confirm VGPR and CR. o Clarified that MDS was considered a malignant disease within the context of the exclusion criteria. o Clarified definition of measureable disease for assessment of progression and response in subjects with IgA myeloma.	0

CR = complete response; EBMT = European Group for Blood and Marrow Transplantation; FDA = Food and Drug Administration; IDMC = independent data monitoring committee; IgA = immunoglobulin; MDS = myelodysplastic syndrome; MR = minimal response; PK = pharmacokinetic; REMS = risk evaluation and mitigation strategy; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; US = United States; VGPR = very good partial response

[a] Enrollment numbers reflect time to start of enrollment, which occurred under Protocol Amendments 2.1 and 3.0. Enrollment was complete by the time Protocol Amendment 4 was issued.

A total of 4 subjects (2 in each study arm) had an important protocol deviation resulting in exclusion from the PP Population as defined in the SAP. Three subjects did not meet key selection criteria (1 subject in each study arm had received > 3 prior treatments; and 1 subject in the CRd arm was intolerant to previous lenalidomide or dexamethasone treatment); and 1 subject in the Rd arm used concomitant anticancer therapy before discontinuing study treatment.

A total of 151 (19.1%) subjects had other important protocol deviations. These include an additional 1.5% (6 subjects) in each study arm with deviations related to inclusion or exclusion criteria.

Protocol deviations related to deviations in drug administration routine occurred in 117 subjects (14.8%), which were balanced between the 2 study arms. Corticosteroids for nonmalignant conditions (asthma, inflammatory bowel disease) equivalent to a dexamethasone dose of > 4.0 mg/day or prednisone > 20 mg/day were not permitted per protocol. A total of 37 subjects in the CRd arm and 34 subjects in the Rd arm received corticosteroids for nonmalignant conditions for short-term medical use to treat AEs (range of 1–10 days in the CRd arm and 1–27 days in the Rd arm). A total of 17 subjects in the CRd arm and 25 subjects in the Rd arm remained on study beyond 1 cycle (30 days) after confirmed investigator assessment of disease progression per IMWG. Reasons for keeping subjects on study treatment past progression included delay in receiving laboratory reports or clinical judgment by the investigator before a final assessment of progression could be made. There were 5 subjects (4 in the CRd arm and 1 in the Rd arm) who received higher than prescribed doses of dexamethasone (1 or 2 doses) or lenalidomide (1 dose). One of these 5 subjects reported Grade 2 vomiting with a single higher dose (80 mg *versus* the prescribed dose of 40 mg) of dexamethasone; no other subjects reported new or worsening AEs. Two subjects continued to receive carfilzomib after Cycle 18, Day 16 due to a site error. Once the issue was identified, these subjects continued to receive carflizomib during the follow-up phase as new antimyeloma therapy.

There were 22 subjects (2.8%) who were randomized to the wrong strata via the IVRS system and analyzed according to their assigned stratum. The issues were related to β2 microglobin levels (20 subjects), and prior lenalidomide (1 subject, CRd arm) and bortezomib (1 subject, Rd arm) where the sites selected the wrong value on the telephone keypad (< 2.5 mg/L or ≥ 2.5 mg/L for β2 microglobin; no or yes for prior lenalidomide or bortezomib exposure).

Baseline data

Demographic and baseline characteristics are shown in Table 22 and in Table 23, respectively.

Table 19. Demographic Characteristics – ITT Population (Study PX-171-009)

Demographic	CRd (n = 396)	Rd (n = 396)	Total (N = 792)
Age (years)			
Median (min, max)	64.0 (38.0, 87.0)	65.0 (31.0, 91.0)	64.0(31.0, 91.0)
Age Group (years)			
18–64	211 (53.3%)	188 (47.5%)	399 (50.4%)
65–74	142 (35.9%)	155 (39.1%)	297 (37.5%)
≥ 75	43 (10.9%)	53 (13.4%)	96 (12.1%)
Sex			
Male	215 (54.3%)	232 (58.6%)	447 (56.4%)
Female	181 (45.7%)	164 (41.4%)	345 (43.6%)
Ethnicity			
Hispanic or Latino	20 (5.1%)	14 (3.5%)	34 (4.3%)
Not Hispanic or Latino	376 (94.9%)	381 (96.2%)	757 (95.6%)
Not Reported	0 (0.0%)	1 (0.3%)	1 (0.1%)
Race			
White	377 (95.2%)	377 (95.2%)	754 (95.2%)
Black	12 (3.0%)	11 (2.8%)	23 (2.9%)
Asian/Native Hawaiian/Other Pacific Islander	1 (0.3%)	3 (0.8%)	4 (0.5%)
American Indian or Alaska Native	0 (0.0%)	1 (0.3%)	1 (0.1%)
Other	6 (1.5%)	4 (1.0%)	10 (1.3%)
Geographic Region			
Europe	302 (76.3%)	288 (72.7%)	590 (74.5%)
North America	84 (21.2%)	87 (22.0%)	171 (21.6%)
Rest of World[a]	10 (2.5%)	21 (5.3%)	31 (3.9%)

CRd = carfilzomib/Revlimid (lenalidomide)/dexamethasone arm; ITT = intent-to-treat;
Rd = Revlimid (lenalidomide)/dexamethasone arm

[a] Israel only

Table 20. Baseline characteristics– ITT Population (Study PX-171-009)

	CRd (n = 396)	Rd (n = 396)	Total (N = 792)
Height (cm)			
N	395	391	786
Median (Min, Max)	167.0 (139.0, 196.0)	168.0 (139.0, 195.0)	167.0 (139.0, 196.0)
Weight (kg)			
N	395	393	788
Median (Min, Max)	76.4 (44.0, 148.1)	79.0 (40.6, 133.6)	78.0 (40.6, 148.1)
Body Surface Area (m^2)			
N	395	391	786
Median (Min, Max)	1.9 (1.3, 2.7)	1.9 (1.3, 2.6)	1.9 (1.3, 2.7)
≤ 2.2	365 (92.2%)	342 (86.4%)	707 (89.3%)
> 2.2	30 (7.6%)	49 (12.4%)	79 (10.0%)
Missing	1 (0.3%)	5 (1.3%)	6 (0.8%)
ECOG Performance Status			
0	165 (41.7%)	175 (44.2%)	340 (42.9%)
1	191 (48.2%)	186 (47.0%)	377 (47.6%)
2	40 (10.1%)	35 (8.8%)	75 (9.5%)
Hemoglobin (g/L)			
N	396	396	792
Median (Min, Max)	114.0 (71.0, 154.0)	111.0 (57.0, 166.00)	113.0 (57.0, 166.0)
< 105	133 (33.6%)	142 (35.9%)	275 (34.7%)
≥ 105	263 (66.4%)	254 (64.1%)	517 (65.3%)
Absolute Neutrophils Count (10^9/L)			
N	394	395	789
Median (Min, Max)	2.6 (0.6, 11.8)	2.7 (0.7, 28.2)	2.7 (0.6, 28.2)
< 1.5	36 (9.1%)	37 (9.3%)	73 (9.2%)
≥ 1.5	358 (90.4%)	358 (90.4%)	716 (90.4%)
Missing[a]	2 (0.5%)	1 (0.3%)	3 (0.4%)

Platelets (10^9/L)			
N	396	396	792
Median (Min, Max)	185.0 (32.0, 540.0)	192.5 (25.0, 597.0)	187.0 (25.0, 597.0)
< 150	121 (30.6%)	104 (26.3%)	225 (28.4%)
≥ 150	275 (69.4%)	292 (73.7%)	567 (71.6%)
Corrected Calcium (mg/dL)			
N	388	392	780
Median (Min, Max)	9.4 (6.7, 14.1)	9.5 (4.4, 15.0)	9.4 (4.4, 15.0)
≤ 11.5	381 (96.2%)	381 (96.2%)	762 (96.2%)
> 11.5	7 (1.8%)	11 (2.8%)	18 (2.3%)
Missing	8 (2.0%)	4 (1.0%)	12 (1.5%)
Serum Creatinine (µmol/L)			
N	396	396	792
Median (Min, Max)	82.2 (33.6, 216.0)	82.0 (37.1, 187.4)	82.2 (33.6, 216.0)
Creatinine Clearance Reported (mL/min)			
N	396	396	792
Median (Min, Max)	78.6 (38.7, 211.9)	79.2 (30.0, 207.8)	79.0 (30.0, 211.9)
30 – < 50[b]	19 (4.8%)	32 (8.1%)	51 (6.4%)
50 – < 80	185 (46.7%)	170 (42.9%)	355 (44.8%)
≥ 80	192 (48.5%)	194 (49.0%)	386 (48.7%)
Creatinine Clearance Sponsor Calculated (mL/min)			
N	395	390	785
Median (Min, Max)	80.2 (32.7, 211.2)	81.1 (26.7, 208.2)	80.9 (26.7, 211.2)
< 30	0 (0.0%)	1 (0.3%)	1 (0.1%)
30 – < 50	25 (6.3%)	31 (7.8%)	56 (7.1%)
50 – < 80	171 (43.2%)	153 (38.6%)	324 (40.9%)
≥ 80	199 (50.3%)	205 (51.8%)	404 (51.0%)
Missing	1 (0.3%)	6 (1.5%)	7 (0.9%)
History of Neuropathy			
Yes	199 (50.3%)	188 (47.5%)	387 (48.9%)
No	197 (49.7%)	208 (52.5%)	405 (51.1%)
Presence of Neuropathy at Baseline			
Yes	144 (36.4%)	137 (34.6%)	281 (35.5%)
Grade 1	114 (28.8%)	106 (26.8%)	220 (27.8%)
Grade 2[c]	22 (5.6%)	24 (6.1%)	46 (5.8%)
Missing	8 (2.0%)	7 (1.8%)	15 (1.9%)
No	252 (63.6%)	259 (65.4%)	511 (64.5%)

CRd = carfilzomib/Revlimid (lenalidomide)/dexamethasone arm; ECOG = Eastern Cooperative Oncology Group; ITT = intent-to-treat; Rd = Revlimid (lenalidomide)/dexamethasone arm

[a] Subjects met eligibility criteria at screening.

[b] All subjects met eligibility criteria at screening, except 1 subject described in

[c] One subject in the CRd arm had > Grade 2 neuropathy at baseline

Baseline disease characteristics are reported in Table 24.

Table 21. Baseline disease characteristics – ITT Population (Study PX-171-009)

	CRd (n = 396)	Rd (n = 396)	Total (N = 792)
Time at Baseline Since Initial Multiple Myeloma Diagnosis (Years)			
N	395	396	791
Median (Min, Max)	3.0 (0.4, 19.7)	3.2 (0.5, 27.3)	3.1 (0.4, 27.3)
Time at Baseline Since Last Relapse (Months)			
N	396	394	790
Median (Min, Max)	2.0 (0.3, 48.2)	2.2 (0.1, 63.1)	2.1 (0.1, 63.1)
Disease Stage at Initial Diagnosis			
I	64 (16.2%)	74 (18.7%)	138 (17.4%)
II	99 (25.0%)	94 (23.7%)	193 (24.4%)
III	185 (46.7%)	161 (40.7%)	346 (43.7%)
Unknown	48 (12.1%)	67 (16.9%)	115 (14.5%)

Calculated ISS Disease Stage at Baseline[a]			
I	167 (42.2%)	154 (38.9%)	321 (40.5%)
II	148 (37.4%)	153 (38.6%)	301 (38.0%)
III	73 (18.4%)	82 (20.7%)	155 (19.6%)
Unknown	8 (2.0%)	7 (1.8 %)	15 (1.9%)
Measureable Disease Category			
SPEP and UPEP	63 (15.9%)	68 (17.2%)	131 (16.5%)
SPEP only	299 (75.5%)	298 (75.3%)	597 (75.4%)
UPEP only	34 (8.6%)	30 (7.6%)	64 (8.1%)
Heavy Chain			
IgG	275 (69.4%)	281 (71.0%)	556 (70.2%)
IgA	85 (21.5%)	86 (21.7%)	171 (21.6%)
IgD	2 (0.5%)	1 (0.3%)	3 (0.4%)
IgE	0	1 (0.3%)	1 (0.1%)
IgG IgA	1 (0.3%)	0	1 (0.1%)
Not Detected	33 (8.3%)	27 (6.8%)	60 (7.6%)
Light Chain			
Kappa	271 (68.4%)	256 (64.6%)	527 (66.5%)
Lambda	124 (31.3%)	139 (35.1%)	263 (33.2%)
Not Detected	1 (0.3%)	1 (0.3%)	2 (0.3%)
Serum β2 Microglobulin (mg/L) per Covance			
< 2.5	68 (17.2%)	71 (17.9%)	139 (17.6%)
≥ 2.5	324 (81.8%)	319 (80.6%)	643 (81.2%)
Missing[b]	4 (1.0%)	6 (1.5%)	10 (1.3%)
Serum β2 Microglobulin (mg/L) per IVRS			
< 2.5	77 (19.4%)	77 (19.4%)	154 (19.4%)
≥ 2.5	319 (80.6%)	319 (80.6%)	638 (80.6%)
Plasma Cell Involvement (%)			
Median (Min, Max)	19.0 (<0.01, 96.0)	20.0 (<0.01, 100.0)	20.0 (<0.01, 100.0)
< 50	295 (74.5%)	288 (72.7%)	583 (73.6%)
≥ 50	82 (20.7%)	86 (21.7%)	168 (21.2%)
Missing	19 (4.8%)	22 (5.6%)	41 (5.2%)
Presence of ≥ 1 Plasmacytoma			
Yes	15 (3.8%)	24 (6.1%)	39 (4.9%)

Presence of ≥ 1 Bone Lesion			
Yes	300 (75.8%)	304 (76.8%)	604 (76.3%)
FISH			
High-risk group[c]	48 (12.1%)	52 (13.1%)	100 (12.6%)
Standard-risk group[c]	147 (37.1%)	170 (42.9%)	317 (40.0%)
Unknown-risk group[c]	201 (50.8%)	174 (43.9%)	375 (47.3%)

CRd = carfilzomib/Revlimid (lenalidomide)/dexamethasone arm; FISH = Fluorescent in Situ Hybridization; ISS = International Staging System; ITT = intent-to-treat; IVRS = interactive voice recognition system; Rd = Revlimid (lenalidomide)/dexamethasone arm

[a] ISS Disease Stage Sponsor Derived using data reported by Central Laboratory data for beta 2 microglobulin and local laboratory data for Albumin. ISS Stage I: β2 microglobulin < 3.5 mg/L and albumin ≥ 3.5 g/dL; Stage II: β2 microglobulin < 3.5 mg/L and albumin < 3.5 g/dL; or β2 microglobulin 3.5 mg/L-5.5 mg/L irrespective of the serum albumin; Stage III: β2 microglobulin ≥ 5.5 mg/L

[b] Ten subjects (4 in the CRd arm, 6 in the Rd arm) were randomized to the correct strata based on β2 microglobulin collected by a local laboratory.

[c] The high-risk group consisted of the genetic subtypes t(4; 14), t(14;16), or deletion 17p in ≥ 60% of plasma cells. The standard-risk group consisted of subjects without t(4; 14), t(14;16), and < 60% of plasma cells with deletion 17p. The unknown risk group included subjects with FISH results not collected or not analyzed.

The medical history concerning prior treatments of the enrolled subjects are shown in Table 25.

Table 22. Prior Therapy for Multiple Myeloma – ITT Population (Study PX-171-009)

	CRd (n = 396)	Rd (n = 396)	Total (N = 792)
Subjects with[a]			
Prior systemic therapy for multiple myeloma	396 (100.0%)	396 (100.0%)	792 (100.0%)
Prior transplant	217 (54.8%)	229 (57.8%)	446 (56.3%)
Prior radiotherapy for multiple myeloma	79 (19.9%)	90 (22.7%)	169 (21.3%)
Prior surgery for multiple myeloma	52 (13.1%)	44 (11.1%)	96 (12.1%)
Number of Prior Regimens			
N	396	396	792
Median (Min, Max)	2.0 (1, 4)	2.0 (1, 4)	2.0 (1, 4)
1	184 (46.5%)	157 (39.6%)	341 (43.1%)
2	120 (30.3%)	139 (35.1%)	259 (32.7%)
3	91 (23.0%)	99 (25.0%)	190 (24.0%)
4	1 (0.3%)	1 (0.3%)	2 (0.3%)
Number of Unique Anti-Myeloma Agents			
N	396	396	792
Median (Min, Max)	5.0 (1, 11)	5.0 (1, 15)	5.0 (1, 15)
Time Since Last Prior Regimen (Months)			
N	377	376	753
Median (Min, Max)	11.6 (0.0, 113.1)	10.7 (0.5, 243.4)	11.0 (0.0, 243.4)
Refractory to Last Prior Regimen	110 (27.8%)	119 (30.1%)	229 (28.9%)
Nonresponsive (< MR) to last prior regimen	48 (12.1%)	59 (14.9%)	107 (13.5%)
Progression during last prior regimen	46 (11.6%)	45 (11.4%)	91 (11.5%)
Progression within 60 days of completion of last prior regimen	44 (11.1%)	50 (12.6%)	94 (11.9%)
Refractory to			
Bortezomib in any prior regimen	60 (15.2%)	58 (14.6%)	118 (14.9%)
Nonresponsive (< MR) to any regimen	20 (5.1%)	27 (6.8%)	47 (5.9%)
Progression during any regimen[b]	20 (5.1%)	11 (2.8%)	31 (3.9%)
Progression within 60 days of completion of any regimen	32 (8.1%)	26 (6.6%)	58 (7.3%)
Lenalidomide in any prior regimen	29 (7.3%)	28 (7.1%)	57 (7.2%)
Bortezomib and an IMiD in any prior regimen	24 (6.1%)	27 (6.8%)	51 (6.4%)

Prior Therapy Received			
Bortezomib	261 (65.9%)	260 (65.7%)	521 (65.8%)
Lenalidomide	79 (19.9%)	78 (19.7%)	157 (19.8%)
Thalidomide	176 (44.4%)	171 (43.2%)	347 (43.8%)
Pomalidomide	0	0	0
IMiD	233 (58.8%)	229 (57.8%)	462 (58.3%)
Bortezomib and IMiD	146 (36.9%)	139 (35.1%)	285 (36.0%)
Corticosteroids	389 (98.2%)	387 (97.7%)	776 (98.0%)
Anthracycline	149 (37.6%)	136 (34.3%)	285 (36.0%)
Alkylators	340 (85.9%)	349 (88.1%)	689 (87.0%)
Received in Last Prior Regimen			
Bortezomib	194 (49.0%)	174 (43.9%)	368 (46.5%)
Lenalidomide	49 (12.4%)	50 (12.6%)	99 (12.5%)

CRd = carfilzomib/Revlimid (lenalidomide)/dexamethasone arm; IMid = immunomodulatory drug (thalidomide, lenalidomide, pomalidomide); ITT = intent-to-treat; MR = minimal response; Rd = Revlimid (lenalidomide)/dexamethasone arm.

[a] Subjects could be counted in more than 1 category.

[b] Although these subjects were reported as having progression during a bortezomib-containing regimen, the progression date occurred after bortezomib had been stopped and these subjects were eligible for enrollment.

Numbers analysed

The analysis populations of Study PX-171-009 are summarized in Table 26.

Table 23. PX-171-009- Analysis Populations

	CRd (n = 396)	**Rd (n = 396)**	**Total (N = 792)**
ITT Population	396 (100.0%)	396 (100.0%)	792 (100.0%)
Safety Population	392 (99.0%)	389 (98.2%)	781 (98.6%)
PP Population	390 (98.5%)	387 (97.7%)	777 (98.1%)

Outcomes and estimation

Primary endpoint: PFS

Results in terms of Progressive-Free Survival assessed by IRC are reported in Table 27 and in Figure 3.

Table 24. Progression-Free Survival as Determined by the Independent Review Committee (ITT Population, Study PX-171-009)

	CRd (N = 396)	Rd (N = 396)
Total Events	207 (52.3%)	224 (56.6%)
Progressed	**167 (42.2%)**	**200 (50.5%)**
Died without disease progression	40 (10.1%)	24 (6.1%)
Total Censored	189 (47.7%)	172 (43.4%)
Reasons Censored		
No post baseline disease assessment	0	1 (0.3%)
Alive without progression	140 (35.4%)	100 (25.3%)
Event after missed more than 1 assessment	5 (1.3%)	6 (1.5%)
Started new anticancer treatment	**35 (8.8%)**	**48 (12.1%)**
Lost to follow up or withdrew consent	9 (2.3%)	17 (4.3%)
PFS Duration (months)[a]		
N	396	396
Median (95% CI)	**26.3 (23.3, 30.5)**	**17.6 (15.0, 20.6)**
Min, Max (+ for censored)	0+, 43+	0+, 46+
P-value (1-sided)[b]	<0.0001	
Hazard Ratio (CRd/Rd) (95% CI)[c]	0.690 (0.570, 0.834)	
KM Event-free Rate[a]		
12 months (95% CI)	76.8 (72.2, 80.7)	62.5 (57.2, 67.3)
18 months (95% CI)	64.4 (59.3, 69.1)	47.9 (42.5, 53.1)
24 months (95% CI)	54.9 (49.6, 59.9)	40.0 (34.7, 45.3)
36 months (95% CI)	36.7 (30.5, 43.0)	30.7 (24.8, 36.8)
Follow-up for PFS (months)[a,d]		
N	396	396
Median (95% CI)	31.4 (30.7, 31.9)	30.1 (28.8, 31.4)
Min, Max (+ for censored)	0, 43	0, 46

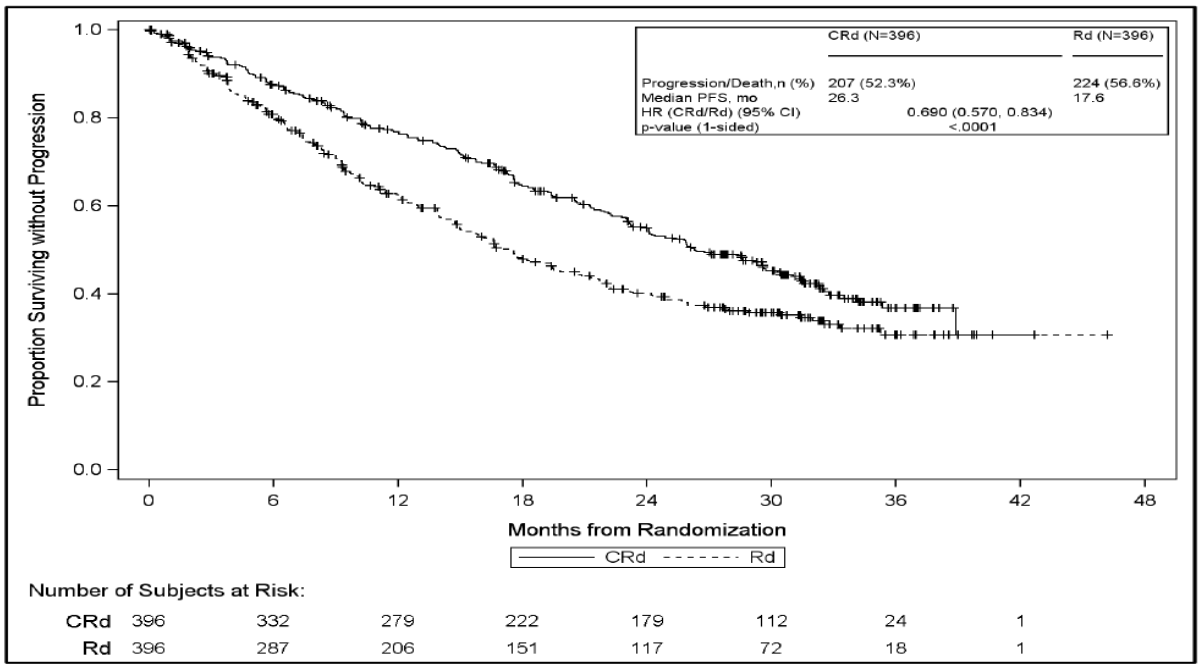
[a] Median, percentiles, and event-free rate were estimated using the Kaplan-Meier method. Confidence intervals for median and percentiles were estimated using the method by Klein and Moeschberger (1997) with log-log transformation. Confidence intervals for event-free rates were estimated using the method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

[b] P-value from stratified log-rank test stratified with β2 microglobulin levels (<2.5 mg/L vs ≥2.5 mg/L), prior bortezomib (no vs yes), and prior lenalidomide (no vs yes) as stratification factors.

[c] Hazard ratio and 95%CI from Cox proportional hazard model with β2 microglobulin levels (<2.5 vs ≥2.5mg/L), prior bortezomib (no vs yes) and prior lenalidomide (no vs yes) as stratification factors.

[d] Estimated using reverse Kaplan-Meier method (Schemper 1996).

Figure 3. Kaplan-Meier Plot of Progression-Free Survival as Determined by the Independent Review Committee (ITT Population, PX-171-009)



CI = confidence interval; CRd = carfilzomib/Revlimid (lenalidomide)/dexamethasone arm; HR = hazard ratio; ITT = intent-to-treat; PFS = progression-free survival; Rd = Revlimid (lenalidomide)/dexamethasone arm

PFS results from additional sensitivity analyses are reported in Table 28.

Table 25. Sensitivity Analyses of Progression-Free Survival (ITT Population, Study PX-171-009)

	CRd (N = 396)			Rd (N = 396)				
Analysis[a]	**N**	**No. of Events (%)**	**Median (months) (95% CI)**	**N**	**No. of Events (%)**	**Median (months) (95% CI)**	**Hazard Ratio (CRd/Rd) (95% CI)**	**P-value 1-sided**
Primary Analysis PFS as Assessed by IRC	396	207 (52.3)	26.3 (23.3, 30.5)	396	224 (56.6)	17.6 (15.0, 20.6)	0.690 (0.570, 0.834)	<0.0001
PFS as Assessed by the Investigators	396	209 (52.8)	26.1 (23.2, 29.7)	396	240 (60.6)	16.6 (14.5, 19.4)	0.651 (0.540, 0.785)	<0.0001
PFS as Assessed by ORCA	396	215 (54.3)	25.8 (22.3, 29.6)	396	231 (58.3)	16.7 (14.5, 19.5)	0.706 (0.585, 0.851)	0.0001
Unstratified Analysis	396	207 (52.3)	26.3 (23.3, 30.5)	396	224 (56.6)	17.6 (15.0, 20.6)	0.712 (0.589, 0.861)	0.0002
Analysis Using Interval Censoring	396	207 (52.3)	25.9 (22.7, 30.3)	396	224 (56.6)	17.6 (14.8, 20.5)	0.718 (0.594, 0.868)	0.0003

Initiation of Non-Protocol Anti-Cancer Therapy Treated as PFS Event	396	241 (60.9)	23.3 (20.8, 26.2)	396	268 (67.7)	14.7 (12.4, 16.6)	0.676 (0.567, 0.805)	<0.0001
Initiation of Non-Protocol Anti-Cancer Therapy Treated as Neither a PFS Event nor a Censoring Event	396	212 (53.5)	26.3 (23.3, 30.5)	396	234 (59.1)	16.8 (14.9, 19.5)	0.680 (0.564, 0.820)	<0.0001
Analysis Based on Scheduled Assessment Dates Instead of Actual Assessment Dates	396	207 (52.3)	26.0 (23.2, 30.5)	396	224 (56.6)	16.7 (14.8, 20.3)	0.689 (0.569, 0.833)	<0.0001
Analysis After Adjusting for Bias due to Stopping at Interim[b]	396	207 (52.3)	26.3 (23.3, 30.5)	396	224 (56.6)	17.6 (15.0, 20.6)	0.686 (0.566, 0.831)	<0.0001

ORCA = Onyx Response Computational Assessment

a The primary analysis refers to primary, stratified analysis of PFS using the disease outcomes assessed by the IRC and the prespecified censoring rules. The sensitivity analyses deviate from the primary analysis with respect to disease outcome assessor (IRC, investigators, sponsor), analysis methods (stratified, unstratified, bias adjusted, right censored, interval censored), censoring rules (e.g., censoring by the initiation of non-protocol, anti-cancer therapy vs. not initiating such therapy) and assessment schedules (observed vs. scheduled).

b Analysis after adjusting for the bias due to stopping at interim was based on Emerson and Fleming (1990). Adjusted hazard ratio (95% CI) and p-value were based on the statistics from a stratified log-rank test.

Secondary endpoint: Overall Survival

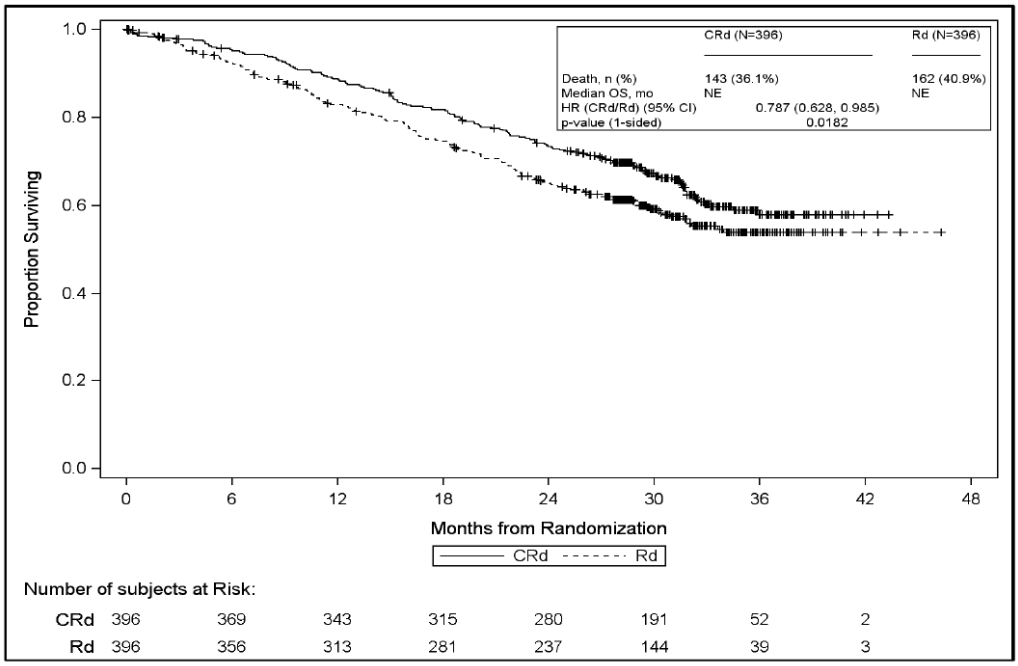
Results in terms of OS are presented in Table 29 and in Figure 4.

Table 26. Overall Survival (ITT Population, Study PX-171-009)

	CRd (N = 396)	**Rd (N = 396)**
Survival Status		
Died	143 (36.1%)	162 (40.9%)
Censored	253 (63.9%)	234 (59.1%)
Reasons Censored		
Alive	240 (60.6%)	211 (53.3%)
Withdrew consent	10 (2.5%)	19 (4.8%)
Lost to follow-up	3 (0.8%)	4 (1.0%)
	CRd (N = 396)	**Rd (N = 396)**
OS Duration (months)[a]		
N	396	396
Median (95% CI)	NE (NE, NE)	NE (32.1, NE)
Min, Max (+ for censored)	0+, 43+	0, 46+
P-value (1-sided)[b]	0.0182	
Hazard Ratio (CRd/Rd) (95% CI)[c]	0.787 (0.628, 0.985)	
Follow-up for OS (months)[a,d]		
N	396	396
Median (95% CI)	32.3 (31.7, 33.2)	31.5 (30.8, 32.5)
Min, Max (+ for censored)	0, 43	0+, 46

a. Medians were estimated using the KM method. CI for median were estimated using the method by Klein and Moeschberger (1997) with log-log transformation.
b. P-value was from stratified log-rank test stratified with β2 microglobulin levels (<vs $\geq$ 2.5 mg/L), prior bortezomib (no vs. yes), and prior lenalidomide (no vs. yes) as stratification factors.
c. Hazard ratio and 95% CI were from Cox proportional hazard model with β2 microglobulin levels (< vs. $\geq$ 2.5 mg/L), prior bortezomib (no vs. yes), and prior lenalidomide (no vs. yes) as stratification factors.
Estimated using reverse Kaplan-Meier method (Schemper 1996)

Figure 4. Kaplan-Meier Plot of Overall Survival (Study PX-171-009; ITT Population)



CI = confidence interval; CRd = carfilzomib/Revlimid (lenalidomide)/dexamethasone arm; HR = hazard ratio; ITT = intent-to-treat; NE = not estimable; OS = overall survival; Rd = Revlimid (lenalidomide)/dexamethasone arm

Secondary endpoint: Overall Response Rate

The results of the Overall Response Rate are provided in Table 30.

Table 27. Overall Response Rate (ITT Population) PX-171-009; ITT Population)

	IRC-assessment		Investigators-assessment		Sponsor-Assessment (ORCA)	
	CRd N = 396	**Rd N = 396**	**CRd N = 396**	**Rd N = 396**	**CRd N = 396**	**Rd N = 396**
Best Overall Response[a]						
sCR	56 (14.1%)	17 (4.3%)	67 (16.9%)	25 (6.3%)	42 (10.6%)	13 (3.3%)
CR	70 (17.7%)	20 (5.1%)	91 (23.0%)	31 (7.8%)	61 (15.4%)	16 (4.0%)
VGPR	151 (38.1%)	123 (31.1%)	109 (27.5%)	104 (26.3%)	148 (37.4%)	108 (27.3%)
PR	68 (17.2%)	104 (26.3%)	86 (21.7%)	117 (29.5%)	96 (24.2%)	133 (33.6%)
MR	15 (3.8%)	38 (9.6%)	9 (2.3%)	21 (5.3%)	9 (2.3%)	26 (6.6%)
SD	7 (1.8%)	43 (10.9%)	11 (2.8%)	55 (13.9%)	7 (1.8%)	53 (13.4%)
PD	7 (1.8%)	16 (4.0%)	8 (2.0%)	22 (5.6%)	16 (4.0%)	25 (6.3%)
Not Evaluable	22 (5.6%)	35 (8.8%)	15 (3.8%)	21 (5.3%)	17 (4.3%)	22 (5.6%)
ORR[a]	345 (87.1%)	264 (66.7%)	353 (89.1%)	277 (69.9%)	347 (87.6%)	270 (68.2%)
95% CI of ORR[b]	83.4%, 90.3%	61.8%, 71.3%	85.7%, 92.0%	65.2%, 74.4%	84.0%, 90.7%	63.3%, 72.7%
P-value (1-sided)[c]	< 0.0001		< 0.0001		< 0.0001	
Odds Ratio of CRd/Rd (95%CI)[d]	3.472 (2.411, 5.001)		3.633 (2.467, 5.352)		3.324 (2.304, 4.796)	

[a] Best overall response was defined a subject's best response during the study based on IMWG-URC, MR determined by EBMT criteria. Subjects evaluated for ORR had a best overall response of PR or better.

[b] Clopper-Pearson interval.

[c] P-value was from Cochran-Mantel Haenszel chi-square test with β2 microglobulin levels (< vs. ≥2.5mg/L), prior bortezomib (no vs yes) and prior lenalidomide (no vs yes) as stratification factors.

[d] The odds ratio and 95% CI were estimated using the Mantel-Haenszel method.

Secondary endpoint: Duration of Response

As of the data cut-off date, a total of 49.6% of responders in the CRd arm and 52.2% in the Rd arm had either progressed and/or died. Results in terms of DOR are shown in Table 31.

Table 28. Duration of Response as Determined by the Independent Review Committee (PX-171-009; ITT Population)

	CRd(N = 396)	Rd(N = 396)
Number of Subjects with Overall Response[a]	345	264
Progressed	141 (40.9%)	125 (47.3%)
Death without disease progression	30 (8.7%)	13 (4.9%)
Censored	174 (50.4%)	126 (47.7%)
Duration of Response		
N	345	264
Median (95% CI)	28.6 (24.9, 31.3)	21.2 (16.7, 25.8)
Min, Max (+ for censored)	1, 42+	0+, 39+

The median DOR as determined by the investigators was 26.7 months (95% CI: 24.0, 30.5) in the CRd arm and 18.5 months (95% CI: 15.7, 23.3) in the Rd arm. The median DOR as determined by ORCA was 27.4 months (95% CI: 23.1, 30.4) in the CRd arm and 21.0 months (95% CI: 16.6, 25.0) in the Rd arm.

Secondary endpoint: Disease Control Rate

The DCR was 92.7% (95% CI: 89.7, 95.0) in the CRd arm *versus* 87.1% (95% CI: 83.4, 90.3) in the Rd arm (Odds Ratio = 1.90 [95% CI: 1.17, 3.08]; p = 0.0044). As determined by the investigators, the DCR was 94.2% (95% CI: 91.4, 96.3) in the CRd arm *versus* 89.1% (95% CI: 85.7, 92.0) in the Rd arm (Odds Ratio = 1.99 [95% CI: 1.17, 3.38]; p = 0.0048). As determined by ORCA, the DCR was 91.7% (95% CI: 88.5, 94.2) in the CRd arm *versus* 88.1% (95%CI: 84.5, 91.1) in the Rd arm (Odds Ratio = 1.48 [95% CI: 0.93, 2.37]; p = 0.0487).

Secondary endpoint: Duration of Disease Control

As of the data cut-off date, a total of 51.2% of subjects who achieved a best overall response of SD (≥ 8 weeks) or better in the CRd arm and 56.2% in the Rd arm had either progressed and/or died. The median DDC was 28.7 months [95% CI: 24.4, 31.6] in the CRd arm and 18.9 months [95% CI: 16.6, 22.2]) in the Rd arm.

The median DDC as determined by the investigators was 27.1 months (95% CI: 24.1, 31.4) in the CRd arm *versus* 18.2 months (95% CI: 15.9, 21.9) in the Rd arm. The median DDC as determined by ORCA was 27.1 months (95% CI: 24.1, 31.4) in the CRd arm *versus* 18.9 months (95% CI: 16.6, 22.0) in the Rd arm.

Secondary endpoint: Global Health Status/Quality of Life Scale of the EORTC Quality of Life Core Module QLQ-C30

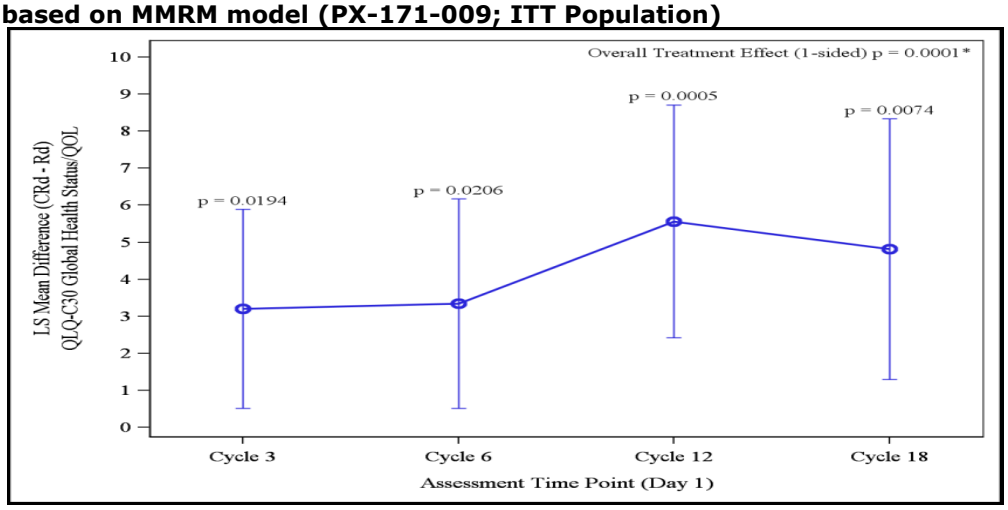
Using a restricted maximum likelihood-based mixed model for repeated measures (MMRM) analysis under the assumption of missing at random (MAR), subjects treated with CRd reported improved global health status with higher QLQ-C30 Global Health Status/QoL scores compared with Rd over 18 cycles of treatment (p-value = 0.0001).) The MID is 5 points according to the literature (Cocks 2011; Kvam 2010; Kvam 2011; Delforge 2012), and this MID was met at Cycle 12 (5.56) and approached at Cycle 18 (4.81) when comparing CRd *versus* Rd (Results shown in Table 32 and in Figure 5).

Table 29. Primary Health-Related Quality of Life Analysis of Treatment Difference Over Time in QLQ-C30 Global Health Status/Quality of Life Based on Mixed Model for Repeated Measures (PX-171-009; ITT Population)

Summary of Study Subjects			**CRd (N = 396)**			**Rd (N = 396)**
Number of Subjects with at Least 1 Assessment at Cycles 1, 3, 6, 12, and 18			365			348
Least Squares Mean Estimates						
Visit	**Mean Estimate**		**Difference: CRd – Rd (SE)**	**DF**	**95% CI**	**P-Value (2-Sided)**
	CRd	**Rd**				
Cycle 3, Day 1	60.44	57.23	3.20 (1.369)	1548	0.52-5.89	0.0194
Cycle 6, Day 1	62.64	59.30	3.34 (1.443)	1645	0.51-6.17	0.0206
Cycle 12, Day 1	62.32	56.75	5.56 (1.605)	1855	2.42-8.71	0.0005
Cycle 18, Day 1	63.35	58.54	4.81 (1.793)	2005	1.29-8.33	0.0074
P-Value for Overall Treatment Effect (1-Sided): 0.0001						

DF = degrees of freedom; SE = standard of error
The model included the fixed, categorical effects of treatment, visit, and treatment-by-visit; the fixed, continuous covariates of baseline HRQL score and baseline score-by-visit, as well as the randomization stratification factors: β2 microglobulin levels (< vs. ≥ 2.5 mg/L), prior bortezomib (no vs. yes), and prior lenalidomide (no vs. yes) as fixed factors. Random subject effect was modeled using within subject error correlation structure.

Figure 5. Least Squares Mean Difference (CRd-Rd) and 95% CI on the QLQ-C30 Global Health Status/QoL based on MMRM model (PX-171-009; ITT Population)



MMRM = mixed model for repeated measures; QoL = quality of life
* 1-sided p-value for overall treatment effect based on type 3 test for fixed effects [MMRM]). Confidence intervals above 0 indicate statistically significant treatment difference in favour of CRd. Cycle p-values are 2-sided p-values from MMRM model.

Questionnaire completion at baseline was very similar between the study arms, with 94.9% of subjects in the CRd arm *versus* 93.2% in the Rd arm completing the questionnaires. As a proportion of the randomized study population, just under half of subjects completed the QLQ-C30 questionnaire (47.3%) at Cycle 18. A higher proportion of subjects randomized to CRd completed the QLQ-C30 questionnaire at each cycle compared to Rd subjects. This difference was largest at Cycle 18, with 57.3% in the CRd arm *versus* 37.4% in the Rd arm, respectively. The questionnaires were completed by subjects up to Cycle 18 or until disease progression or death, whichever occurred first, and at End of Treatment. Given there were more subjects

who progressed in the Rd group, the difference in QLQ-C30 completion rates was to be expected, as shown in Table 32.

Exploratory Efficacy Endpoint: Time to Progression

A total of 42.2% of subjects in the CRd arm and 50.5% in the Rd arm had progression of multiple myeloma by the time of the data cut-off. The median TTP was 31.4 months [95% CI: 26.4, NE] in the CRd arm and 19.4 months [95% CI: 16.6, 23.2] in the Rd arm. The median follow-up for disease progression was 30.6 months (95% CI: 29.5, 31.4) in the CRd arm and 29.3 months (95% CI: 27.8, 30.5) in the Rd arm.

Exploratory Efficacy Endpoint: Clinical Benefit Rate

The CBR was 90.9% [95% CI: 87.6, 93.6]) in the CRd arm and 76.3% [95% CI: 71.8, 80.4] in the Rd arm. Among the responders, the median duration of clinical benefit was 28.3 months [95% CI: 24.3, 30.5] in the CRd arm and 20.3 months [95% CI: 16.6, 24.0] in the Rd arm.

Among the responders, the median duration of clinical benefit (DCB) was 28.3 months [95% CI: 24.3, 30.5] in the CRd arm and 20.3 months [95% CI: 16.6, 24.0] in the Rd arm.

As determined by investigators, the CBR was 91.4% (95% CI: 88.2, 94.0) in the CRd arm and 75.3% (95% CI: 70.7, 79.4) in the Rd arm; the median duration of clinical benefit was 27.6 months (95% CI:23.3, 31.3) in the CRd arm and 19.3 months (95% CI: 16.5, 23.9) in the Rd arm.

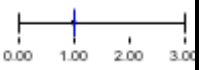
Exploratory Efficacy Endpoint: Time to Next Treatment

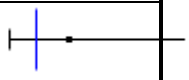
A total of 38.1% of subjects in the CRd arm and 46.5% of subjects in the Rd arm had started a new anti-myeloma treatment by the time of the data cut-off. Among subjects who received new anti-myeloma therapy, the median time from randomization to new treatment was 17.3 months [range: 0.46–37.6]) in the CRd arm and 12.1 months [range: 0.26–33.5] in the Rd arm. The Kaplan-Meier estimate of median time to next treatment among all randomized subjects was also longer in the CRd arm (37.6 months [95% CI: 31.8, NE]) than in the Rd arm (24.5 months [95% CI: 20.8, 32.8]). The median follow-up for next therapy was 31.5 months (95% CI: 30.7, 32.0) in the CRd arm and 30.0 months (95% CI: 29.3, 31.2) in the Rd arm.

Ancillary analyses

Results from subgroup analyses on PFS and ORR as determined by IRC are presented in Table 33, Table 34 and Table 35.

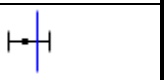
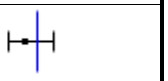
Table 30. Subgroup Analyses of Progression-Free Survival as Determined by the Independent Review Committee (PX-171-009; ITT Population)

	CRd			Rd				
Subgroup	**N**	**No of Events (%)**	**Median (months) (95% CI)**	**N**	**No. of Events (%)**	**Median (months) (95% CI)**	**Hazard Ratio (CRd/Rd) (95% CI)**	**Plot of Hazard Ratio** 
Overall	**396**	207 (52.3)	26.3 (23.3, 30.5)	396	224 (56.6)	17.6 (15.0, 20.6)	0.690 (0.570, 0.834)	
Age (years)								
18–64	211	105 (49.8)	29.7 (24.1, 35.3)	188	111 (59.0)	16.1 (11.9, 19.4)	0.601 (0.459, 0.786)	
≥ 65	185	102 (55.1)	24.2 (20.8, 29.6)	208	113 (54.3)	18.5 (15.6, 24.9)	0.846 (0.647, 1.106)	
18–74	353	185 (52.4)	26.2 (23.2, 30.5)	343	193 (56.3)	17.6 (14.9, 21.5)	0.726 (0.593, 0.888)	
≥ 75	43	22 (51.2)	30.3 (18.0, NE)	53	31 (58.5)	16.6 (10.3, 22.0)	0.623 (0.360, 1.079)	
Sex								
Male	215	117 (54.4)	26.8 (20.8, 31.4)	232	135 (58.2)	16.7 (14.0, 20.7)	0.742 (0.579, 0.951)	
Female	181	90 (49.7)	26.2 (23.1, 35.3)	164	89 (54.3)	17.7 (14.0, 25.0)	0.684 (0.510, 0.918)	
Race								
White	377	198 (52.5)	26.3 (23.2, 30.5)	377	213 (56.5)	16.8 (14.8, 21.3)	0.719 (0.592, 0.873)	
Black	12	7 (58.3)	23.1 (1.9, NE)	11	6 (54.5)	18.0 (6.8, NE)	0.665 (0.220, 2.008)	
Other	7	2 (28.6)	NE (6.5, NE)	8	5 (62.5)	19.5 (1.9, NE)	0.332 (0.063, 1.759)	

Subgroup	CRd			Rd			Hazard Ratio (CRd/Rd) (95% CI)	Plot of Hazard Ratio
	N	No of Events (%)	Median (months) (95% CI)	N	No. of Events (%)	Median (months) (95% CI)		
Ethnicity								
Hispanic or Latino	20	14 (70.0)	26.3 (9.3, 31.0)	14	5 (35.7)	NE (10.3, NE)	1.580 (0.562, 4.439)	
Not Hispanic or Latino	376	193 (51.3)	26.4 (23.3, 31.4)	381	219 (57.5)	16.7 (14.8, 19.5)	0.684 (0.563, 0.831)	
Geographic Region								
Europe	302	163 (54.0)	26.3 (23.1, 30.5)	288	170 (59.0)	16.6 (14.0, 20.9)	0.695 (0.560, 0.862)	
North America	84	39 (46.4)	29.3 (19.4, NE)	87	41 (47.1)	19.8 (16.1, 32.6)	0.883 (0.569, 1.370)	
Rest of World	10	5 (50.0)	31.4 (0.4, NE)	21	13 (61.9)	13.9 (6.6, 21.9)	0.387 (0.133, 1.125)	
Body Surface Area (m^2)								
≤ 2.2	365	190 (52.1)	26.2 (23.2, 30.5)	342	191 (55.8)	17.8 (15.6, 21.9)	0.739 (0.604, 0.904)	
> 2.2	30	16 (53.3)	29.7 (19.6, NE)	49	29 (59.2)	12.9 (9.3, 22.1)	0.563 (0.304, 1.044)	
Baseline ECOG PS								
0	165	83 (50.3)	28.7 (23.3, 34.2)	175	98 (56.0)	17.6 (14.9, 23.6)	0.668 (0.498, 0.896)	
1	191	101 (52.9)	26.2 (22.1, 31.4)	186	102 (54.8)	18.0 (14.0, 22.2)	0.764 (0.580, 1.007)	
2	40	23 (57.5)	20.6 (16.6, 30.3)	35	24 (68.6)	7.5 (2.3, 21.3)	0.633 (0.356, 1.125)	
Baseline Hemoglobin (g/L)								
< 105	133	85 (63.9)	18.5 (15.4, 24.2)	142	92 (64.8)	13.0 (8.5, 17.6)	0.726 (0.540, 0.976)	
≥ 105	263	122 (46.4)	31.4 (26.1, NE)	254	132 (52.0)	21.5 (16.6, 27.7)	0.701 (0.548, 0.897)	

Subgroup	CRd			Rd			Hazard Ratio (CRd/Rd) (95% CI)	Plot of Hazard Ratio
	N	No of Events (%)	Median (months) (95% CI)	N	No. of Events (%)	Median (months) (95% CI)		
Baseline ANC (10^9/L)								
< 1.5	36	20 (55.6)	22.8 (15.2, NE)	37	22 (59.5)	14.9 (7.2, 21.7)	0.498 (0.271, 0.916)	
≥ 1.5	358	185 (51.7)	28.4 (24.1, 31.4)	358	201 (56.1)	17.7 (15.0, 21.5)	0.734 (0.601, 0.897)	
Baseline Platelets (109/L)								
<150	121	80 (66.1)	18.5 (15.2, 23.2)	104	66 (63.5)	12.9 (8.3, 17.6)	0.723 (0.521, 1.003)	
≥150	275	127 (46.2)	31.4 (26.0, NE)	292	158 (54.1)	19.4 (15.8, 25.0)	0.666 (0.527, 0.842)	
Baseline Corrected Calcium (mg/dL)								
≤ 11.5	381	195 (51.2)	27.1 (24.1, 31.4)	381	213 (55.9)	17.6 (15.0, 21.3)	0.702 (0.578, 0.853)	
> 11.5	7	6 (85.7)	12.3 (1.0, 31.6)	11	8 (72.7)	5.7 (2.0, NE)	1.200 (0.415, 3.471)	
Baseline Creatinine Clearance Sponsor Calculated (mL/min)								
30 – <50	25	12 (48.0)	27.1 (17.8, NE)	31	20 (64.5)	16.6 (9.6, 28.9)	0.579 (0.282, 1.189)	
50 – <80	171	99 (57.9)	23.2 (18.3, 29.3)	153	88 (57.5)	16.6 (12.5, 20.9)	0.811 (0.608, 1.082)	
≥ 80	199	95 (47.7)	31.4 (24.4, NE)	205	114 (55.6)	18.0 (14.6, 23.2)	0.641 (0.488, 0.843)	
Presence of Neuropathy at Baseline								
No	252	124 (49.2)	31.0 (25.9, 34.2)	259	150 (57.9)	16.8 (14.2, 21.5)	0.610 (0.480, 0.774)	
Yes	144	83 (57.6)	23.2 (18.0, 25.9)	137	74 (54.0)	17.6 (13.9, 26.0)	**0.947** (0.692, 1.296)	
Grade 1	114	70 (61.4)	21.3 (15.8, 25.9)	106	57 (53.8)	16.7 (12.4, 26.0)	1.007 (0.709, 1.429)	

Subgroup	CRd			Rd			Hazard Ratio (CRd/Rd) (95% CI)	Plot of Hazard Ratio
	N	No of Events (%)	Median (months) (95% CI)	N	No. of Events (%)	Median (months) (95% CI)		
≥Grade2	22	12 (54.5)	24.2 (19.6, NE)	24	14 (58.3)	14.8 (7.4, NE)	0.695 (0.321, 1.507)	
Stage at Initial Diagnosis								
I	64	29 (45.3)	**28.6** (19.6, NE)	74	34 (45.9)	**28.9** (14.5, NE)	0.797 (0.485, 1.310)	
II	99	55 (55.6)	24.9 (18.0, 31.4)	94	56 (59.6)	17.6 (11.3, 22.2)	0.732 (0.504, 1.064)	
III	185	99 (53.5)	28.7 (23.1, 32.3)	161	96 (59.6)	15.0 (12.4, 18.0)	0.636 (0.479, 0.844)	
Unknown	48	24 (50.0)	24.4 (17.6, 38.9)	67	38 (56.7)	18.9 (12.9, 24.3)	0.753 (0.451, 1.256)	
Plasma Cell Involvement								
< 50%	295	146 (49.5)	28.7 (24.2, 32.8)	288	158 (54.9)	19.4 (15.8, 24.2)	0.703 (0.561, 0.881)	
≥ 50%	82	48 (58.5)	21.3 (16.0, 31.6)	86	54 (62.8)	14.8 (10.2, 17.7)	0.716 (0.484, 1.058)	
Not done	19	13 (68.4)	17.7 (8.5, NE)	22	12 (54.5)	11.3 (5.7, NE)	0.824 (0.373, 1.820)	
Risk Group by FISH								
High	48	31 (64.6))	23.1 (12.5, 24.2)	52	32 (61.5)	13.9 (9.5, 16.7)	0.703 (0.426, 1.160)	
Standard	147	68 (46.3)	29.6 (24.1, NE)	170	94 (55.3)	19.5 (14.8, 26.0)	0.656 (0.480, 0.897)	
Unknown	201	108 (53.7)	28.4 (22.1, 32.3)	174	98 (56.3)	17.6 (14.0, 22.2)	0.742 (0.564, 0.976)	
Serum β2 Microglobulin (mg/L) per IVRS								
< 2.5	68	25 (36.8)	NE (24.4, NE)	71	32 (45.1)	**32.0** (16.1, NE)	0.604 (0.357, 1.021)	

Subgroup	CRd			Rd			Hazard Ratio (CRd/Rd) (95% CI)	Plot of Hazard Ratio
	N	No of Events (%)	Median (months) (95% CI)	N	No. of Events (%)	Median (months) (95% CI)		
≥ 2.5	324	178 (54.9)	25.8 (21.4, 29.3)	319	192 (60.2)	15.9 (13.9, 18.5)	0.705 (0.575, 0.865)	
Number of Prior Regimens								
1	184	91 (49.5)	29.6 (23.2, 33.5)	157	88 (56.1)	17.6 (15.0, 22.2)	0.713 (0.532, 0.957)	
2	120	65 (54.2)	26.2 (21.9, 32.3)	139	78 (56.1)	18.5 (14.0, 25.0)	0.745 (0.536, 1.036)	
3[a]	92	51 (55.4)	24.1 (19.6, 32.6)	100	58 (58.0)	14.8 (10.0, 22.1)	0.682 (0.468, 0.995)	
Prior Transplant								
Yes	217	115 (53.0)	26.3 (23.1, 32.3)	229	127 (55.5)	17.8 (14.5, 22.2)	0.678 (0.526, 0.873)	
No	179	92 (51.4)	26.4 (20.5, 31.4)	167	97 (58.1)	16.6 (13.9, 21.7)	0.760 (0.571, 1.011)	
Prior Bortezomib per IVRS								
Yes	261	143 (54.8)	24.4 (21.9, 29.6)	260	152 (58.5)	16.6 (12.5, 20.9)	0.699 (0.556, 0.879)	
No	135	64 (47.4)	30.3 (25.3, NE)	136	72 (52.9)	18.2 (15.3, 26.0)	0.726 (0.518, 1.018)	
Prior Lenalidomide per IVRS								
Yes	79	46 (58.2)	19.4 (15.0, 31.0)	78	41 (52.6)	13.9 (9.7, 27.9)	0.796 (0.522, 1.215)	
No	317	161 (50.8)	28.7 (24.9, 32.3)	318	183 (57.5)	17.7 (15.8, 21.5)	0.685 (0.554, 0.847)	
Refractory to Prior Bortezomib								
Yes	60	35 (58.3)	**22.3** (16.7, 29.3)	58	31 (53.4)	**19.4** (8.8, 30.5)	0.799 (0.492, 1.297)	
No	336	172 (51.2)	28.6 (24.1, 31.6)	338	193 (57.1)	16.8 (14.9, 20.9)	0.696 (0.566, 0.855)	

Subgroup	CRd			Rd			Hazard Ratio (CRd/Rd) (95% CI)	Plot of Hazard Ratio
	N	No of Events (%)	Median (months) (95% CI)	N	No. of Events (%)	Median (months) (95% CI)		
Refractory to Prior IMiD								
Yes	85	59 (69.4)	**20.8** (14.8, 25.8)	88	60 (68.2)	**11.1** (8.8, 14.8)	0.636 (0.442, 0.914)	
No	311	148 (47.6)	29.6 (25.3, 34.2)	308	164 (53.2)	19.5 (16.6, 24.3)	0.721 (0.577, 0.901)	
Double Refractory to Bortezomib and IMiD								
Yes	24	17 (70.8)	**14.9** (9.3, 23.8)	27	16 (59.3)	**9.3** (5.8, 22.1)	0.889 (0.447, 1.768)	
No	372	190 (51.1)	28.7 (24.2, 31.4)	369	208 (56.4)	17.6 (15.0, 21.3)	0.699 (0.574, 0.852)	

ANC = absolute neutrophil count; FISH = florescence in situ hybridization; IMiD = immunomodulatory drug; ITT= intent-to-treat; IVRS = interactive voice recognition system; NE = not estimable;

[a] Including 2 subjects with 4 prior regimens

Table 31. Additional Subgroup Analyses of Progression-Free Survival as Determined by the Independent Review Committee (PX-171-009; ITT Population)

	CRd			Rd			
	N	No. of Events (%)	Median (months) (95% CI)	N	No. of Events (%)	Median (months) (95% CI)	Hazard Ratio (CRd/Rd) (95% CI)
Overall Population							
	396	207 (52.3)	26.3 (23.3, 30.5)	396	224 (56.6)	17.6 (15.0, 20.6)	0.690 (0.570, 0.834)
Received Any Prior Bortezomib							
Yes	261	143 (54.8)	24.4 (21.9, 29.6)	260	152 (58.5)	16.6 (12.5, 20.9)	0.699 (0.556, 0.879)
No	135	64 (47.4)	30.3 (25.3, NE)	136	72 (52.9)	18.2 (15.3, 26.0)	0.726 (0.518, 1.018)
Received Any Prior Lenalidomide							
Yes	79	46 (58.2)	19.4 (15.0, 31.0)	78	41 (52.6)	13.9 (9.7, 27.9)	0.796 (0.522, 1.215)
No	317	161 (50.8)	28.7 (24.9, 32.3)	318	183 (57.5)	17.7 (15.8, 21.5)	0.685 (0.554, 0.847)
Refractory to Prior Bortezomib							
Yes	60	35 (58.3)	22.3 (16.7, 29.3)	58	31 (53.4)	19.4 (8.8, 30.5)	0.799 (0.492, 1.297)
No	336	172 (51.2)	28.6 (24.1, 31.6)	338	193 (57.1)	16.8 (14.9, 20.9)	0.696 (0.566, 0.855)
Refractory to Prior Lenalidomide							
Yes	29	21 (72.4)	11.3 (7.0, 21.4)	28	17 (60.7)	9.0 (4.0, 10.3)	0.637 (0.333, 1.219)
No	367	186 (50.7)	28.6 (24.1, 31.6)	368	207 (56.3)	17.8 (15.8, 21.9)	0.702 (0.576, 0.856)
Double-Refractory to Lenalidomide and Dexamethasone in Same Regimen							
Yes	21	16 (76.2)	10.3 (6.5, 14.9)	22	15 (68.2)	8.8 (4.0, 9.7)	0.602 (0.275, 1.318)
No	NR	NR	NR	NR	NR	NR	NR

CI = confidence interval; CRd = carfilzomib/Revlimid (lenalidomide)/dexamethasone arm; ITT= intent-to-treat; Rd = lenalidomide/dexamethasone arm; NE = not estimable; NR: not reported

Source: Table 14.2.2.5 in the PX-171-009 CSR; ad hoc analysis Table 14.2.2.5.1, Table 150527r64b-14.2.2.1

Table 32. PX-171-009: Subgroup Analyses of Overall Response as Determined by Independent Review Committee (ITT Population)

	CRd			Rd			
Characteristic	N	No. of responses	ORR (%) (95% CI)	N	No. of responses	ORR (%) (95% CI)	Odds Ratio (CRd/Rd) (95% CI)
All	396	345	87.1 (83.4, 90.3)	396	264	66.7 (61.8, 71.3)	3.382 (2.358, 4.851)
Received Any Prior Bortezomib							
Yes	261	225	86.2 (81.4, 90.1)	260	165	63.5 (57.3, 69.3)	3.598 (2.334, 5.548)
No	135	120	88.9 (82.3, 93.6)	136	99	72.8 (64.5, 80.1)	2.990 (1.551, 5.763)
Received Any Prior Lenalidomide							
Yes	79	64	81.0 (70.6, 89.0)	78	39	50.0 (38.5, 61.5)	4.267 (2.084, 8.733)
No	317	281	88.6 (84.6, 91.9)	318	225	70.8 (65.4, 75.7)	3.226 (2.114, 4.924)
Refractory to Prior Bortezomib							
Yes	60	48	80.0 (67.7, 89.2)	58	35	60.3 (46.6, 73.0)	2.629 (1.155, 5.985)
No	336	297	88.4 (84.5, 91.6)	338	229	67.8 (62.5, 72.7)	3.625 (2.419, 5.431)
Refractory to Prior Lenalidomide							
Yes	29	20	69.0 (49.2, 84.7)	28	7	25.0 (10.7, 44.9)	5.590 (1.663, 18.79)
No	NR	NR	NR	NR	NR	NR	NR
Double-refractory to Lenalidomide and Dexamethasone in Same Regimen							
Yes	21	13	61.9 (38.4, 81.9)	22	5	22.7 (7.8, 45.4)	3.659 (0.912, 14.68)
No	NR	NR	NR	NR	NR	NR	NR

CI = confidence interval; CRd = carfilzomib/lenalidomide/dexamethasone arm; ITT= intent-to-treat; NR = not reported; ORR = overall response rate; Rd = lenalidomide/dexamethasone arm.

Source: PX 171-009 CSR Table 14.2.4.4; ad hoc analysis Table 150527r95b-14.2.4.1, Table 150527r64b-14.2.4.1

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 33. Summary of Efficacy for trial Study PX-171-009

Title: A Randomized, Multicenter, Phase 3 Study Comparing Carfilzomib, Lenalidomide, and Dexamethasone vs. Lenalidomide and Dexamethasone in Subjects with Relapsed Multiple Myeloma			
Study identifier	PX-171-009 (ASPIRE)		
Design	Randomized (ratio 1:1), open-label, multicentre study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		3 years 11 months not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Carfilzomib + Lenalidomide + Dexamethasone (CRd)		Cycle 1 to 12: Carfilzomib 20 mg/m^2 intravenously (IV) on Days 1 and 2 of Cycle 1, escalating to 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 Cycle 2 through Cycle 12 + Lenalidomide 25 mg orally on Days 1 to 21 + Dexamethasone 40 mg orally or IV on Days 1, 8, 15, and 22 Cycle 13 to 18: Carfilzomib 27 mg/m^2 IV on Days 1, 2, 15, and 16 + Lenalidomide 25 mg orally on Days 1 to 21 + Dexamethasone 40 mg orally or IV on Days 1, 8, 15, and 22 Cycle 19 and higher: Lenalidomide 25 mg orally on Days 1 to 21 + Dexamethasone 40 mg orally or IV on Days 1, 8, 15, and 22 28-day cycles until disease progression or unacceptable toxicity; 396 randomized
	Lenalidomide + Dexamethasone (Rd)		Cycle 1 and higher: Lenalidomide: 25 mg orally on Days 1 to 21 + Dexamethasone: 40 mg orally or IV on Days 1, 8, 15, and 22 28-day cycles until disease progression or unacceptable toxicity; 396 randomized
Endpoints and definitions	Primary endpoint	Progressive Free Survival (PFS)	Duration from the date of randomization to the date of confirmed PD or death due to any cause, whichever was earlier; determined by independent review committee using IMWG-URC
	Secondary endpoint	Overall Survival (OS)	Duration from the date of randomization to the date of death due to any cause
	Secondary endpoint	Overall Response Rate (ORR)	Proportion of subjects who achieved a best response of sCR, CR, VGPR or PR according to IMWG-URC
Database lock	16 June 2014		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (N=792)		
Descriptive statistics and estimate variability	Treatment group	CRd arm	Rd arm
	Number of subject	396	396
	Median PFS (months)	26.3	17.6
	95% CI	23.3, 30.5	15.0, 20.6
	Median OS (months)	NE	NE
	95% CI	NE, NE	32.1, NE
	ORR N (%)	345 (87.1%)	264 (66.7%)
	95% CI	83.4%, 90.3%	61.8%, 71.3%
Effect estimate per comparison	PFS	Comparison groups	CRd vs Rd
		HR	0.690
		95% CI	0.570, 0.834
		P-value (1-sided)	<0.0001
	OS	Comparison groups	CRd vs Rd
		HR	0.787
		95% CI	0.628, 0.985
		P-value (1-sided)	0.0182
	ORR	Comparison groups	CRd vs Rd
		Odds Ratio	3.472
		95% CI	2.411, 5.001
		P-value	<0.0001
Notes	Randomization was stratified by β2 microglobulin level (< vs. $\geq$ 2.5 mg/L), prior bortezomib exposure (no vs. yes), and prior lenalidomide exposure (no vs. yes)		

Analysis performed across trials (pooled analyses and meta-analysis)

Table 34. Summary of Efficacy Endpoints: Relapsed Multiple Myeloma Studies with the 20/27 mg/m^2 Dose

	CFZ Monotherapy PX-171-004 – Part 2 (Phase 2) 20/27 mg/m^2 Cohort (N = 67)[a]	KRd Combination Therapy		
		PX-171-006 (Phase 1b) MPD Cohort (N = 51)	PX-171-009 (Phase 3)[a]	
			KRd Arm (N = 396)	Rd Arm (N = 396)
PFS months median (95% CI)	NE (11.3, NE)	15.4 (9.9, 34.1)	26.3 (23.3, 30.5)	17.6 (15.0, 20.6)
HR (95% CI); 1-sided p-value[b]	—	—	0.69 (0.57, 0.83); < 0.0001	
OS months median (95% CI)	37.3 (31.5, NE)	—	NE (NE, NE)	NE (32.1, NE)
HR (95% CI); 1-sided p-value[c]	—	—	0.79 (0.63, 0.99); 0.0182	
ORR n (%)	35 (53.0)	40 (78.4)	345 (87.1)	264 (66.7)
sCR	0 (0)	2 (3.9)	56 (14.1)	17 (4.3)
CR	1 (1.5)	1 (2.0)	70 (17.7)	20 (5.1)
VGPR	18 (27.3)	19 (37.3)	151 (38.1)	123 (31.1)
PR	16 (24.2)	18 (35.3)	68 (17.2	104 (26.3)
95% CI of ORR	40.3, 65.4	64.7, 88.7	83.4, 90.3	61.8, 71.3
1-sided p-value[c]	—	—	< 0.0001	
DOR months median (95% CI)	NE (NE, NE)	22.1 (9.5, 38.0)	28.6 (24.9, 31.3)	21.2 (16.7, 25.8)
TTR months median[d] (min, max)	1.90 (0.5, 3.7)	0.95 (0.5, 4.6)	1 (1, 14)	1 (1, 16)
CBR n (%)	43 (65.2)	40 (78.4)	360 (90.9)	302 (76.3)
95% CI of CBR	52.4, 76.5	64.7, 88.7	87.6, 93.6	71.8, 80.4
DCB months median (95% CI)	NE (NE, NE)	22.6 (9.5, 39.8)	28.3 (24.3, 30.5)	20.3 (16.6, 24.0)
DCR n (%)	53 (79.1)	43 (84.3)	367 (92.7)	345 (87.1)
95% CI of DCR	67.4, 88.1	71.4, 93.0	89.7, 95.0	83.4, 90.3
1-sided p-value[c]	—	—	0.0044	
TTP months median (95% CI)	NE (11.3, NE)	15.4 (9.9, 34.1)	31.4 (26.4, NE)	19.4 (16.6, 23.2)
HR (KRd/Rd) (95% CI); 1-sided p-value[c]	—	—	0.619 (0.503, 0.762); < 0.0001	
Time to Next Treatment — months median	—	—	37.6 (31.8, NE)	24.5 (20.8, 32.8)
HR (KRd/Rd) (95% CI); 1 sided p-value[c]	—	—	0.626 (0.504, 0.777); < 0.0001	

CBR = clinical benefit rate; CI = confidence interval; CR = complete response; DCB = duration of clinical benefit; DCR = disease control rate; DOR = duration of response; HR = hazard ratio; K-M = Kaplan-Meier; MPD = maximum protocol-defined dose; NE = not estimable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; sCR = stringent complete response; TTR = time to response; VGPR = very good partial response.

[a] As determined by an Independent Review Committee using standard objective IMWG response criteria.

[b] The p-value is statistically significant.

[c] The interim OS analysis did not meet the protocol-specified early stopping boundary for OS (p = 0.0051) and hence due to the hierarchical nature of the study design all subsequent p-values are provided for descriptive purposes only.

[d] This is a sample median, not a K-M median.

Clinical studies in special populations

No studies in special populations have been submitted (see discussion on clinical pharmacology and discussion on clinical safety). However Subgroup Analyses of Overall Response Rate in Relapsed Multiple Myeloma Studies was performed on different age groups. The results are presented in Table 30.

Table 35. Subgroup Analyses of Overall Response Rate in Relapsed Multiple Myeloma Studies: Age

	PX-171-004 – Part 2 20 and 20/27 mg/m^2 cohorts (Response-Evaluable Population)			PX-171-006 MPD cohort			PX-171-009						
							CRd			Rd			Odds Ratio (CRd/Rd) (95% CI)
Characteristic	N	No. of responses	ORR (%) (95% CI)	N	No. of responses	ORR (%) (95% CI)	N	No. of responses	ORR (%) (95% CI)	N	No. of responses	ORR (%) (95% CI)	
Overall	126	60	47.6 (38.7, 56.7)	52	40	76.9 (63.2, 87.5)	396	345	87.1 (83.4, 90.3)	396	264	66.7 (61.8, 71.3)	3.382 (2.358, 4.851)
Age (years)													
18–64	58	34	58.6 (44.9, 71.4)	32	28	87.5 (71.0, 96.5)	211	178	84.4 (78.7, 89.0)	188	118	62.8 (55.4, 69.7)	3.200 (1.990, 5.144)
≥ 65	68	26	38.2 (26.7, 50.8)	20	12	60.0 (36.1, 80.9)	185	167	90.3 (85.1, 94.1)	208	146	70.2 (63.5, 76.3)	3.940 (2.229, 6.965)
18–74	—	—	—	—	—	—	353	308	87.3 (83.3, 90.5)	343	231	67.3 (62.1, 72.3)	3.319 (2.257, 4.880)
≥ 75	—	—	—	—	—	—	43	37	86.0 (72.1, 94.7)	53	33	62.3 (47.9, 75.2)	3.737 (1.340, 10.426)

Supportive studies

Study PX-171-004

This was a single-arm phase 2 study evaluating carfilzomib monotherapy at 20 and/or 20/27 mg/m^2 in bortezomib-treated (Part 1, N=35) and bortezomib-naïve (Part 2, N=129) subjects with relapsed MM after 1 to 3 prior lines of therapy, but not refractory to standard first-line therapy. The median time on carfilzomib treatment was 3.3 months and in the bortezomib-treated cohort, subjects with relapsed or refractory disease after a median of 3 prior therapeutic treatments were enrolled. The primary endpoint was ORR.

The IRC-assessed ORR for the bortezomib-treated cohort was 16.1% (95% CI: 5.5% to 33.7%). In the Bortezomib-naïve cohort treated with 20 mg/m^2, the IRC-assessed ORR was 39.6% (95% CI: 26.5% to 54%).In the Bortezomib-naïve cohort treated with 20/27 mg/m^2, the IRC-assessed ORR was 53.0% (95% CI: 40.3% to 65.4%) and the CBR was 65.2% (95% CI: 52.4% to 76.5%).

Study PX-171-006

This was a phase 1b, open-label, multicentre, dose-escalation study evaluated the combination of carfilzomib (15 to 20/27 mg/m^2) in combination with lenalidomide (10 to 25 mg) and low-dose dexamethasone (40 mg) in subjects with relapsed MM, 1 to 3 prior lines which may have included bortezomib, lenalidomide and/or thalidomide. The primary objective was to evaluate the safety and maximum tolerated dose (MTD) of CRd.

A total of 58 subjects in the overall response-evaluable population (n = 83) achieved a best response of PR or better, with 34 subjects achieving VGPR or better. The ORR was 69.9% (95% CI: 58.8% to 79.5%) in this population, and included 4 subjects with a CR. The CBR was 77.1% (95% CI: 66.6% to 85.6%) and the DCR was 85.5% (95% CI: 76.1% to 92.3%). The median PFS was 14.6 months (95% CI: 7.9 to 23.7 months) and the median TTP was 14.8 months (95% CI: 9.9 to 23.7 months). The responses were durable with a median DOR of 18.8 months (95% CI: 9.7 to 33.4 months). For the 58 subjects who achieved a response of PR or better, the median TTR was rapid, at 0.95 month (range: 0.5 to 29.9 months).

In the maximum planned dose cohort (MPD), the ORR by Onyx's computational algorithm was 78.4% (95%CI: 64.7% to 88.7%) and 3 of the 4 subjects who achieved CRs in this study were treated in the MPD cohort. The CBR in the MPD cohort was 78.4% (95% CI: 64.7% to 88.7%) and the DCR was 84.3% (95% CI: 71.4% to 93.0%). In subjects refractory to lenalidomide (n=23), the ORR was 69.6% (95% CI: 47.1% to 86.8%); in subjects who were lenalidomide-naïve (n=14), the ORR was 85.7% (95% CI: 57.2% to 98.2%). Median PFS and TTP were each 15.4months (95% CI: 9.9 to 34.1 months) in the MPD cohort. The responses were rapid, with median TTR of 0.95 months. The responses were durable; median DOR was 22.1 months (95% CI: 9.5–38.0) in the MPD group.

A post-hoc subgroup analyses in the MPD group suggested that less heavily pretreated subjects lacking high-risk disease features such as poor cytogenetics, ISS Stages II and III, and serum β-2 microglobulin ≥ 2.5 mg/L did better in terms of ORR, DOR, TTP, and PFS. The subjects who were refractory to lenalidomide (n=23) were comparable to bortezomib-refractory subjects (n=13) in terms of ORR (69.6% vs. 69.2% by Onyx computational algorithm), but had shorter median DOR (10.8 vs. 22.1months), TTP and PFS (7.9 vs. 15.4 months). As expected, the subgroup of subjects with no prior lenalidomide exposure (n=14) had the best outcome, demonstrating an ORR of 85.7% with median PFS that was not estimable at the time of analysis.

Study PX-171-011

Study PX-171-011 (N = 315) was an open-label Phase 3 evaluated Kyprolis monotherapy versus low-dose corticosteroids with optional cyclophosphamide in subjects with relapsed and refractory myeloma (≥ 3 prior therapies). A total of 157 subjects were randomized to the carfilzomib monotherapy arm and 158 subjects were randomized to the control arm. More than half the subjects (52.1%) were above 65 years of age, and 15.6% were ≥ 75 years of age. The median age of subjects was 63.0 years in the carfilzomib arm as compared to 66.0 years in the control arm. The percentage of male subjects was 52.2% in the carfilzomib arm and 60.8% in the control arm.

Overall, the subjects enrolled in this study were heavily pretreated and had received a median of 5 prior regimens (range: 3 to 17); 28.3% of subjects had received > 6 prior regimens (28.7% carfilzomib; 27.8% control). Subjects had received a median of 8 unique antimyeloma drugs. All subjects (100%) had received an alkylator, bortezomib, an IMiD, and a corticosteroid, as required by the protocol, and 75.9% of subjects had received an anthracycline. A total of 66.3% of subjects had prior transplant (68.2% carfilzomib; 64.6% control). A total of 99.7% (314 of 315) of subjects were refractory to their last prior regimen, with 62.5% of subjects refractory to both bortezomib and an IMiD. In any prior regimen, 67.0% of subjects were refractory to bortezomib, and in last prior regimen, 24.4% of subjects were refractory to bortezomib. These prior treatments were balanced in both study arms.

The primary endpoint was Overall Survival. The median OS was 10.2 months (95% CI: 8.4 to 14.4 months) in the carfilzomib arm, *versus* 10.0 months (95% CI: 7.7 to 12.0 months) in the control arm (HR =0.975, 95% CI: 0.760,1.249; p=0.4172). The median OS follow-up was 27.8 months (95% CI: 24.6 to 33.7 months) and 29.8 months (95% CI: 24.3 to 33.6 months), respectively.

PX-171-003 – Part 2 (A1)

PX-171-003 – Part 2 (A1) enrolled subjects with relapsed and refractory myeloma who had received at least 2 prior therapies and were previously treated with both bortezomib and either of 2 IMiDs (thalidomide or lenalidomide). Ptients received carfilzomib monotherapyat 20/27 mg/m^2.

Two hundred sixty-six (266) subjects enrolled in the study. The median age was 63.0 years (range: 37.0 to 87.0 years); both genders were well represented; 71.4%were White, and 19.9% Black subjects. Subjects were heavily pretreated, with a median of 5 prior treatment regimens (range: 1 to 20); 81.6% had received ≥ 4 regimens, and 74.4% had previously received an ASCT. All subjects (100%) had been exposed to an IMiD (93.6% had received lenalidomide; 74.8% had received thalidomide), and 99.6% had received bortezomib (including 49.6% in their last prior regimen). Of note, 94.7% of subjects had disease refractory to their most recent multiple myeloma treatment, with 83.1%, 72.9%, and 44.4% of subjects refractory in any prior regimen to lenalidomide, bortezomib and thalidomide, respectively. The primary endpoint was ORR.

The IRC-assessed ORR on study was 22.9% (95% CI: 18.0% to 28.5%). Response rates were also assessed by investigator and Onyx's computational algorithm: ORR was 22.6% by investigator and 23.3% by Onyx's computational algorithm. The majority of responses were durable (lasting ≥ 6 months). Of the responders with PR or better, 62.0% of the subjects maintained their response for at least 6 months and 27.1% of the subjects maintained their response for over 12 months, per the corresponding Kaplan-Meier estimate of event-free rate at each time point. The median DOR was 7.8 months (95% CI: 5.6 to 9.2 months) for the responses of PR or better. The median PFS was 3.7 months (95% CI: 2.8 to 4.6 months), and the median TTP estimated by the Kaplan-Meier method was 3.9 months (95% CI: 3.0 to 4.8 months). The median OS for was 15.4 months (95% CI: 12.4 to 19.2 months); the median OS follow-up was 38.5 months.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of Kyprolis was evaluated in a randomised, open-label, multicentre study of 792 patients with relapsed multiple myeloma, which evaluated the combination of Kyprolis with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone, randomised 1:1 (SmPC, section 5.1).

The disease status and other baseline characteristics were well balanced between the two arms, including age (64 years, range 31 91 years), gender (56% male), ECOG performance status (48% with performance status 1), high risk genetic mutations, consisting of the genetic subtypes t(4;14), t(14;16), or deletion 17p in ≥ 60% of plasma cells (13%), unknown risk genetic mutations, which included subjects with results not collected or not analysed (47%), and baseline ISS stage III disease (20%). Subjects had received 1 to 3 prior lines of therapy (median of 2), including prior treatment with bortezomib (66%), thalidomide (44%) and lenalidomide (20%) (SmPC, section 5.1).

Subjects were required to have relapsed or progressed on or after at least 1, but no more than 3, prior multiple myeloma therapies. The study did not restrict the types of prior therapies a subject may have received (including a prior alkylator and/or transplant), and allowed enrollment of subjects who may have received bortezomib (but who did not progress during treatment) and subjects who may have received lenalidomide or dexamethasone (but did not progress during the first 3 months of therapy, or at any time on therapy if it was the last regimen prior to study entry, or discontinued due to intolerance). Therefore, purely refractory to bortezomib and/or lenalidomide were not allowed.

Overall, baseline characteristics were evenly balanced between groups.

Efficacy data and additional analyses

Results from the interim analysis on PFS have shown that patients in the CRd arm had a significantly longer PFS than the Rd arm (HR = 0.69 [95% CI: 0.57, 0.83]). The gain of 8.7 months (26.3 months in the CRd

arm versus 17.6 months in the control group) in PFS is considered clinically significant. The sensitivity analyses were overall consistent among different subgroups and confirmed the reliability of the main outcome, with HR quite similar among them.

During the initial evaluation, the CHMP raised a major objection about the indication needing to be further discussed, with reference to subjects who have progressed while on bortezomib or Rd therapy who were excluded from the pivotal study. For patients "refractory to bortezomib" (they did not progress during treatment) in the pivotal study (15% of the whole study population) medians PFS was 22.3 months versus 19.4 months in CRd and Rd arms respectively (HR 0.799; 95%CI:0.492-1.297). Overall response rate was 80% and 60.3% in CRd and Rd arms respectively. For patients "refractory to lenalidomide" (they did not progress during the first 3 months of therapy, or at any time on therapy if it was the last regimen prior to study entry, or discontinued due to intolerance) in the pivotal study (19% of the whole study population) medians PFS was 11.3 months versus 9 months in CRd and Rd arms respectively (HR 0.637; 95%CI:0.333-1.219). ORR was 69% and 25% in CRd and Rd arms respectively. Data in patients double-refractory to lenalidomide and dexamethasone in the same regimen were pretty similar to those obtained in the subset of "refractory to lenalidomide". In the light of these results, there could be a proportion of patients within the applicant's definition of refractory disease (nonresponsive to any regimen; progression during any regimen; or progression within 60 days of completion of any regimen), who might obtain benefit from treatment with the combination of carfilzomib, lenalidomide and dexamethasone. Therefore it does not seem reasonable to exclude the refractory population from the indication. Section 5.1 of the SmPC reflects that the pivotal study did not evaluate the benefit/risk ratio in the broader refractory population.

The assessment of proportional hazards assumption for treatment over time, revealed the lack of benefit beyond the 18 months, which reflects the duration of the treatment. Treatment with Kyprolis combined with lenalidomide and dexamethasone for longer than 18 cycles should be based on an individual benefit risk assessment, as the data on the tolerability and toxicity of carfilzomib beyond 18 cycles are limited (SmPC, section 4.2).

The main secondary endpoint, OS, did not cross the prespecified early stopping boundary for the interim analysis, even though the result points out a clear positive trend in favour of CRd (HR = 0.79 [95% CI: 0.63, 0.99]; log-rank p = 0.0182) with more deaths in the control arm at the time of the cut-off (143 [36.1%] vs 162 [40.9%]). The median OS was not reached on either arm and analysis at 12, 18, 24, 30, and 36 months reveal a higher survival rate for KRd subjects at every time point. Notably, the Kaplan-Meier (K-M) event-free rate at 24 months was 73.3% (95% CI: 68.6%–77.5%) in the KRd arm and 65.0% (95% CI: 59.9%–69.5%) in the Rd arm. The curves are separated from the beginning and during the time. This interim analysis was carried out with 60% of final number of events required. Despite the fact that CRd is pointing out a clear trend in OS benefit, the data are still immature. The Applicant was recommended to submit the OS mature data when available.

Subgroup analyses of OS do not reveal any unexpected results, considering the limited sample sized of some subsets.

The use of the combination of CRd provided a positive benefit in terms of ORR (CRd 87.1%; Rd 66.7%; p < 0.0001), duration of response (CRd 28.6 months; Rd 21.2 months), and QoL. More patients in the CRd arm had a Stringent Complete Response (14% vs 3%), CR (18% vs 5%) and VGPR (38% vs 31%). ORR determined by investigators and ORCA was consistent with that observed by the IRC. The time to progression was also positive for the experimental arm (31.4 months [95% CI: 26.4, NE]) vs (19.4 months [95% CI: 16.6, 23.2] CRd vs Rd respectively).

In addition, Studies PX-171-006 and PX-171-004 provided supportive evidence of efficacy in the relapsed setting, one evaluated the KRd regimen (PX-171-006) and the other evaluated Kyprolis monotherapy (PX-171-004). Only the Phase 1b KRd dose-finding study PX-171-006, which enrolled a cohort of subjects (N = 52, maximum planned dose [MPD] cohort) who received the same KRd combination dose as in PX-171-009, is to some extend comparable to the pivotal one. These studies enrolled subjects that were more heavily pretreated than PX-171-009. A higher proportion of subjects in the 20/27 mg/m^2 cohorts in both studies were lenalidomide-exposed (70.0–73.1%) or refractory (41.4–44.2%) than in the KRd arm of PX-171-009 (19.9% lenalidomide-exposed, 71% lenalidomide refractory). Per study design more than 95% of subjects in PX-171-004 were bortezomib-naïve compared to 34.2% in PX-171-009.

Additional clinical experience has been generated with Kyprolis monotherapy in patients with relapsed and refractory multiple myeloma. Study PX-171-011 was an open-label randomised phase 3 study (N = 315; exposure to ≥ 3 prior therapies required). Patients enrolled to study PX 171-011 were more heavily pre-treated with lower organ and marrow function as compared to those enrolled in study PX 171-009. PX 171-011 evaluated Kyprolis monotherapy versus a control arm (corticosteroids and cyclophosphamide). The study did not meet its primary efficacy endpoint of demonstrating superiority of Kyprolis monotherapy over the active control arm in overall survival (HR = 0.975 [95% CI: 0.760-1.249]. PX 171-003A1 was a single-arm phase 2 study (N = 266; exposure to ≥ 2 prior therapies required), which met its primary efficacy endpoint of IRC-assessed ORR (22.9%). Both studies showed that carfilzomib has antitumor activity in last line.

2.5.4. Conclusions on the clinical efficacy

The addition of carfilzomib to Rd resulted in a clinically meaningful and statistically significant improvement in the primary endpoint of PFS compared to Rd with a positive trend in overall survival and high response rates in adult patients with multiple myeloma who have received at least one prior therapy.

2.6. Clinical safety

Data from the 11 completed clinical studies (N = 2123) were pooled and analysed as part of the integrated safety database and forms the primary basis for evaluation of carfilzomib safety in this application (Table 39).

Table 36. Studies Contributing to Overall Carfilzomib Safety Profile (cut-off date: 30 June 2014)

Population	Study	No. of Subjects Treated
Primary (Carfilzomib/Lenalidomide/Dexamethasone [CRd]) Combination Therapy Population in Subjects with Multiple Myeloma		**865**
Carfilzomib 20/27 mg/m^2	***PX-171-009***	392[a]
	PX-171-006	52
Carfilzomib < 20/27 mg/m^2	PX-171-006	32
No carfilzomib (Rd alone)	PX-171-009 Control Arm	389[a]
Monotherapy Population in Subjects with Multiple Myeloma		941
Carfilzomib 20/27 mg/m^2	***PX-171-011***	157[b]
	PX-171-003 – Part 2 (A1)	266
	PX-171-004 – Part 2	70
	2011-002	105
	Total	**598**
Carfilzomib < 20/27 mg/m^2	PX-171-003 – Part 1 (A0)	46
	PX-171-004 – Part 1	35
	PX-171-004 – Part 2	59
	PX-171-005	50
	Total	190
No carfilzomib (corticosteroids and optional cyclophosphamide only)	PX-171-011 Control Arm	153[b]
Supportive Studies Population		**317**
Phase 1 Studies in Subjects with Multiple Myeloma and Other Hematologic Malignancies	PX-171-001	29
	PX-171-002 – Part 1	37
	PX-171-002 – Part 2	11
	Total	77
Carfilzomib and Dexamethasone Combination Therapy in Subjects with Multiple Myeloma	2011-002	223
Studies in Subjects with Solid Tumors	PX-171-008	17
Total Safety Population		**2123**

In this report a treatment-emergent adverse event ([TEAE] henceforth referred to as an AE) is defined as an event that began in the interval between the first dose of study treatment and 30 days after the last dose, or a pre-existing condition that worsened in severity during study treatment**.** However, due to differences in reporting criteria for grade changes of the *same* AE term between studies (some studies only required the highest grade to be reported while others required all grade changes to be reported separately), the most conservative approach was taken for this analysis**.** All Grade 2 or higher AEs were considered to be TEAEs even if they had a start date *before* the treatment start date.

Adverse drug reactions (ADRs) were identified using the threshold criteria defined below for subject incidence differences between study arms in the 2 randomized clinical studies (PX-171-009 and PX-171-011).

1. Any grade AE with a subject incidence ≥ 5% and difference ≥ 2% between study arms

2. ≥ Grade 3 AEs with a subject incidence ≥ 2% and difference ≥ 1% between study arms

3. Serious AEs with a subject incidence ≥ 1% and difference ≥ 1% between study arms

On-study deaths, defined as death that occurred within 30 days from the last dose of treatment (or deaths due to AEs that started within 30 days from last dose).

Patient exposure

The median exposure of carfilzomib per administration in PX-171-009 was 26.84 mg/m^2 (26.83 mg/m^2 in pooled CRd safety population), and 26.42 mg/m^2 in PX-171-011 (24.00 mg/m^2 in pooled monotherapy population). The relative dose intensity was high, with a median of > 90%, for all study treatment drugs in both Phase 3 studies.

The median duration of exposure in PX-171-009 was 70.3 weeks, in contrast to 16.3 weeks in PX-171-011 which enrolled subjects with more advanced disease.

Primary Analysis Population – Primary CRd Combination Therapy Population

The Primary CRd Combination Therapy Population comprises subjects who received carfilzomib in combination with lenalidomide and dexamethasone. All subjects in this group have relapsed multiple myeloma and have received from 1 to 3 prior lines of therapy. Information regarding specific study subjects that are included in the primary analysis population is as follows:

- Carfilzomib 20/27 mg/m^2 (N = 444, referred to as the pooled CRd cohort): includes 392 subjects from Phase 3 Study PX-171-009 randomized to receive CRd. Additionally, 52 subjects from Cohorts 6 and 7 of Phase 1b study PX-171-006 are also included, all of whom were to receive the same dose of CRd as in PX 171-009.
  - Data from the 392 subjects enrolled in Phase 3 study PX 171-009 (referred to as the CRd arm) were also presented separately as well in order to facilitate direct comparison within the randomized study.

  - Carfilzomib less than 20/27 mg/m^2 (N = 32): includes subjects from Cohorts 1 to 5 of Phase 1b study PX-171-006 who received carfilzomib 15 to 20 mg/m^2, lenalidomide 10 mg to 25 mg and dexamethasone 40 mg.

- Control arm (N = 389, referred to as Rd arm): includes subjects randomized to receive lenalidomide and dexamethasone but not carfilzomib in the Phase 3 Study PX-171-009. This data was provided separately for comparison and is not part of the pooled analysis.

The disposition of the subjects who initiated treatment with 20/27 mg/m^2 carfilzomib, as of the data cut-off date (16 June 2014), is shown in Table 40.

Table 37. Summary of Disposition in the Primary CRd

	Number of Subjects (%)		
	Pooled Carfilzomib CRd 20/27 mg/m^2 from 2 Studies[a] (N = 444)	PX-171-009	
		CRd Arm 20/27 mg/m^2 (N = 392)	Control Arm (Rd) (N = 389)
Number of subjects who received study treatment	444 (100)	392 (100)	389 (100)
Number of subjects continuing treatment	120 (27.0)	118 (30.1)	86 (22.1)
Number of subjects who discontinued treatment	324 (73.0)	274 (69.9)	303 (77.9)
Primary reason for study treatment discontinuation			
Disease progression	180 (40.5)	156 (39.8)	195 (50.1)
Adverse event	72 (16.2)	60 (15.3)	69 (17.7)
Disease progression reported as an adverse event	2 (0.5)	0 (0)	0 (0)
Withdrew consent	8 (1.8)	7 (1.8)	11 (2.8)
Protocol violation	2 (0.5)	2 (0.5)	1 (0.3)
Other[b]	62 (14.0)	49 (12.5)	27 (6.9)

CRd = carfilzomib/lenalidomide/dexamethasone; Rd = lenalidomide/dexamethasone.

a. Includes all subjects receiving carfilzomib in combination with Rd at 20/27 mg/m^2 in PX-171-006 and PX-171-009.

b. Other category includes the following reasons from PX-171-009 and PX-171-006: subject decision/too frequent study visits, but agree to follow-up; completed therapy/good response to study treatment/transplant/new therapy; multiple AEs/poor quality of life; achievement of maximal response; decision to undergo consolidation therapy with autologous stem cell transplant; decision to withdraw following completion of 17 cycles; decision to undergo maintenance therapy; inadequate transportation to trial site; noncompliance, and subject's choice.

The treatment duration in the Safety Population is reported in Table 41.

Table 38. Summary of Exposure to Study Treatments in the Primary CRd Combination Therapy Population (Safety Population)

	Carfilzomib		Lenalidomide			Dexamethasone		
	Pooled Carfilzomib CRd 20/27 mg/m^2 from 2 Studies[a] (N = 444)	PX-171-009 CRd Arm 20/27 mg/m^2 (N = 392)	Pooled Carfilzomib CRd 20/27 mg/m^2 from 2 Studies[a] (N =444)	PX-171-009 CRd Arm 20/27 mg/m^2 (N =392)	PX-171-009 Rd (N = 389)	Pooled Carfilzomib CRd 20/27 mg/m^2 from 2 Studies[a] (N = 444)	PX-171-009 CRd Arm 20/27 mg/m^2 (N = 392)	PX-171-009 Rd (N = 389)
Treatment Duration (weeks)								
n	444	392	443	391	388	444	392	389
Median	70.29	70.29	78.86	85.00	56.21	72.21	79.36	47.86
Min, Max	0.1, 180.4	0.1, 91.4	0.1, 184.0	0.1, 184.0	0.4, 200.7	0.1, 181.3	0.1, 177.1	0.1, 200.1
Dose Escalated to 27 mg/m^2 (n [%])[b]	430 (96.8)	382 (97.4%)	–	–	–	–	–	–
Number of Cycles Started								
Median	18.0	18.0	20.0	21.0	14.0	18.0	20.0	12.0
Min, Max	1, 45	1, 18	1, 46	1, 46	1, 51	1, 45	1, 45	1, 51
Number of Subjects on Treatment in Each Cycle (n [%])								
Cycle 6	374 (84.2)	339 (86.5)	375 (84.5)	343 (87.5)	308 (79.2)	370 (83.3)	338 (86.2)	299 (76.9)
Cycle 12	298 (67.1)	279 (71.2)	288 (64.9)	270 (68.9)	225 (57.8)	284 (64.0)	267 (68.1)	209 (53.7)
Cycle 18	253 (57.0)	239 (61.0)	243 (54.7)	230 (58.7)	164 (42.2)	238 (53.6)	226 (57.7)	151 (38.8)
Cycle 24	11 (2.5)	0	187 (42.1)	177 (45.2)	123 (31.6)	173 (39.0)	164 (41.8)	113 (29.0)
Average dose per administration[c]								
Median	26.83	26.84	25.00	25.00	25.00	40.00	40.00	40.00
Min, Max	15.3, 27.0	15.3, 26.9	6.3, 25.1	6.3, 25.1	6.6, 25.0	4.0, 42.0	13.9, 42.0	13.6, 53.3
Relative Dose Intensity (%)								
Median	95.85	96.22	88.93	91.03	91.90	92.62	94.54	95.39
Min, Max	35.2, 135.0	35.2, 112.6	13.3, 103.7	19.4, 101.3	19.3, 101.2	10.0, 103.3	30.7, 103.3	32.1, 112.0

CRd = carfilzomib/lenalidomide/dexamethasone arm; Max = maximum; Min = minimum; Rd = lenalidomide/dexamethasone.
Notes: Relative dose intensity (%) = 100 × actual dose intensity/planned dose intensity. Actual (planned) dose intensity is actual (planned) cumulative dose (mg/m^2) divided by actual (planned) treatment duration (weeks).
[a] Includes all subjects receiving carfilzomib in combination with Rd at 20/27 mg/m^2 in PX-171-006 and PX-171-009.
[b] Of the 382 subjects who escalated to 27 mg/m^2 in PX-171-009, 371 subjects escalated to 27 mg/m^2 per protocol on C1D8.
[c] Doses were in mg/m^2 for carfilzomib and in mg for lenalidomide and dexamethasone.

Monotherapy Population

The Monotherapy Population includes subjects with relapsed and/or refractory myeloma who received carfilzomib as a single agent with no other combination antimyeloma drug. Information regarding specific study subjects that are included in the Monotherapy Population is as follows:

- Carfilzomib monotherapy (all dose levels, N = 788; also referred to as all pooled carfilzomib monotherapy cohort): includes 157 subjects enrolled in the Phase 3 Study PX-171-011. The remaining 631 subjects are from five Phase 2 studies (PX-171-003 – Part 1 [A0], PX-171-003 – Part 2 [A1], PX-171-004 [Parts 1 and 2], PX-171-005, and 2011-002). Data from these subjects have been integrated and presented together as well as further subdivided by intended dose of carfilzomib into the following subpopulations.
  - Carfilzomib 20/27 mg/m^2 (N = 598): includes 157 subjects from the Phase 3 Study PX-171-011 randomized to receive carfilzomib. Additionally, subjects from the Phase 2 Study PX-171-003 – Part 2 (A1), the 20/27 mg/m^2 cohort of Phase 2 study PX-171-004 – Part 2, and subjects in 2011-002) who received carfilzomib monotherapy are also included.
    - Data from the 157 subjects enrolled into Study PX 171-011 (referred to as the carfilzomib arm) are further presented separately as well in order to facilitate direct comparison within the randomized study.
- Carfilzomib less than 20/27 mg/m^2 (N = 190): includes subjects from Phase 2 Studies PX-171-003 – Part 1 (A0), PX-171-004 – Part 1, and PX-171-005, and the 20 mg/m^2 cohort of Phase 2 study PX-171-004 – Part 2.

- In PX-171-005, carfilzomib was escalated from a dose of 15 mg/m^2 to 20 mg/m^2 (Cycle 2 Day 1) and then to 27 mg/m^2 (Cycle 3 Day 1). Although a total of 27 of 50 enrolled subjects escalated their carfilzomib dose to 27 mg/m^2 during the study period, the entire enrolled population of 50 subjects is considered under the "< 20/27 mg/m^2" grouping in this SCS because the Cycle 1 dosing was 15 mg/m^2 for all subjects. Twenty-eight subjects in PX-171-005 who received dexamethasone 40 mg/week at varying time points after Cycle 2 are also included; this small number is not expected to impact the assessment of safety of this dose level.

- Control arm (N = 153): includes subjects randomized to receive corticosteroids with optional cyclophosphamide but not carfilzomib in the Phase 3 Study PX-171-011. This data is provided separately for comparison and is not part of the pooled analysis.

Of the 788 subjects in the all pooled carfilzomib monotherapy cohort who initiated treatment with carfilzomib (any dose), 0.8% are currently being treated, and 99.2% have discontinued treatment: 51.8% due to PD and 15.6% due to an AE. In the carfilzomib and control arms in PX-171-011, a total of 74.5% and 65.4%, respectively, discontinued treatment due to PD and 14.6% and 20.3% discontinued treatment due to an AE.

For subjects receiving carfilzomib in the all pooled carfilzomib monotherapy cohort, the median duration of carfilzomib treatment was 14.9 weeks (range: 0.1 to 138.4 weeks) with a median of 4 cycles initiated. The number of subjects who dose escalated to 27 mg/m^2 in the all pooled carfilzomib monotherapy cohort was lower than the carfilzomib arm of PX-171-011 (70.2% *versus* 95.5%, respectively). This difference was primarily driven by a different dose escalation schedule in PX-171-011 where subjects escalated to 27 mg/m^2 on C1D8, while in most earlier studies, dose escalation occurred on C2D1. Consequently, in Study PX-171-003 – Part 2 (A1), which makes up a third of the subjects in the all pooled carfilzomib monotherapy cohort, 19.2% of subjects discontinued in Cycle 1 prior to escalating to 27 mg/m^2.

In PX-171-011, the median duration of treatment with carfilzomib was 16.29 weeks, with a median of 5.0 cycles initiated. In the control arm of that study, the median duration of treatment with corticosteroids and cyclophosphamide were 10.71 and 10.14 weeks, respectively, with a median number of 3.0 cycles of each initiated. The median relative dose intensity of carfilzomib in the all pooled carfilzomib monotherapy cohort was 95.2% (100% in the carfilzomib arm of PX-171-011).

Adverse events

An overview of AEs in PX-171-009 study and in the pooled CRd arm is presented in Table 42.

Table 39. Summary of Adverse Events In Subjects in the Primary CRd Combination Therapy Population (Safety Population)

	Number of Subjects (%)		
	Pooled Carfilzomib CRd 20/27 mg/m^2 from 2 Studies[a] (N = 444)	PX-171-009	
		CRd Arm 20/27 mg/m^2 (N =392)	Control Arm (Rd) (N = 389)
Subjects with at least 1			
AE	432 (97.3)	380 (96.9)	380 (97.7)
Treatment-related AE	383 (86.3)	332 (84.7)	329 (84.6)
Grade 3 or higher AE	377 (84.9)	328 (83.7)	316 (81.2)
AE leading to discontinuation of study drug	123 (27.7)	102 (26.0)	98 (25.2)
Disease progression AE leading to discontinuation	3 (0.7)	0	0
Serious AE	263 (59.2)	235 (59.9)	210 (54.0)
Grade 5 AE	38 (8.6)	36 (9.2)	36 (9.3)
Disease progression AE	2 (0.5)	1 (0.3)	7 (1.8)

AE = adverse event; CRd = carfilzomib/lenalidomide/dexamethasone; CRF = case report form; Rd = lenalidomide/dexamethasone.
Note: Adverse events are those that occurred or worsened between the first dose of study drug and 30 days after the last dose. Treatment-related AEs are AEs considered related to at least 1 study drug by the investigator, and includes AEs with missing relationship on the CRF. Disease progression AEs are events with the preferred term of disease progression," "multiple myeloma," or "plasmacytoma."
[a] Includes all subjects receiving carfilzomib in combination with Rd at 20/27 mg/m^2 in PX-171-006 and PX-171-009.

In the monotherapy population, AEs were reported in 98.1% of subjects in the carfilzomib arm and in 93.5% in control arm (Study PX-171-011). At least 1 AE assessed by the investigator as related to study treatment was reported in 61.1% and 49.7% of subjects in the carfilzomib and control arms, respectively. The subject incidence rate of AEs having a severity of Grade 3 or higher in the carfilzomib and control arms in PX-171-011 were 75.2% and 71.2%, respectively. The subject incidence rate of SAEs were higher in the carfilzomib arm than in the controlarm in PX-171-011 (58.6% *versus* 51.0%). Overall, 18.5% of the subjects in the carfilzomib arm in PX-171-011 died while on study treatment or within 30 days of their last dose of study treatment, compared with 22.2% in the control arm. Since the protocol required all deaths due to PD within 30 days of last dose to be reported as an AE, this includes 8.9% and 9.2% of subjects in the 2 arms, respectively, who died due to PD. Rates of study drug discontinuation due to an AE were lower in the carfilzomib arm in PX-171-011 than in the control arm (14.6% *versus* 20.3%).

A summary of the Common Adverse Events occurred in the Primary CRd Combination Therapy Population is reported in Table 43.

Table 40. Adverse Events Occurring in ≥ 10%* of Subjects in Any Cohort in the Primary CRd Combination Therapy Population by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Number of Subjects (%)		
	Pooled Carfilzomib CRd 20/27 mg/m^2 from2 Studies[a] (N = 444)	PX-171-009	
		CRd Arm 20/27 mg/m^2 (N = 392)	Control Arm (Rd) (N = 389)
Subjects with at least 1 AE	432 (97.3)	380 (96.9)	380 (97.7)
Infections and Infestations	348 (78.4%)	310 (79.1)	270 (69.4)
Upper Respiratory Tract Infection	132 (29.7)	112 (28.6)	76 (19.5)
Nasopharyngitis	92 (20.7)	84 (21.4)	63 (16.2)
Bronchitis	77 (17.3)	74 (18.9)	54 (13.9)
Pneumonia	77 (17.3)	68 (17.3)	56 (14.4)
Respiratory Tract Infection	43 (9.7)	43 (11.0)	39 (10.0)
General Disorders and Administration Site Conditions	318 (71.6)	269 (68.6)	242 (62.2)
Fatigue	165 (37.2)	129 (32.9)	120 (30.8)
Pyrexia	135 (30.4)	112 (28.6)	81 (20.8)
Oedema Peripheral	104 (23.4)	85 (21.7)	75 (19.3)
Asthenia	79 (17.8)	73 (18.6)	56 (14.4)
Gastrointestinal Disorders	301 (67.8)	260 (66.3)	220 (56.6)
Diarrhoea	196 (44.1)	166 (42.3)	131 (33.7)
Nausea	96 (21.6)	78 (19.9)	55 (14.1)
Constipation	93 (20.9)	79 (20.2)	67 (17.2)
Vomiting	59 (13.3)	47 (12.0)	32 (8.2)
Blood and Lymphatic System Disorders	284 (64.0)	244 (62.2)	232 (59.6)
Anaemia	186 (41.9)	169 (43.1)	155 (39.8)
Neutropenia	167 (37.6)	148 (37.8)	131 (33.7)
Thrombocytopenia	131 (29.5)	115 (29.3)	89 (22.9)
Musculoskeletal and Connective Tissue Disorders	267 (60.1)	226 (57.7)	216 (55.5)
Muscle Spasms	124 (27.9)	104 (26.5)	82 (21.1)
Back Pain	86 (19.4)	69 (17.6)	80 (20.6)
Arthralgia	62 (14.0)	49 (12.5)	51 (13.1)
Pain in Extremity	59 (13.3)	46 (11.7)	41 (10.5)
Bone Pain	43 (9.7)	40 (10.2)	36 (9.3)
Metabolism and Nutrition Disorders	266 (59.9)	225 (57.4)	175 (45.0)
Hypokalaemia	121 (27.3)	108 (27.6)	52 (13.4)
Hypophosphataemia	72 (16.2)	52 (13.3)	29 (7.5)

Hypocalcaemia	70 (15.8)	63 (16.1)	46 (11.8)
Hyperglycaemia	63 (14.2)	49 (12.5)	38 (9.8)
Decreased Appetite	55 (12.4)	44 (11.2)	35 (9.0)
Hypomagnesaemia	47 (10.6)	36 (9.2)	25 (6.4)
Respiratory, Thoracic and Mediastinal Disorders	258 (58.1)	218 (55.6)	162 (41.6)
Cough	134 (30.2)	113 (28.8)	69 (17.7)
Dyspnoea	96 (21.6)	77 (19.6)	58 (14.9)
Nervous System Disorders	228 (51.4)	188 (48.0)	188 (48.3)
Headache	64 (14.4)	53 (13.5)	31 (8.0)
Dizziness	55 (12.4)	48 (12.2)	44 (11.3)
Skin and Subcutaneous Tissue Disorders	183 (41.2)	151 (38.5)	129 (33.2)
Rash	62 (14.0)	52 (13.3)	60 (15.4)
Vascular Disorders	166 (37.4)	148 (37.8)	98 (25.2)
Hypertension	61 (13.7)	57 (14.5)	29 (7.5)
Investigations[b]	174 (39.2)	144 (36.7)	132 (33.9)
Psychiatric Disorders	158 (35.6)	133 (33.9%)	111 (28.5)
Insomnia	94 (21.2)	77 (19.6)	64 (16.5)
Eye Disorders[b]	119 (26.8)	103 (26.3)	70 (18.0)
Cardiac Disorders[b]	99 (22.3)	85 (21.7)	72 (18.5)
Injury, Poisoning and Procedural Complications[b]	95 (21.4)	77 (19.6)	66 (17.0)
Renal and Urinary Disorders[b]	74 (16.7)	61 (15.6)	53 (13.6)

CRd = carfilzomib/lenalidomide/dexamethasone; Rd = lenalidomide/dexamethasone.
Note: Subjects were counted only once for each preferred term. MedDRA Version 15.1 was used for coding.
* The source table lists all AEs experienced by all subjects including those experienced by < 10%.
a. Includes all subjects receiving carfilzomib 20/27 mg/m^2 (intended dose) given in combination with Rd from studies PX-171-006 and PX-171-009.
b. System organ class terms were reported in ≥ 10% of subjects in any cohort in the Primary CRd Combination Therapy Population, however, preferred terms were not and thus are not listed in the table.

Within the monotherapy population (Study PX-171-011), the 3 most frequently reported AEs in both study arms were anaemia (88% and 75% in the carfilzomib and control arm, respectively), thrombocytopenia (59% and 46%, respectively), and pyrexia (44% and 30%, respectively). Adverse events observed in more subjects in the carfilzomib arm than the control arm (≥ 5% difference) include anaemia, thrombocytopenia, pyrexia, nausea (32% vs 14%), hypertension (23% vs 9%), dyspnoea (23% vs 13%), cough (19% vs 10%), headache (17% vs 6%), URTI (16% vs 3%), acute renal failure (16% vs 6%), vomiting (15% vs 5%), and dizziness (11% vs 3%). Conversely, insomnia (4% vs 18%), constipation (10% vs 20%), and pneumonia (12% vs 20%) were observed in more control arm subjects than carfilzomib arm subjects (≥ 5% difference).

The incidence of Grade 3-4 AEs in the Primary CRd Combination Therapy Population is shown in Table 44.

Table 41. Common ≥ Grade 3 Adverse Events Occurring in ≥ 1%* of Subjects in the Primary CRd Combination Therapy Population (Safety Population)

System Organ Class / Preferred Term	All Adverse Reaction / Frequency	Grade ≥ 3 Adverse Reaction / Frequency	Serious Adverse Reaction / Frequency
Blood and Lymphatic System Disorders			
Anaemia	907 (44.4%)	423 (20.7%)	34 (1.7%)
Thrombocytopenia	647 (31.7%)	406 (19.9%)	29 (1.4%)
Neutropenia	401 (19.6%)	259 (12.7%)	11 (0.5%)
Lymphopenia	228 (11.2%)	176 (8.6%)	–
Leukopenia	178 (8.7%)	71 (3.5%)	2 (< 0.1%)
Febrile neutropenia	38 (1.9%)	32 (1.6%)	28(1.4%)
Thrombotic microangiopathy	2 (< 0.1%)	1 (< 0.1%)	2 (< 0.1%)
Thrombotic thrombocytopenic purpura	1 (< 0.1%)	1 (< 0.1%)	1 (< 0.1%)
Cardiac Disorders			
Cardiac Failure	88 (4.3%)	56 (2.7%)	53 (2.6%)
Tachycardia	75 (3.7%)	3 (0.1%)	1 (< 0.1%)
Palpitations	58 (2.8%)	1 (< 0.1%)	–
Atrial fibrillation	41 (2.0%)	20 (1.0%)	19 (0.9%)
Myocardial infarction	14 (0.7%)	12 (0.6%)	11 (0.5%)
Cardiac arrest	11 (0.5%)	11 (0.5%)	11 (0.5%)
Myocardial ischaemia	6 (0.3%)	4 (0.2%)	4 (0.2%)
Eye Disorders			
Vision blurred	100 (4.9%)	2 (< 0.1%)	–
Cataract	58 (2.8%)	18 (0.9%)	2 (< 0.1%)
Gastrointestinal Disorders			
Diarrhoea	676 (33.1%)	53 (2.6%)	18 (0.9%)
Nausea	595 (29.1%)	20 (1.0%)	4 (0.2%)
Constipation	360 (17.6%)	5 (0.2%)	1 (< 0.1%)
Vomiting	335 (16.4%)	15 (0.7%)	8 (0.4%)
Abdominal pain	212 (10.4%)	24 (1.2%)	12 (0.6%)
Dyspepsia	123 (6.0%)	5 (0.2%)	–
Toothache	49 (2.4%)	2 (< 0.1%)	–

A pooled dataset of all company-sponsored clinical studies with carfilzomib was used to determine the frequencies of all adverse drug reactions (ADRs).

Table 42. Carfilzomib Adverse Drug Reactions (Pooled Safety Population)

System Organ Class / Preferred Term	All Adverse Reaction / Frequency	Grade ≥ 3 Adverse Reaction / Frequency	Serious Adverse Reaction / Frequency
Blood and Lymphatic System Disorders			
Anaemia	907 (44.4%)	423 (20.7%)	34 (1.7%)
Thrombocytopenia	647 (31.7%)	406 (19.9%)	29 (1.4%)
Neutropenia	401 (19.6%)	259 (12.7%)	11 (0.5%)
Lymphopenia	228 (11.2%)	176 (8.6%)	–
Leukopenia	178 (8.7%)	71 (3.5%)	2 (< 0.1%)
Febrile neutropenia	38 (1.9%)	32 (1.6%)	28(1.4%)
Thrombotic microangiopathy	2 (< 0.1%)	1 (< 0.1%)	2 (< 0.1%)
Thrombotic thrombocytopenic purpura	1 (< 0.1%)	1 (< 0.1%)	1 (< 0.1%)
Cardiac Disorders			
Cardiac Failure	88 (4.3%)	56 (2.7%)	53 (2.6%)
Tachycardia	75 (3.7%)	3 (0.1%)	1 (< 0.1%)
Palpitations	58 (2.8%)	1 (< 0.1%)	–
Atrial fibrillation	41 (2.0%)	20 (1.0%)	19 (0.9%)
Myocardial infarction	14 (0.7%)	12 (0.6%)	11 (0.5%)
Cardiac arrest	11 (0.5%)	11 (0.5%)	11 (0.5%)
Myocardial ischaemia	6 (0.3%)	4 (0.2%)	4 (0.2%)
Eye Disorders			
Vision blurred	100 (4.9%)	2 (< 0.1%)	–
Cataract	58 (2.8%)	18 (0.9%)	2 (< 0.1%)
Gastrointestinal Disorders			
Diarrhoea	676 (33.1%)	53 (2.6%)	18 (0.9%)
Nausea	595 (29.1%)	20 (1.0%)	4 (0.2%)
Constipation	360 (17.6%)	5 (0.2%)	1 (< 0.1%)
Vomiting	335 (16.4%)	15 (0.7%)	8 (0.4%)
Abdominal pain	212 (10.4%)	24 (1.2%)	12 (0.6%)
Dyspepsia	123 (6.0%)	5 (0.2%)	–
Toothache	49 (2.4%)	2 (< 0.1%)	–

System Organ Class / Preferred Term	All Adverse Reaction / Frequency	Grade ≥ 3 Adverse Reaction / Frequency	Serious Adverse Reaction / Frequency
General Disorders and Administration Site Conditions			
Fatigue	825 (40.4%)	119 (5.8%)	3 (0.1%)
Pyrexia	576 (28.2%)	36 (1.8%)	61 (3.0%)
Oedema peripheral	445 (21.8%)	14 (0.7%)	2 (< 0.1%)
Asthenia	283 (13.8%)	42 (2.1%)	4 (0.2%)
Chills	186 (9.1%)	2 (< 0.1%)	2 (< 0.1%)
Pain	126 (6.2%)	23 (1.1%)	10 (0.5%)
Chest pain	91 (4.5%)	7 (0.3%)	7 (0.3%)
Infusion site reactions	64 (3.1%)	2 (< 0.1%)	–
Multi-organ failure	8 (0.4%)	8 (0.4%)	7 (0.3%)
Hepatobiliary Disorders			
Hyperbilirubinaemia	40 (2.0%)	12 (0.6%)	–
Cholestasis	6 (0.3%)	1 (< 0.1%)	–
Hepatic failure	4 (0.2%)	3 (0.1%)	3 (0.1%)
Immune System Disorders			
Drug hypersensitivity	16 (0.8%)	3 (0.1%)	1 (< 0.1%)
Infections and Infestations			
Respiratory tract infection	540 (26.4%)	65 (3.2%)	43 (2.1%)
Pneumonia	272 (13.3%)	199 (9.7%)	197 (9.6%)
Nasopharyngitis	223 (10.9%)	1 (< 0.1%)	1 (< 0.1%)
Bronchitis	191 (9.3%)	26 (1.3%)	22 (1.1%)
Urinary tract infection	143 (7.0%)	29 (1.4%)	19 (0.9%)
Influenza	70 (3.4%)	7 (0.3%)	10 (0.5%)
Viral infection	39 (1.9%)	–	2 (< 0.1%)
Sepsis	35 (1.7%)	33 (1.6%)	29 (1.4%)

System Organ Class / Preferred Term	All Adverse Reaction / Frequency	Grade ≥ 3 Adverse Reaction / Frequency	Serious Adverse Reaction / Frequency
Investigations			
Blood creatinine increased	294 (14.4%)	39 (1.9%)	10 (0.5%)
Platelet count decreased	125 (6.1%)	61 (3.0%)	4 (0.2%)
Aspartate aminotransferase increased	120 (5.9%)	32 (1.6%)	2 (< 0.1%)
Alanine aminotransferase increased	116 (5.7%)	43 (2.1%)	2 (< 0.1%)
Blood uric acid increased	61 (3.0%)	18 (0.9%)	–
Lymphocyte count decreased	60 (2.9%)	40 (2.0%)	–
Creatinine renal clearance decreased	54 (2.6%)	12 (0.6%)	–
C-reactive protein increased	29 (1.4%)	6 (0.3%)	–
Gamma-glutamyltransferase increased	23 (1.1%)	11 (0.5%)	–
Ejection fraction decreased	16 (0.8%)	6 (0.3%)	–
Metabolism and Nutrition Disorders			
Hypokalaemia	300 (14.7%)	82 (4.0%)	4 (0.2%)
Decreased appetite	279 (13.6%)	8 (0.4%)	–
Hyperglycaemia	260 (12.7%)	86 (4.2%)	8 (0.4%)
Hypocalcaemia	177 (8.7%)	43 (2.1%)	3 (0.1%)
Hypophosphataemia	174 (8.5%)	99 (4.8%)	1 (< 0.1%)
Hypomagnesaemia	168 (8.2%)	9 (0.4%)	–
Hyponatraemia	134 (6.6%)	78 (3.8%)	5 (0.2%)
Hypercalcaemia	124 (6.1%)	45 (2.2%)	30 (1.5%)
Hyperuricaemia	120 (5.9%)	28 (1.4%)	–
Hyperkalaemia	94 (4.6%)	28 (1.4%)	3 (0.1%)
Hypoalbuminaemia	86 (4.2%)	31 (1.5%)	1 (< 0.1%)
Dehydration	73 (3.6%)	16 (0.8%)	11 (0.5%)
Tumour lysis syndrome	14 (0.7%)	12 (0.6%)	11 (0.5%)

System Organ Class / Preferred Term	All Adverse Reaction / Frequency	Grade ≥ 3 Adverse Reaction / Frequency	Serious Adverse Reaction / Frequency
Musculoskeletal and Connective Tissue Disorders			
Back pain	386 (18.9%)	52 (2.5%)	18 (0.9%)
Muscle spasms	338 (16.5%)	9 (0.4%)	–
Arthralgia	276 (13.5%)	18 (0.9%)	3 (0.1%)
Pain in extremity	249 (12.2%)	18 (0.9%)	3 (0.1%)
Musculoskeletal chest pain	176 (8.6%)	8 (0.4%)	3 (0.1%)
Musculoskeletal pain	175 (8.6%)	26 (1.3%)	3 (0.1%)
Bone pain	161 (7.9%)	28 (1.4%)	9 (0.4%)
Muscular weakness	134 (6.6%)	26 (1.3%)	5 (0.2%)
Myalgia	113 (5.5%)	6 (0.3%)	1 (< 0.1%)
Nervous System Disorders			
Headache	402 (19.7%)	21 (1.0%)	6 (0.3%)
Peripheral neuropathy	256 (12.5%)	26 (1.3%)	2 (< 0.1%)
Dizziness	221 (10.8%)	10 (0.5%)	1 (< 0.1%)
Paraesthesia	167 (8.2%)	4 (0.2%)	1 (< 0.1%)
Hypoaesthesia	129 (6.3%)	3 (0.1%)	–
Cerebrovascular accident	8 (0.4%)	8 (0.4%)	7 (0.3%)
Posterior reversible encephalopathy syndrome	2 (< 0.1%)	1 (< 0.1%)	2 (< 0.1%)
Psychiatric Disorders			
Insomnia	372 (18.2%)	18 (0.9%)	–
Anxiety	122 (6.0%)	5 (0.2%)	–
Renal and Urinary Disorders			
Renal failure acute	114 (5.6%)	80 (3.9%)	78 (3.8%)
Renal failure	65 (3.2%)	32 (1.6%)	19 (0.9%)
Renal impairment	33 (1.6%)	11 (0.5%)	5 (0.2%)

System Organ Class / Preferred Term	All Adverse Reaction / Frequency	Grade ≥ 3 Adverse Reaction / Frequency	Serious Adverse Reaction / Frequency
Respiratory, Thoracic and Mediastinal Disorders			
Dyspnoea	568 (27.8%)	88 (4.3%)	47 (2.3%)
Cough	498 (24.4%)	4 (0.2%)	2 (< 0.1%)
Oropharyngeal pain	149 (7.3%)	–	–
Epistaxis	146 (7.1%)	10 (0.5%)	4 (0.2%)
Wheezing	58 (2.8%)	1 (< 0.1%)	–
Dysphonia	52 (2.5%)	–	–
Pulmonary embolism	36 (1.8%)	28 (1.4%)	31 (1.5%)
Pulmonary oedema	31 (1.5%)	19 (0.9%)	17 (0.8%)
Pulmonary hypertension	20 (1.0%)	5 (0.2%)	5 (0.2%)
Pneumonitis	7 (0.3%)	7 (0.3%)	5 (0.2%)
Acute respiratory distress syndrome	4 (0.2%)	4 (0.2%)	4 (0.2%)
Acute respiratory failure	4 (0.2%)	4 (0.2%)	2 (< 0.1%)
Interstitial lung disease	3 (0.1%)	2 (< 0.1%)	2 (< 0.1%)
Skin and Subcutaneous Tissue Disorders			
Rash	154 (7.5%)	11 (0.5%)	5 (0.2%)
Pruritus	118 (5.8%)	1 (< 0.1%)	–
Erythema	88 (4.3%)	1 (< 0.1%)	–
Hyperhidrosis	73 (3.6%)	–	–
Vascular Disorders			
Hypertension	351 (17.2%)	110 (5.4%)	11 (0.5%)
Hypotension	112 (5.5%)	26 (1.3%)	15 (0.7%)
Flushing	67 (3.3%)	1 (< 0.1%)	–
Deep vein thrombosis	66 (3.2%)	23 (1.1%)	21 (1.0%)
Hypertensive crisis	4 (0.2%)	4 (0.2%)	1 (< 0.1%)
Hypertensive emergency	2 (< 0.1%)	1 (< 0.1%)	1 (< 0.1%)

The frequency was calculated based on carfilzomib-treated subjects (N = 2044) in Studies 2011-002, PX-171-001, PX-171-002, PX-171-003, PX-171-004, PX-171-005, PX-171-006, PX-171-008, PX-171-009 (Aspire), PX-171-011, and 2011-003.

AEs of special interest

Cardiac Adverse Events: Cardiac failure

Cardiac failure AEs were increased in CRd subjects (6.4% all grades, 3.8% ≥ Grade 3) compared to the Rd control arm in PX-171-009 (4.1% all grades, 1.8% ≥ Grade 3) and 0.5% of subjects in the CRd arm discontinued treatment as a result. Cardiac failure events resolved in more than 60% of the subjects in the CRd arm. Cardiac failure typically occurred early in the course of Carfilzomib therapy and therefore, is less likely to be due to cumulative toxicity: median onset was Cycles 3/4 in CRd subjects *versus* Cycles 9/10 in Rd control subjects. In PX-171-011, increase in cardiac failure AEs was also noted in the carfilzomib monotherapy arm (7.6% all grades, 5.7% ≥ Grade 3) compared to control (4.6% all grades, 3.3% ≥ Grade 3).

Overall, the median age of carfilzomib-treated subjects that experienced an AE of cardiac failure across studies was generally higher than the respective overall study population, and it was generally higher in the carfilzomib-treated subjects in both populations experiencing an AE of cardiac failure than the respective control arms, with a higher proportion of subjects being ≥ 75 years of age.

There were 4 (1%) subjects with Grade 5 cardiac failure events in each arm of PX-171-009.

Cardiac Adverse Events: Myocardial infarction

Myocardial Infarction AEs were reported in 3.4% (2.5% ≥ Grade 3) of subjects in the pooled CRd cohort and 3.6%(2.6% ≥ Grade 3) of subjects in the CRd arm of PX-171-009, respectively, compared to 1.3% (1.0% ≥ Grade 3) of subjects in the Rd arm of PX-171-009. Myocardial infarction and acute myocardial infarction were the most frequently reported AEs in the pooled CRd cohort, and CRd and Rd arms of PX-171-009. Serious AEs of myocardial infarction were reported at a subject incidence rate of 2.5% and 2.6% in the pooled CRd cohort and CRd arm of PX-171-009, respectively, compared to 1% in the Rd arm. There were three Grade 5 AEs of myocardial infarction in the CRd arm of PX-171-009. The Rd arm of PX-171-009 also had two Grade 5 AEs, 1 case of myocardial infarction and 1 case of acute coronary syndrome. Discontinuations due to these events were ≤ 1.3% in CRd subjects and the events resolved in most subjects. The median onset of myocardial infarction and myocardial ischemia was Cycle 5 in the CRd arm of PX-171-009 and approximately 1 cycle later in the Rd arm.

Cardiac Adverse Events: Ischemic Heart Disease

The subject incidence rates (all grades and ≥Grade 3 AEs) of Ischemic Heart Disease (IHD) AEs were 5.6% (3.4% ≥ Grade 3) and 5.9% (3.3% ≥ Grade 3) in the pooled CRd cohort and CRd arm of PX-171-009 respectively, compared to 4.6%(2.1%≥ Grade 3) in the Rd arm. For the 32 subjects in the Phase 1/2 dose-escalation study PX-171-006 who received < 20/27 mg/m^2 of carfilzomib, there were no reports of an IHD AE. Six (1.4%) subjects and 5 (1.3%) subjects discontinued any study treatment in the pooled CRd cohort and CRd arm of PX-171-009, respectively, compared to 2 subjects (0.5%) in the Rd arm due to an AE of IHD. Dose reduction was reported at a subject incidence rate of ≤ 0.5% in any cohort. The median time from first dosing date to first SMQB_IHD AE was 140 days in the pooled CRd cohort and CRd arm of PX-171-009 compared to 164 days in the Rd arm.

Cardiac Adverse Events: Cardiac Arrhythmias

The subject incidence rates of cardiac arrhythmias AEs were 17.3% (5.0% ≥ Grade 3) and 16.6% (5.4% ≥ Grade 3) in the pooled CRd cohort and CRd arm of PX-171-009, respectively, compared to 15.2% (5.1% ≥Grade 3) in the Rd arm of PX-171-009. The subject incidence rates of treatment discontinuation were

comparable between the pooled CRd cohort and the study arms of PX-171-009 and were < 1% in both the CRd cohorts. All events for 54 out of the 76 (71.1%) subjects in the pooled CRd cohort who had Cardiac arrhythmia events were reported as resolved by the investigator. Serious AEs of cardiac arrhythmia were reported in 4.3% and 4.6% of subjects in the pooled CRd cohort and CRd arm of PX-171-009, respectively, compared to 3.1% in the Rd arm. There were three Grade 5 AEs in the CRd arm of PX-171-009 (2 cases of cardiac arrest and 1 sudden death). Two Grade 5 AEs were also noted in the Rd arm of PX-171-009 and included 1 sudden death and 1 arrhythmia (non-specified).

No imbalance between the pooled CRd cohort and study arms of PX-171-009 in the Torsade de pointes_QT prolongation was observed.

Vascular Events

The subject incidence rates of grouped venous embolic and thrombotic events (VTE) were 15.3% (5.6% ≥ Grade 3) in the CRd arm of PX-171-009, compared to 9.0% (3.9% ≥ Grade 3) in the Rd arm. This included AEs of thrombophlebitis (2.0% in CRd arm, 0.8% in Rd arm) and superficial thrombophlebitis (2.8% in CRd arm, 1.5% in Rd arm), which were more likely to occur in subjects on receiving CRd due to the IV route of administration of carfilzomib. The subject incidence rate of treatment discontinuations/dose reductions due to AEs of Venous Embolic and Thrombotic Events (VTE) were 1.0%/2.3% in the CRd arm of PX-171-009, compared to 1.3%/1.3% in the Rd arm. Thrombotic prophylaxis was required in both study PX-171-009 and PX-171-006.

Subject incidence rates for Hypertension in which the PT of hypertension were reported at 15.8% (5.6% ≥ Grade 3) in the CRd arm of PX-171-009, compared to 8.2% (2.1% ≥Grade 3) in the Rd arm. Less than 1% of subjects in any treatment cohort dose-reduced or discontinued treatment as a result. Approximately 49% of subjects both in the pooled CRd cohort and CRd arm of PX-171-009 had a medical history of hypertension, compared to 44.2% in the Rd arm.

Pulmonary Events

Incidence rates of grouped dyspnoea AEs (HLT) were 25.2% (2.9% ≥ Grade 3) and 22.7% (3.1% ≥ Grade 3) in the pooled CRd cohort and CRd arm of PX-171-009, respectively, compared to 18.0% (2.1% ≥ Grade 3) in the Rd arm of PX-171-009. No carfilzomib-treated subject discontinued treatment while dose reduction was required in1.4% and 1.3% of subjects in the pooled CRd cohort and CRd arm of PX-171-009, respectively. Dyspnoea was the most frequently reported AE in this grouping in the pooled CRd cohort (21.6% [2.5% ≥ Grade 3]), and CRd (19.6% [2.8% ≥ Grade 3]) and Rd (14.9% [1.8% ≥ Grade 3]) arms of PX-171-009. Serious AEs were reported in< 1.5% of subjects in all treatment cohorts. Median time to onset of the first episode of a dyspnoea AE was earlier in the carfilzomib treated subjects (study treatment days 44 and 58 in the pooled CRd and CRd arm of PX-171-009, respectively) compared to study treatment day 84 in the Rd arm. An analysis of clinically related concomitant AEs was performed to evaluate whether dyspnoea was part of a broader symptomatology or indicative of a more serious condition.Productive cough was ≥Grade 3 in1 CRd-treated subject (in PX-171-009) and 1 CRd-treated subject discontinued treatment due to cough. Cough was reported as resolved or resolved with sequelae in a majority of subjects with 4.7% and 4.3% of subjects in the pooled CRd cohort and the CRd arm of PX-171-009, respectively, reporting cough as "not resolved". More than 70% of subjects with an AE of cough also reported an AE of URTI in the all pooled CRd cohort as well as the CRd and Rd arms of PX-171-009. Where an AE ofcough was reported, a subject incidence rate of 47.8% and 52.2% of lower respiratory tract infection was also reported in the pooled CRd cohort and CRd arm of PX-171-009.

Acute Renal Failure

Subject incidence rates of acute renal failure AEs including ≥ Grade 3 AEs were 8.4% (all grades) and 3.3% (≥ Grade 3) in CRd arm, and 7.2% (all grades) and 3.1% (≥ Grade 3) in the Rd arms of PX-171-009, with <1% of subjects discontinuing treatment as a result. Dialysis was performed in 2 subjects in the CRd arm of PX-171-009 while no subject in the Rd arm required dialysis. The subject incidence rates of acute renal failure AEs were reported at 17.9% (4.6% ≥ Grade 3) in the CRd arm of PX-171-009, compared to 13.1% (3.9% ≥Grade 3) in the Rd arm. The corresponding rates of AEs leading to treatment discontinuation (≤ 1%), requiring dose reduction (≤ 6%), and SAEs (≤ 2%) were comparable among the cohorts/arms. The incidence rates of dose reduction were 2.0% in the CRd arm of PX-171-009, compared to 1.8% in the Rd arm. Subjects with lower baseline CrCL in both populations were more likely to experience a renal AE. There were no Grade 5 AEs in the CRd arm of PX-171-009 and one Grade 5 AE of acute renal failure in the Rd arm.

In Study PX-171-011, the overall incidence of adverse events of acute renal failure was higher in the carfilzomib monotherapy arm (24.8%) compared with control (9.2%). The high incidence of adverse events of acute renal failure in Study PX-171-011 may be attributable to the subject population being a more heavily pretreated subject population. Therefore, Study PX-171-011 was the only study with elevated relative risk for acute renal failure for low baseline CrCL.

Hepatic Events: Hepatic Toxicity and Hepatic Failure

The subject incidence rate of AEs in this category (Hepatic failure, fibrosis and cirrhosis and other liver damage related conditions) were 2.0% (0.5% ≥Grade 3) in the CRd arm of PX-171-009, compared to 0.5% (0.3% ≥Grade 3) in the Rd arm. The subject incidence rates of individual AEs under this grouping occurred in < 1% of subjects in any cohort/study arm. One of these subjects also met the biochemical criteria for Hy's law. One subject dose-reduced and 1 subject discontinued treatment in each treatment arm of PX-171-009 as a result.

There were 2 subjects with SAEs, both in the CRd arm of PX-171-009: 1 subject with an SAE of hypoalbuminemia and 1 with an SAE of increased ALT. No carfilzomib-treated subject discontinued any study treatment due to an AE of Liver related investigations, signs, and symptoms.

Gastrointestinal Events

Gastrointestinal disorders were reported in 66.3% of subjects in the CRd arm of PX-171-009, compared to 56.6% of subjects in the Rd arm. Diarrhoea, nausea, constipation, and vomiting were the most frequently reported AEs of any grade in this category. Of these, diarrhoea and nausea were reported at a subject incidence rate that was ≥ 5% higher in the CRd-treated subjects (pooled CRd cohort and CRd arm of PX-171-009) compared to the Rd arm. Most GI AEs were low-grade and non-serious events. Grade 3 and higher diarrhoea AEs were reported in 3.8% (1.4% SAEs) of subjects in the CRd arm of PX-171-009, compared to 4.1% (2.3% SAEs) of subjects in the Rd arm. Diarrhoea led to dose reduction of any study drug in 2.6% of subjects in the CRd arm of PX-171-009, compared to 3.6% of subjects in the Rd arm.

In subjects who reported diarrhoea as resolved or resolved with sequelae, the median duration of the longest episode of diarrhoea was 10 days in the pooled CRd cohort and CRd arm of PX-171-009, compared to 9 days in the Rd arm. The median number of episodes was 1 and 2, respectively, in the pooled CRd cohort and the CRd arm of PX-171-009, and 1 in the Rd arm. Antidiarrheal agents as concomitant medications were reported in 23% and 22.4% of subjects in the pooled CRd cohort and the CRd arm of PX-171-009, respectively, compared to 18.3% of subjects in the Rd arm.

Vomiting was reported as resolved or resolved with sequelae in 52 of 59 subjects and 41 of 47 subjects in the pooled CRd cohort and the CRd arm of PX-171-009, respectively, compared to 30 of 32 subjects in the Rd arm. In subjects who reported vomiting as resolved or resolved with sequelae, the median duration of the longest episode was 1 day in the pooled CRd cohort and CRd arm of PX-171-009 compared to 3 days in the control arm. The median number of episodes was 1 in all cohorts. Antiemetics and antinauseants were reported as concomitant medications in 16.9% and 13% of subjects in the pooled CRd cohort and the CRd arm of PX-171-009, respectively, compared to 5.9% of subjects in the Rd arm.

Hematologic Events: Anaemia

Subject incidence rates of grouped anaemia AEs of all grades were 44.6% (18.4% ≥ Grade 3) in the CRd arm of PX-171-009, compared to 40.4% (18.0% ≥ Grade 3) in the Rd arm. There were no treatment discontinuations in CRd arm of PX-171-009, while 4 (1.0%) subjects in the Rd arm discontinued treatment. Four (1.0%) subjects in the CRd arm of PX-171-009, required dose reductions compared to 8 (2.1%) subjects in the Rd arm of PX-171-009.

Hematologic Events: Leukopenia

Subject incidence rates of grouped leukopenia AEs were 45.7% (34.9% ≥Grade 3) in the CRd arm of PX-171-009, compared to and 40.4% (30.6% ≥Grade 3) in the Rd arm. Treatment discontinuations were 1.3% in the CRd arm of PX-171-009, compared to 0.8% in the Rd arm. The subject incidence rates for dose reductions were 14.8% in the CRd arm (14.8%) of PX-171-009, compared to the 9.8% in the Rd arm. Grade 4 neutropenia was noted in 31 subjects in the pooled CRd cohort, of whom 6 subjects, all enrolled in PX-171-009, also experienced an AE of sepsis compared to 4 of 31 subjects in the Rd arm.

The subject incidence rates of SAEs for Haematopoietic leukopenia were comparable across all cohorts (2.8% and 2.6% in the CRd and Rd arms of PX-171-009, respectively). Febrile neutropenia was the most frequent SAE in this grouping being reported in 2.0% of subjects in the PX-171-009 CRd arm compared to 1% in the Rd arm. None of these were Grade 5 AEs.

Hematologic Events: Thrombocytopenia

Subject incidence rates of thrombocytopenia were 32.4% (19.9% ≥ Grade 3) in the CRd arm of PX-171-009, compared to 25.2% (14.4% ≥Grade 3) in the Rd arm. While the subject incidence rates for dose reduction were 9.2% in the CRd arm of PX-171-009, the incidence rate of discontinuation from treatment was < 2%. Thrombocytopenia was the most frequently reported AE and occurred at a subject incidence rate of 29.3% (16.8% ≥ Grade 3) in CRd arm of PX-171-009, compared to 22.9% (12.3% ≥ Grade 3) in the Rd arm. Grade 4 was noted in 14 subjects (34.1%). Twelve of 38 subjects (31.6%) in the CRd arm of PX-171-009 compared to 6 of 23 subjects (26.1%) in the Rd arm who had Grade 4 thrombocytopenia also experienced a bleeding event on study. Serious AEs of Thrombocytopenia were reported at subject incidence rates of 1.5% in the CRd arm of PX-171-009, compared to 0.8% in the Rd arm. Less than 2% of the CRd and carfilzomib treated subjects dose reduced or discontinued carfilzomib as a consequence of thrombocytopenia.

Subject incidence rates of haemorrhage were 17.3% (1.3% ≥ Grade 3) in the CRd arm of PX-171-009, compared to 15.9% (2.3% ≥ Grade 3) in the Rd arm. Less than 1% of subjects either reduced the dose or discontinued treatment in any cohort. Epistaxis, contusion, and ecchymosis were the 3 most frequently reported AEs in the pooled CRd cohort, and CRd and Rd arms of PX-171-009. Serious AEs of Haemorrhage terms were reported at subject incidence rates of 1.0% in the CRd arm of PX-171-009, compared to 1.0% in the Rd arm. There were a total of three Grade 5 AEs of haemorrhage, all of which occurred in PX-171-009.

Two of these subjects were enrolled in the CRd arm and died due to subdural hematoma and intracranial haemorrhage while the third subject was enrolled in the Rd arm and died due to a cerebral haemorrhage.

Peripheral Neuropathy Adverse Events

Peripheral neuropathy AEs were 29.3% (4.3% ≥ Grade 3) in the CRd arm of PX-171-009, compared to 27.5% (5.4% ≥ Grade 3) in the Rd arm. The subject incidence rates of dose reduction were similar among cohorts/arms occurring in 6.6% CRd arm, and 6.2% Rd arm. Less than 1% of peripheral neuropathy AEs were reported as SAEs in any treatment cohort and similarly, ≤ 1% subjects discontinued treatment as a consequence of a peripheral neuropathy AE. Grade 3 and higher AEs and SAEs were infrequent across all carfilzomib-treated subjects and were mostly reported in subjects with baseline peripheral neuropathy. Dose reduction and discontinuation of treatment was also infrequent in all treatment cohorts.

Infections: Respiratory Tract Infections

The subject incidence rates for grouped URTIs (Upper Respiratory Tract Infections NEC) were 49.0% (3.1% ≥ Grade 3) in the CRd arm of PX-171-009, compared to 38.3% (1.8% ≥ Grade 3) in the Rd arm of PX-171-009. Less than 1% of subjects discontinued treatment in either the pooled CRd cohort or the CRd arm of PX-171-009. Serious AEs of Upper Respiratory Tract Infections NEC were reported at subject incidence rates of 2.3% in the CRd arm of PX-171-009, compared to 0.8% of in the Rd arm.

The incidence rate of grouped lower respiratory tract infections were 38.8% (17.3% ≥ Grade 3) in the CRd arm of PX-171-009, compared to 29.6% (14.1% ≥ Grade 3) in the Rd arm. The subject incidence rates of treatment discontinuation/dose reduction were 1.5%/3.1% in the CRd arm of PX-171-009, compared to 1.0%/2.6% in the Rd arm. Bronchitis and pneumonia were the 2 most frequently reported AEs in the CRd and Rd arms of PX-171-009.

Serious AEs in the category of Lower Respiratory Tract Infections NEC were reported at a subject incidence rate of 18.4% in the CRd arm of PX-171-009, compared to 14.1% in the Rd arm. Serious AEs of bronchitis were reported at an incidence rate of 2% for both the pooled CRd cohort and CRd arm of PX-171-009, and 1.5% in the Rd arm. Serious AEs of pneumonia were reported at an incidence rate of 14.3% in the CRd arm of PX-171-009, compared to 11.1% in the Rd arm. There were two Grade 5 AEs of pneumonia in each arm of PX-171-009.

Ciprofloxacin or other appropriate prophylactic antibacterial agent was recommended during Cycle 1 in all subjects receiving carfilzomib in the two Phase 3 studies as well, as in PX-171-006.

Infections: Urinary Tract Infections

Urinary tract infection (PT) was reported in 8.7% (1.0% ≥ Grade 3) of subjects in the CRd arm of PX-171-009 compared to 5.4% (0.3% ≥Grade 3) of subjects in the Rd arm. No subject in any of these 2 groups discontinued treatment as a result. Three subjects (0.7%) in the CRd arm of PX-171-009 compared to 2 subjects (0.5%) in the Rd arm experienced SAEs of urinary tract infection.

Infections: Herpes Virus Infections

Subject incidence rates of Herpes virus infections were 3.3% (0% ≥ Grade 3) in the CRd arm of PX-171-009, compared to 4.9% (0.3% ≥ Grade 3) in the Rd arm. No subject in the CRd arm of PX-171-009 required dose reduction or treatment discontinuation for this AE. The most frequently reported AE under this grouping was oral herpes and occurred at a subject incidence rate of 1.5% and 1.3% in the CRd and Rd arms of PX-171-009, respectively. No ≥ Grade 3 AEs or SAEs were observed in any cohort/study arm, except for one Grade 5 AE of disseminated herpes zoster in the Rd arm of PX-171-009.

Antiviral therapy in the form of acyclovir or a comparable agent was recommended in most clinical trials of carfilzomib (including PX-171-009).

Infections: Opportunistic Infections

Opportunistic fungal infection AEs such as candidiasis and aspergillosis were reported with a low subject incidence (< 2% for all individual PTs) and differed by < 2% between the CRd-treated subjects (pooled CRd and CRd arm of PX-171-009) and the Rd arm. Cytomegalovirus infection was reported in 3 subjects in the pooled CRd cohort(2 subjects in the CRd arm of PX-171-009) while no subject in the Rd arm experienced that infection.

The incidence rates were generally higher (across all cohorts) in the Primary CRd Combination Therapy population (range: 38.3% to 49.0%) compared to Monotherapy (range: 11.1% to 28.4%).

Grouped lower respiratory tract infections were also consistently higher in all cohorts in the Primary CRd Combination Therapy Population(range: 29.6% to 38.8%) compared to the Monotherapy Population (range: 16.2% to26.1%). The notable difference was that the subject incidence of grouped lower respiratory tract infections, notably pneumonia in the control arm of PX-171-011 was higher (≥ 5% difference) than the carfilzomib arm of that study, as well as the all pooled carfilzomib monotherapy cohort. No significant differences between the 2 populations were reported for other categories of infections.

Tumour Lysis Syndrome Adverse Events

Tumour lysis syndrome (TLS) had been observed in some carfilzomib-treated subjects with multiple myeloma in early studies (ie, PX-171-003 and PX-171-004). Therefore, TLS prophylaxis measures were instituted in all ongoing and subsequent carfilzomib studies as of March 2008, which was accompanied by a decreased incidence of TLS events (0.5%). Therefore, TLS prophylaxis measures were instituted included mandatory IV hydration before and after carfilzomib dosing in Cycle 1 and optional IV hydration in Cycles 2 and beyond, as well as the optional use of allopurinol in subjects at high risk for TLS.

In the Primary CRd Combination Therapy Population subject incidence rates of TLS were 26.1% and 26.3% in the pooled CRd cohort and the CRd arm of PX-171-009, respectively, compared to 17.0% in the Rd arm. However, most of these events were AEs of electrolyte abnormalities with hypocalcaemia and hyperuricaemia being the 2 most frequent PTs accounting for 15.8% and 5.2% of AEs in the pooled CRd cohort. No subjects had a fatal event of TLS during a clinical study.

In the Monotherapy Population, the subject incidence rate of TLS was 32.0% and 32.5% in the all pooled monotherapy cohort and the carfilzomib arm of PX-171-011, respectively, compared to 18.3% in the control arm.

Infusion Reactions

In carfilzomib trials, 42.3%–56.2% of subjects experienced one or more symptoms (pyrexia, dyspnoea, asthenia, vomiting, arthralgia, and/or chills) within a day of carfilzomib dosing that have been defined as infusion reactions. These symptoms were predominantly low grade and non-serious with infrequent reports of more clinically important events within a day of dosing such as angina pectoris (0.5%-1.2%) and syncope (0.3%–0.9%) across the studies. These events were not specifically associated with the first dose of carfilzomib (approximately 10% reported any event within a day of the first dose of carfilzomib) and equally likely to occur within 1 day of any carfilzomib dosing. There were no differences in types or frequencies of AEs between the CRd subjects who received much higher doses of dexamethasone than the monotherapy subjects who received 4 mg of dexamethasone premedication.

The subject incidence rate of AEs within 1 day of carfilzomib dosing for any dose in the infusion reaction grouping was 45.3% and 42.3% in the pooled CRd cohort and CRd arm of PX-171-009, respectively with, 7.9% and 7.4% occurred within1 day of the first dose in these 2 cohorts, respectively. Most of these events were low grade (Grades 1 and 2) and non-serious. Events that were ≥ Grade 3 were reported at a subject incidence rate of 3.4% and 3.6% in the pooled CRd cohort and CRd arm ofPX-171-009, respectively. Serious AEs were reported at a subject incidence rate of 2.9% and 3.3% SAEs in the pooled CRd cohort and CRd arm of PX-171-009, respectively. None were Grade 5 events. Two (0.5%) subjects in the CRd arm ofPX-171-009 and 3 (0.7%) subjects in the pooled CRd cohort discontinued treatment as a result of an AE in this grouping.

One subject each in the CRd arm of PX-171-009 experienced AEs of anaphylactic reaction (Grade 1), cytokine release syndrome (Grade 3, considered treatment-related by the investigator) and systemic inflammatory response syndrome (Grade 3).

Comparing across the Primary CRd Combination Therapy and Monotherapy Populations, the rates and types of all grade and ≥ Grade 3 AEs typically associated with infusion reactions reported within 1 day of any dose of carfilzomib were comparable across the various treatment cohorts. The rates of these AEs in the all pooled carfilzomib monotherapy cohort were higher (≥ 5% higher) than the carfilzomib arm ofPX-171-011 as well as the Primary CRd population.

Second Primary Malignancies

Second primary malignancies were reported at a subject incidence rate of 3.8% (1.8% ≥ Grade 3) and 4.1% (1.8% ≥ Grade 3) in the pooled CRd cohort and CRd arm of PX-171-009, respectively, compared to 3.1 %(1.8% ≥ Grade 3) in the Rd arm of PX-171-009. A review of the Neoplasms, Benign, Malignant and Unspecified SOC identified a subject with an AE of GI stromal tumour in the Rd arm that is not part of the grouped term analysis. Myelodysplastic syndrome was reported in 1 subject (Grade 3) in the pooled CRd cohort (in Study PX-171-009) compared to 4 subjects (1.0%) in the Rd arm; 2 of the 4 subjects had a Grade 5 AE of MDS in the RD arm. Based on that review, the subject incidence of invasive SPMs was 2.8% and 3.3% in the CRd and Rd arms ofPX-171-009, respectively with four Grade 5 AEs (1.0%) in either arm. Non-invasive SPMs were reported in 1.5% of subjects in either treatment arm and included PTs of basal cell carcinoma, squamous cell carcinoma, and squamous cell carcinoma of the skin.

Hypertension including hypertensive crises

Hypertensive crises (hypertensive urgency or hypertensive emergency) have occurred following administration of Kyprolis. Some of these events have been fatal. In clinical studies, hypertension adverse events occurred in approximately 20% of subjects and approximately 30% of these events were grade ≥ 3, but hypertensive crises occurred in < 0.5% of subjects. The incidence of hypertension adverse events was similar between those with or without a prior medical history of hypertension.

Posterior Reversible Encephalopathy Syndrome and Thrombotic Thrombocytopenic Purpura/Haemolytic Uremic Syndrome

Three cases of PRES were identified in subjects receiving carfilzomib. The time to onset of the event of PRES for these 3 cases, were 37 day and 13 day in Cd arm and in the second cycle in CRd arm (since the first dose of carfilzomib).

Thrombotic Thrombocytopenic Purpura/Haemolytic Uremic Syndrome

TTP/HUS and Thrombotic Microangiopathy: 7 cases of TTP/HUS and 4 cases of thrombotic microangiopathy were identified in subjects receiving Carfilzomib. Eight of the 11 subjects were receiving doses of carfilzomib

above the dose proposed for commercial use in this application and 2 subjects were receiving carfilzomib in combination with other antimyeloma drugs (panobinostat or thalidomide and dexamethasone). The events typically resolved with discontinuation and/or plasma exchange. Two subjects had a fatal outcome, both in the setting of significant comorbidities and complicated hospital admissions (including sepsis in one subject).

Serious adverse event/deaths/other significant events

Serious Adverse Events

An overview of the SAEs occurred in the Primary CRd Combination Therapy population is reported in Table 46.

Table 43. Summary of Serious Adverse Events Occurring in ≥ 1%* of CRd Subjects in the Primary CRd Combination Therapy Population (Safety Population)

MedDRA Preferred Term	Number of Subjects (%)		
	Pooled Carfilzomib CRd 20/27 mg/m^2 from 2 Studies[a] (N = 444)	PX-171-009	
		CRd Arm 20/27 mg/m^2 (N =392)	Control Arm (Rd) (N = 389)
Subjects with at least one SAE	263 (59.2)	235 (59.9)	210 (54.0)
Pneumonia	61 (13.7)	56 (14.3)	43 (11.1)
Respiratory Tract Infection	15 (3.4)	15 (3.8)	6 (1.5)
Pyrexia	15 (3.4)	14 (3.6)	9 (2.3)
Pulmonary Embolism	13 (2.9)	12 (3.1)	8 (2.1)
Deep Vein Thrombosis	9 (2.0)	9 (2.3)	6 (1.5)
Anaemia	10 (2.3)	8 (2.0)	10 (2.6)
Bronchitis	9 (2.0)	8 (2.0)	6 (1.5)
Febrile Neutropenia	8 (1.8)	8 (2.0)	4 (1.0)
Renal Failure Acute	8 (1.8)	6 (1.5)	4 (1.0)
Atrial Fibrillation	7 (1.6)	6 (1.5)	7 (1.8)
Myocardial Infarction	7 (1.6)	6 (1.5)	2 (0.5)
Thrombocytopenia	7 (1.6)	6 (1.5)	3 (0.8)
Diarrhoea	6 (1.4)	6 (1.5)	9 (2.3)
Dyspnoea	6 (1.4)	5 (1.3)	3 (0.8)
Basal Cell Carcinoma	5 (1.1)	5 (1.3)	3 (0.8)
Bronchopneumonia	5 (1.1)	5 (1.3)	7 (1.8)
Cardiac Failure Congestive	5 (1.1)	5 (1.3)	4 (1.0)
Acute Myocardial Infarction	5 (1.1)	4 (1.0)	1 (0.3)
Disease Progression	5 (1.1)	4 (1.0)	8 (2.1)
Neutropenia	5 (1.1)	4 (1.0)	5 (1.3)
Rash	5 (1.1)	4 (1.0)	1 (0.3)
Abdominal Pain	4 (0.9)	4 (1.0)	3 (0.8)
Cardiac Failure	4 (0.9)	4 (1.0)	3 (0.8)
Femur Fracture	4 (0.9)	4 (1.0)	2 (0.5)
Gastroenteritis	4 (0.9)	4 (1.0)	4 (1.0)
Pulmonary Oedema	4 (0.9)	4 (1.0)	0
Sepsis	4 (0.9)	4 (1.0)	4 (1.0)
Upper Respiratory Tract Infection	4 (0.9)	4 (1.0)	0

CRd = carfilzomib/lenalidomide/dexamethasone; Rd = lenalidomide/dexamethasone.
Note: Subjects were counted only once for each preferred term. MedDRA Version 15.1 was used for coding.
* The source table lists all SAEs experienced by all subjects including those experienced by < 1%.
a. Includes all subjects receiving carfilzomib 20/27 mg/m^2 (intended dose) given in combination with Rd from studies PX-171-006 and PX-171-009.

Deaths

The summaries of deaths occurred in the Primary CRd Combination Therapy Population are reported in Table 47.

Table 44. Deaths in the Primary CRd Combination Therapy Population Due Causes other than PD (ie, Deaths due to 'Adverse Events' or 'Other') (Safety Population)

System Organ Class	Number of Subjects			
	Pooled Carfilzomib CRd 20/27 mg/m^2 from 2 Studies[a,b] (N = 444)	PX-171-009		
		CRd Arm 20/27 mg/m^2 (N = 392)		Control Arm (Rd) (N = 389)
		≤ 30 days after last dose of any drug (of CFZ[c])	> 30 days after last dose of CFZ but ≤ 30 days after last dose of Rd	
Total number of on-study non-PD deaths	29	28 (22)	6	28
Cardiac	10	10 (9)	1	7
Infection	9	9 (6)	3	10
Renal	0	0	0	1
Other AEs[d]	10	9 (7)	2	10

CFZ = carfilzomib; CRd = carfilzomib/lenalidomide/dexamethasone; Rd = lenalidomide/dexamethasone.
Note: Subjects were counted only once for each preferred term**.** MedDRA Version 15.1 was used for coding.
a. Includes all subjects receiving carfilzomib 20/27 mg/m^2 (intended dose) given in combination with Rd from studies PX-171-006 and PX-171-009.
b. Only one death due to an AE was reported in PX-171-006**.** One subject died in their sleep on Study Treatment Day 3, one day after the last dose of carfilzomib with underlying disease noted as a secondary cause of death.
c. Subjects who died ≤ 30 days after last dose of carfilzomib are a subset of subject who died ≤ 30 days after last dose of any drug.
" Other AEs" in the Pooled CRd subjects include deaths from AEs of 'death' (3), acute respiratory distress syndrome (2), subdural hematoma (1), intracranial hemorrhage (1), multiorgan failure (1), sudden death (1), and suicide (1)**.** "Other AEs" in the Rd arm of PX-171-009 include 'death' (2), myelodysplastic syndrome (2), multiorgan failure (1), sudden death (1), pulmonary embolism (1), respiratory failure (1), coma (1) and disease progression (1).

Adverse events of infection were the most common cause of on-study deaths in PX-171-009 (9 subjects in CRd arm, 10 subjects in Rd arm), included 8 deaths due to sepsis/septic shock (4 subjects in each arm), and 7 deaths due to pneumonia/bronchopneumonia (3 subjects in CRd arm, 4 subjects in Rd arm). In the remaining 4 subjects, the primary causes of death were URTI and endocarditis in the CRd arm and urosepsis and hepatic infection in the Rd arm.

Cardiovascular AEs were reported as the primary cause of death in 10 subjects in the CRd arm and 7 subjects in the Rd arm. These included 5 deaths due to ischemic heart disease (3 subjects in CRd arm, 2 subjects in Rd arm), 7 deaths due to cardiac failure (3 subjects in CRd arm, 4 subjects Rd arm), 2 deaths due to cardiac arrest (both on CRd arm) and 1 death each due to circulatory collapse, left ventricular dysfunction (both on CRd arm), and arrhythmia (Rd arm). Of the 10 deaths due to cardiovascular AEs in the CRd arm, subjects had been receiving study treatment for varying lengths of time ranging from 4 days to 453 days. Nine of the 10 occurred within 30 days of the last dose of carfilzomib. The death due to circulatory collapse in the CRd arm occurred more than 30 days after the last dose of carfilzomib but within 30 days of the last dose of lenalidomide and/or dexamethasone. Deaths in 12 subjects in the CRd arm and 7 subjects in the Rd arm were adjudicated as cardiac deaths. Six and 5 deaths, respectively, in the CRd and Rd arm were adjudicated as sudden cardiac deaths, fatal acute coronary syndrome was the adjudicated cause of death in 3 and 1 subjects in the CRd and Rd arm, respectively, while 2 deaths in the CRd arm and 1 in the Rd arm were adjudicated as cardiac failure deaths. One subject in the CRd arm was adjudicated as "other" cardiac death.

No deaths were considered by the investigator to be related specifically to carfilzomib alone. Two of the deaths in the CRd arm were considered by the investigator to be related to both carfilzomib and lenalidomide. Eight of the deaths (events of septic shock, sepsis, hepatic infection, respiratory failure, pulmonary

embolism, myelodysplastic (MDS), acute coronary syndrome, and acute renal failure) in the Rd arm were considered by the investigator to be related to study treatment.

Laboratory findings

Analysis of Electrolyte Tests

Grade 3 or 4 decreased potassium was experienced by 71 (16.0%) subjects in the pooled CRd cohort, and 65 (16.6%) subjects in the CRd and 35 (9.0%) subjects in the Rd arms of PX-171-009. Of these subjects, 46 in the pooled CRd cohort, including 42 in the CRd arm of PX-171-009, and 18 in the Rd arm reported an AE of hypokalaemia. Grade 3 or 4 decreased potassium was experienced by 31 (3.9%) subjects in the all pooled monotherapy carfilzomib cohort, and 10 (6.4%) subjects in the carfilzomib and 3 (2.0%) subjects in the control arms of PX-171-011. Of these subjects, 25 in the all pooled carfilzomib monotherapy cohort, including 5 in the carfilzomib arm of PX-171-011, and 1 in the control arm reported an AE of hypokalaemia.

Grade 3 or 4 decreased magnesium was experienced by 11 (2.5%) subjects in the pooled CRd cohort, and 10 (2.6%) subjects in the CRd and 13 (3.3%) subjects in the Rd arms of PX-171-009. Of these subjects, 3 in the pooled CRd cohort (all in PX-171-009), and 1 in the Rd arm reported an AE of hypomagnesaemia. Grade 3 or 4 decreased magnesium was experienced by 6 (0.8%) subjects in the all pooled carfilzomib monotherapy cohort, and 2 (1.3%) subjects each in the carfilzomib and control arms of PX-171-011. Of these subjects, no subjects in the all pooled carfilzomib monotherapy cohort or carfilzomib arm, and both subjects in the control arm reported an AE of hypomagnesaemia.

Grade 3 or 4 decreased phosphorus was experienced by 162 (36.5%) subjects in the pooled CRd cohort, and 145 (37.0%) subjects in the CRd and 125 (32.1%) subjects in the Rd arms of PX-171-009. Of these subjects, 41 in the pooled CRd cohort, 31 in the CRd arm, and 18 in the Rd arm reported an AE of hypophosphatemia. Grade 3 or 4 decreased phosphorus was experienced by 63 (8.0%) subjects in the all pooled carfilzomib monotherapy cohort, and 10 (6.4%) subjects in the carfilzomib and 11 (7.2%) subjects in the control arms of PX-171-011. Of these subjects, 34 in the all pooled carfilzomib monotherapy cohort, including 2 in the carfilzomib arm of PX-171-011, and 1 in the control arm reported an AE of hypophosphatemia.

Analysis of Haematology Tests

Grade 3 or 4 decreased platelet count was experienced by 124 (27.9%) subjects in the pooled CRd cohort, and 114 (29.1%) subjects in the CRd and 75 (19.3%) subjects in the Rd arms of PX-171-009. Of these subjects, 87 in the pooled CRd cohort, 79 in the CRd arm, and 48 in the Rd arm reported an AE of Thrombocytopenia.

Grade 3 or 4 decreased platelet count was experienced by 226 (28.7%) subjects in the all pooled carfilzomib monotherapy cohort, and 59 (37.6%) subjects in the carfilzomib and 48 (31.4%) subjects in the control arms of PX-171-011. Of these subjects, 189 in the all pooled carfilzomib monotherapy cohort, 44 in the carfilzomib arm, and 32 in the control arm reported an AE of SMQB Thrombocytopenia.

Grade 3 or 4 decreased absolute neutrophil count was experienced by 191 (43.0%) subjects in the pooled CRd cohort, and 177 (45.2%) subjects in the CRd and 167 (42.9%) subjects in the Rd arms of PX-171-009. Of these subjects, 141 in the pooled CRd cohort, 127 in the CRd arm, and 102 in the Rd arm reported an AE of SMQB_Hematopoietic leukopenia.

Grade 3 or 4 decreased absolute neutrophil count was experienced by 82 (10.4%) subjects in the all pooled carfilzomib monotherapy cohort, and 30 (19.1%) subjects in the carfilzomib and 37 (24.2%) subjects in the

control arms of PX-171-011. Of these subjects, 67 in the all pooled carfilzomib monotherapy cohort, 17 in the carfilzomib arm, and 23 in the control arm reported an AE of SMQB Hematopoietic leukopenia.

Hepatic Tests

Grade 3 or 4 increased transaminases (ALT or AST) were experienced by 28 (6.3%) of subjects in the pooled CRd cohort including 24 subjects (6.1%) in the CRd arm, and 11 (2.8%) subjects in the Rd arm of PX-171-009. Grade 3 or 4 increased total bilirubin was experienced by 22 (5.0%) subjects in the pooled CRd cohort, including 21 (5.4%) in the CRd arm of PX-171-009, and 7 (1.8%) subjects in the Rd arm.

Grade 3 or 4 increased transaminases were experienced by 41 (5.2%) subjects in the all pooled monotherapy cohort, including 8 subjects in the carfilzomib arm of PX-171-011. Grade 3 or 4 increased total bilirubin was experienced by 11 (1.4%) subjects in the all pooled monotherapy cohort including 4 (2.5%) in the carfilzomib arm.

The subject incidence rates for AEs occurring under this category were 13.7% (5.2% ≥ Grade 3) and 12.8% (4.8% ≥ Grade 3) in the pooled CRd cohort and CRd arm of PX-171-009, respectively, compared to 8.2% (1.3% ≥ Grade 3) in the Rd arm of PX-171-009. No subjects in the pooled CRd cohort or CRd arm discontinued treatment due to AEs in this grouping and1 subject in the Rd discontinued treatment. The subject incidence rate of dose reductions were comparable between the pooled CRd cohort (1.6%) and CRd arm(1.5%) of PX-171-009, compared to 0.5% in the Rd arm. Increased ALT/AST, hyperbilirubinemia, and increased blood bilirubin, were the most frequently reported AEs in pooled CRd cohort, and CRd and Rd arms of PX-171-009.The AEs can be minimized by monitoring of liver chemistries while on treatment.

Renal Tests

Grade 3 or 4 increases in serum creatinine were reported in 20 (4.5%) subjects in the pooled CRd cohort, of which 18 (4.6%) subjects were enrolled in the CRd arm ofPX-171-009, and 14 (3.6%) in the Rd arm of PX-171-009.

Grade 3 or 4 increases in serum creatinine were reported in 56 (7.1%) subjects in the all pooled monotherapy cohort, of which 23 (14.6%) subjects were enrolled in the carfilzomib arm of PX-171-011, and 10 (6.5%) subjects in the control arm ofPX-171-011.

ECGs

Vital signs and electrocardiograms (ECGs) were collected in clinical trials, including a triplicate centrally read QTc-PK analysis in Phase 1 trials. Early Phase 1 trials also collected pulmonary function tests (PFTs) and echocardiograms (ECHOs), which are summarized.

Per study protocol in PX-171-009, single ECGs were collected at baseline, every 3 cycles while on study treatment and at end of treatment in order to assess general cardiac status and not specifically to assess QT intervals. A total of 60.8% and 63% of subjects in the pooled CRd cohort and the CRd arm of PX-171-009 had normal ECG at baseline compared to 64.8% in the Rd arm (results in Table 48).

A review of all subjects with QTc abnormalities revealed that most of these subjects were receiving multiple concomitant medications known for their QTc prolongation effects, such as antibiotics, arrhythmia medications, or antinausea medications.

Table 45. 12-Lead Electrocardiogram Findings in the Primary CRd Combination Therapy Population (Safety Population)

	Number of Subjects (%)		
	Pooled Carfilzomib CRd 20/27 mg/m^2 from 2 Studies[a] (N =444)	PX-171-009	
		CRd Arm 20/27 mg/m^2 (N = 392)	Control Arm (Rd) (N = 389)
Absolute QTc Interval Prolongation at End of Treatment			
450–480 ms	52 (11.7%)	47 (12.0%)	45 (11.6%)
481–500 ms	10 (2.3%)	7 (1.8%)	7 (1.8%)
≥ 501 ms	4 (0.9%)	4 (1.0%)	0
Worst Post-baseline Absolute QTc Interval Prolongation			
450–480 ms	122 (27.5%)	117 (29.8%)	109 (28.0%)
481–500 ms	36 (8.1%)	33 (8.4%)	29 (7.5%)
≥ 501 ms	33 (7.4%)	33 (8.4%)	14 (3.6%)
Change from Baseline in QTc Interval at End of Treatment			
Increase from Baseline > 30–60 ms	34 (7.7%)	28 (7.1%)	31 (8.0%)
Increase from Baseline > 60 ms	12 (2.7%)	12 (3.1%)	8 (2.1%)
Maximum Increase from Baseline in QTc Interval			
Increase from Baseline > 30–60 ms	125 (28.2%)	119 (30.4%)	107 (27.5%)
Increase from Baseline > 60 ms	55 (12.4%)	55 (14.0%)	36 (9.3%)

CRd = carfilzomib/lenalidomide/dexamethasone; Rd = lenalidomide/dexamethasone.
[a] Includes all subjects receiving carfilzomib in combination with Rd at 20/27 mg/m^2 in PX-171-006 and PX-171-009.

Safety in special populations

Age

Table 46. Safety in Special Age Populations Among All Carfilzomib Treated Subjects From Completed Studies

Treatment Emergent Adverse Events	<65 N = 1053 n (%)	65-<75 N = 708 n (%)	75-<85 N = 261 n (%)	>= 85 N = 22 n (%)
Total TEAE	1032 (98.0)	697 (98.4)	260 (99.6)	22 (100.0)
Serious AE	478 (45.4)	384 (54.2)	151 (57.9)	14 (63.6)
Fatal	78 (7.4)	63 (8.9)	32 (12.3)	2 (9.1)
Hospitalization/prolong existing hospitalization	429 (40.7)	334 (47.2)	141 (54.0)	14 (63.6)
Life-threatening	75 (7.1)	61 (8.6)	21 (8.0)	2 (9.1)
Disability/incapacity	8 (0.8)	8 (1.1)	5 (1.9)	1 (4.5)
Other (medically significant)	54 (5.1)	53 (7.5)	20 (7.7)	2 (9.1)
AE leading to CFZ discontinuation	178 (16.9)	130 (18.4)	64 (24.5)	8 (36.4)
Psychiatric disorders SOC	326 (31.0)	238 (33.6)	79 (30.3)	8 (36.4)
Nervous system disorders SOC	557 (52.9)	356 (50.3)	146 (55.9)	7 (31.8)
Accidents and injuries SMQN	84 (8.0)	114 (16.1)	30 (11.5)	5 (22.7)
Accidents and injuries SMQB	100 (9.5)	126 (17.8)	35 (13.4)	5 (22.7)
Cardiac disorders SOC	158 (15.0)	167 (23.6)	79 (30.3)	5 (22.7)
Vascular disorders SOC	337 (32.0)	249 (35.2)	104 (39.8)	6 (27.3)
	12 (1.1)	13 (1.8)	5 (1.9)	0

Treatment Emergent Adverse Events	<65 N = 1053 n (%)	65-<75 N = 708 n (%)	75-<85 N = 261 n (%)	>= 85 N = 22 n (%)
Cerebrovascular disorders SMQB	22 (2.1)	22 (3.1)	9 (3.4)	0
Infections and infestations SOC	656 (62.3)	455 (64.3)	169 (64.8)	14 (63.6)
Anticholinergic syndrome SMQN	0	0	0	0
Anticholinergic syndrome SMQB	481 (45.7)	340 (48.0)	124 (47.5)	10 (45.5)
Quality of life decreased PT	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[a]	161 (15.3)	128 (18.1)	53 (20.3)	4 (18.2)
Other AE appearing more frequently in older patients[b]	525 (49.9)	444 (62.7)	176 (67.4)	16 (72.7)
Diarrhoea PT	308 (29.2)	271 (38.3)	88 (33.7)	9 (40.9)
Blood Creatinine Increased PT	115 (10.9)	125 (17.7)	50 (19.2)	4 (18.2)
Asthenia PT	110 (10.4)	113 (16.0)	57 (21.8)	3 (13.6)
Oedema Peripheral PT	203 (19.3)	163 (23.0)	77 (29.5)	2 (9.1)

Studies included are 2011-002 (C-MAP), PX-171-001, PX-171-002, PX-171-003, PX-171-004, PX-171-005, PX-171-006, PX-171-008, PX-171-009 (ASPIRE), PX-171-011(FOCUS), and 2011-003 (ENDEAVOR).
Percentage based on N, number of subjects treated.
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 study drug. Adverse events were coded using MedDRA version 15.1.
CFZ=carfilzomib, SOC=System Organ Class, PT=Preferred Term, SMQN/B=Standard MedDRA Query Narrow/Broad scope
[a] Include orthostatic hypotension, fall, loss of consciousness, syncope, dizziness, dizziness exertional, dizziness postural, procedural dizziness, ataxia PTs and fractures HLGT.
[b] Defined by PTs that were reported with a frequency >=5% higher in subjects >=65 years of age than in subjects <65 years of age.

Gender

There was a trend towards increased subject incidence rates for several AEs in males than females across both treatment arms except neutropenia, acute renal failure and cardiac failure, as shown in Table 50.

Table 47. Selected Treatment Emergent Adverse Events by Gender in the Primary CRd Combination Therapy Population (Safety Population)

Grouped Term	CRd 20/27 mg/m^2 PX-171-009 (N = 392)		Rd PX-171-009 (N = 389)	
	Male (N = 211)	Female (N = 181)	Male (N = 228)	Female (N = 161)
SMQN_Cardiac failure	14 (6.6%)	11 (6.1%)	9 (3.9%)	7 (4.3%)
SMQB_Ischemic heart disease	16 (7.6%)	7 (3.9%)	14 (6.1%)	4 (2.5%)
SMQB_Myocardial infarction[a]	11 (5.2%)	3 (1.7%)	5 (2.2%)	0
SMQN_Liver-related investigations, signs and symptoms	33 (15.6%)	17 (9.4%)	19 (8.3%)	13 (8.1%)
SMQB_Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions	5 (2.4%)	3 (1.7%)	1 (0.4%)	1 (0.6%)
SMQN_Acute renal failure	22 (10.4%)	11 (6.1%)	15 (6.6%)	13 (8.1%)
ONX_Neutropenia	87 (41.2%)	79 (43.6%)	83 (36.4%)	64 (39.8%)
SMQB_Thrombocytopenia	78 (37.0%)	49 (27.1%)	63 (27.6%)	36 (22.4%)
HLT_Dyspnea	55 (26.1%)	34 (18.8%)	44 (19.3%)	26 (16.1%)

CFZ = carfilzomib; CRd = carfilzomib/lenalidomide/dexamethasone; HLT = High Level Term; mg/m^2 = milligram per meter squared; ONX = Onyx defined grouping; Rd = lenalidomide/dexamethasone; SMQB = Standardized MedDRA Query, Broad scope; SMQN = Standardized MedDRA Query, Narrow scope.
Notes: MedDRA Version 15.1 used for coding. Subjects were counted only once for each Onyx Grouped Term and each Preferred Term.
[a] SMQB_Myocardial infarction is a subset of SMQB_Ischemic heart disease.

Race

Adverse events by race in all pooled monotherapy cohort were reported in 99.4%, 100% and 100% of White, Black, and Other race subjects, respectively. Serious AEs by race in all pooled monotherapy cohort were reported in 47.6%, 54.0% and 49.1% of White, Black, and Other race subjects, respectively. The number of non-White subjects in the CRd arm was 17 (10 Black and 7 Other) and 18 in the Rd arm (10 Black and 8 Other), compared to the number of White subjects (375 CRd arm and 371 Rd arm).

Region

In the CRd arm of PX-171-009, the subject incidence of any AE was 100% for North America and 90.3% for Europe. In the Rd arm, the subject incidence of TEAEs was 100% and 88.0% in North America and Europe, respectively. The subject incidence rates of SAEs were 59.8% and 59.3% in North America and Europe respectively in the CRd arm of PX-171-009 while the corresponding rates in the Rd arm were 53.6% and 52.5%.

Baseline ECOG Performance Score

Subject incidence rates of AEs by baseline ECOG performance scores were analysed for ECOG performance scores of 0, 1, and 2. Adverse events by baseline ECOG status in the CRd arm of PX-171-009 were reported in 98.2%, 95.8%, and 97.4% of subjects with an ECOG of 0, 1, and 2, respectively. Serious AEs by the corresponding ECOG status were reported in 59.1%, 60.8%, and 59.0%, respectively. In the Rd arm of PX-171-009, AEs by baseline ECOG status in were reported in 99.4%, 95.6%, and 100% of subjects with an

ECOG of 0, 1, and 2, respectively. Serious AEs by the corresponding ECOG status were reported in 52.9%, 52.5%, and 67.6%, respectively. Selected TEAEs by ECOG status are presented in Table 51.

Table 48. Selected Treatment Emergent Adverse Events by ECOG Status in the Primary CRd Combination Therapy Population (Safety Population)

Grouped Term	CRd 20/27 mg/m² PX-171-009 (N=392)			Rd PX-171-009 (N=389)		
	0 (N = 164)	1 (N = 189)	2 (N = 39)	0 (N = 174)	1 (N = 181)	2 (N = 34)
SMQN_Cardiac failure	10 (6.1%)	12 (6.3%)	3 (7.7%)	6 (3.4%)	8 (4.4%)	2 (5.9%)
SMQB_Ischemic heart disease	6 (3.7%)	16 (8.5%)	1 (2.6%)	5 (2.9%)	11 (6.1%)	2 (5.9%)
SMQB_Myocardial infarction[a]	5 (3.0%)	8 (4.2%)	1 (2.6%)	0	3 (1.7%)	2 (5.9%)
SMQN_Liver-related investigations, signs and symptoms	27 (16.5%)	21 (11.1%)	2 (5.1%)	16 (9.2%)	12 (6.6%)	4 (11.8%)
SMQB_Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions	7 (4.3%)	1 (0.5%)	0	0	2 (1.1%)	0
SMQN_Acute renal failure	13 (7.9%)	16 (8.5%)	4 (10.3%)	11 (6.3%)	12 (6.6%)	5 (14.7%)
ONX_Neutropenia	72 (43.9%)	79 (41.8%)	15 (38.5%)	72 (41.4%)	64 (35.4%)	11 (32.4%)
SMQB_Thrombocytopenia	53 (32.3%)	64 (33.9%)	10 (25.6%)	36 (20.7%)	48 (26.4%)	15 (44.1%)
HLT_Dyspnea	46 (28.0%)	39 (20.6%)	4 (10.3%)	35 (20.1%)	29 (16.0%)	6 (17.6%)

CFZ = carfilzomib; HLT = High Level Term; mg/m² = milligram per meter squared; ONX = Onyx defined grouping; SMQB = Standardized MedDRA Query, Broad scope; SMQN = Standardized MedDRA Query, Narrow scope.
Notes: MedDRA Version 15.1 used for coding. Subjects were counted only once for each Onyx Grouped Term and each Preferred Term.
[a] SMQB_Myocardial infarction is a subset of SMQB_Ischemic heart disease.

Safety related to drug-drug interactions and other interactions

In clinical study PX-171-008, carfilzomib was administered concomitantly with oral midazolam, a CYP3A substrate. Study results showed that the PK of midazolam were unaffected by concomitant carfilzomib administration.

Carfilzomib showed marginal inhibitory effects on P-glycoproteins (P-gp) in vitro and is unlikely to be affected by P-gp inhibitors or inducers (IV administration and extensive metabolization).

In the clinical studies, there were no restrictions on concomitant medication use based on anticipated or reported drug–drug interactions, including those with cytochrome P450 inhibitors or inducers.

Discontinuation due to adverse events

In PX-171-009, AEs led to delay or non administration of ≥ 1 dose of any study treatment (ie, carfilzomib, lenalidomide, or dexamethasone) in 78.6% of subjects in the CRd arm and 63.0% of subjects in the Rd arm. Adverse events that led to delay or non administration of ≥ 1 study treatment with subject incidence ≥ 2% higher in the CRd arm than in the Rd arm included URTI, respiratory tract infection, pyrexia, neutropenia, bronchitis, thrombocytopenia, pneumonia, increased ALT, asthenia, and rash. Amongst the pooled CRd 20/27 mg/m^2 cohort, diarrhoea led to a delay or non administration of ≥ 1 study treatment in 8.1% of subjects, which is ≥ 2% higher than in the Rd arm. In PX-171-009, an AE led to delay or non adminitration specifically of carfilzomib in 63.0% of subjects. The most frequent of such events (in ≥3% of subjects) included

neutropenia, URTI, pneumonia, respiratory tract infection, bronchitis, thrombocytopenia, pyrexia, diarrhoea, and fatigue.

Within PX-171-009, 56.9% of subjects in the CRd arm and 51.9% in the Rd arm had an AE leading to dose reduction of any study treatments (ie, either carfilzomib, lenalidomide, or dexamethasone). The only AEs leading to dose reduction of any study treatment with a ≥ 2% higher subject incidence rate in the CRd arm compared to the Rd arm were neutropenia (13.0% CRd, 8.7% Rd) and thrombocytopenia (7.9% CRd,3.6% Rd). Conversely, the AE of tremor led to dose reduction more frequently in the Rd arm (0.3% CRd, 2.8% Rd). Adverse events specifically leading to reduction of carfilzomib occurred in 11.2% of CRd subjects. The AEs most frequently leading to reduction of carfilzomib within this study include thrombocytopenia, neutropenia, fatigue, and congestive cardiac failure. In the Rd arm, AEs most frequently leading to dose reduction included oedema, anaemia, insomnia, neutropenia, and decreased neutrophil count. Adverse events leading to dose reduction of lenalidomide were reported in 43.4% of subjects in the CRd arm and 38.3% of subjects in the Rd arm. The AEs most frequently leading to reduction of lenalidomide within this study included neutropenia (12.5% CRd, 8.7% Rd) and thrombocytopenia (7.7% CRd, 3.6% Rd). For the pooled CRd cohort, 55.2% of subjects had an AE leading to dose reduction. The only AEs leading to dose reduction with a ≥ 2% higher subject incidence rate in the pooled CRd cohort compared to the control arm of PX-171-009 were thrombocytopenia and neutropenia.

Post marketing experience

Onyx received a total of 2177 post marketing cases that contained 6985 AEs from worldwide sources cumulatively from the International Birth Date through 8 May 2014, of which the majority were non-serious (n = 5422) and the remainder were serious (n = 1563), including 356 events that resulted in a fatal outcome. Of the 6985 total events, the majority were reported under the indication of plasma cell myeloma (multiple myeloma) or plasma cell myeloma in remission (n = 6149 in total). Of the 356 fatal events, the most commonly reported PTs were plasma cell myeloma (n = 128) and PD (n = 63). No overdoses have been reported in subjects receiving carfilzomib in the post-marketing setting.

The SOCs that contained the most number of events included the General Disorders and Administration Site Conditions (n = 1621), Investigations (n = 966), and GI Disorders (n = 588). The most commonly reported listed events within these SOCs were fatigue (n = 400), PD (n = 177), and nausea (n = 158); and most common unlisted events included platelet count decreased (n = 151), haemoglobin decreased (n = 108), and White blood cell count decreased (n = 87).

Overall, the majority of the events (n = 5422) were reported as non-serious. Of all the non-serious and listed events (n = 2362), the most commonly reported events included fatigue, dyspnoea, nausea, asthenia, diarrhoea, PD, pyrexia, headache, pain, insomnia, back pain, and anaemia. Of all the non-serious and unlisted events (n = 3060), the most commonly reported events included decreased platelet count, peripheral neuropathy, decreased haemoglobin, drug ineffective, decreased white blood cell count, nasopharyngitis, decreased red blood cell count, local swelling, increased blood pressure, malaise, infusion site pain, and abnormal blood count.

The remaining events (n = 1563) were reported as serious. Of all the serious and listed events (n = 771), the most commonly reported events included plasma cell myeloma, pneumonia, PD, congestive cardiac failure, renal failure, pyrexia, dyspnoea, acute renal failure, sepsis, anaemia, asthenia, and pain. Of all the serious and unlisted events (n = 792), the most commonly reported events included death, decreased platelet count, dehydration, pulmonary hypertension, myocardial infarction, pulmonary oedema, septic shock,

decreased haemoglobin, cardiac failure, atrial fibrillation, influenza, mental status changes, chest pain, pleural effusion, and confusional state.

The majority of the events reported in the post-marketing setting were non-serious. Overall, a review of the fatal events identified haemorrhagic events with fatal outcomes; review of the serious/non-serious and listed events were consistent with the known safety profile of carfilzomib monotherapy; and review of the serious/non-serious and unlisted events revealed the following notable observations:

A review of the Blood and Lymphatic System Disorders SOC identified unlisted events including pancytopenia and febrile neutropenia. Anaemia, leukaemia, and thrombocytopenia are listed events as per the CDS. There was one fatal event of platelet count decreased (coded to the Investigations SOC) reported. Pancytopenia will continue to be monitored through routine pharmacovigilance activities.Of the 223 events reported under this SOC, 17 were pancytopenia, including 8 as serious (one with a fatal outcome). The case with a fatal outcome described a subject with anaemia and thrombocytopenia prior to the initiation of carfilzomib therapy.

A range of haemorrhagic events were noted in patients administered carfilzomib: epistaxis (n=28), gastrointestinal haemorrhagic events (n=22; 17 reported as serious including 1 with a fatal outcome), contusion (n=14), subdural hematoma (n=8, 6 with a fatal outcome; 2 patients had concurrent events of thrombocytopenia), haemoptysis (n=3), cerebral haemorrhage (n=3, 1 with a fatal outcome), intracranial haemorrhage (n=3, all with a fatal outcome), post-procedural haemorrhage (n=2, 1 with a fatal outcome), and pulmonary haemorrhage (n=1). Haemorrhagic events were observed across a number of SOCs, including Gastrointestinal Disorders, Injury, Poisoning and Procedural Complications, Nervous System Disorders and Respiratory, and Thoracic and Mediastinal Disorders.

A review of the Cardiac Disorders SOC and Cardiac Toxicity EOI identified unlisted events including atrial fibrillation, myocardial infarction, and acute myocardial infarction. Myocardial infarction is a modification of a previously adverse drug reaction, myocardial ischemia, and is a new safety risk identified based on the comprehensive safety assessment of both clinical trial and postmarketing data. Of the 219 events reported under this SOC, 24 were atrial fibrillation, including 12 as serious. There were 4 serious events of acute myocardial infarction and 15 events of myocardial infarction, of which 14 were serious. Fatal outcomes were reported in 2 of the acute myocardial infarction events and in 2 of the myocardial infarction events.

Of the 160 events reported under Injury, Poisoning and Procedural Complications, 26 were coded to the PT of fall, including 4 that were reported as serious (1 with a fatal outcome).

Of the 208 events reported under Metabolism and Nutritional Disorders SOC, 52 were dehydration (a new safety identified risk), including 23 as serious. Many were reported with concurrent listed events of nausea, vomiting and diarrhoea. In addition, there was 1 event of TLS with a fatal outcome reported.

Of the 501 events reported under Nervous System Disorders SOC, 97 were peripheral neuropathy (a new safety identified risk). The outcomes were reported as improved/resolved (6 events), unchanged (55 events), and unknown (36 events). All of them were reported as non-serious and there were events reported with concurrent events of fall. There were 2 events of PRES reported in the post marketing setting during the reporting period. One event of PRES occurred following the initiation of carfilzomib treatment.

There were 178 events received during this reporting period where the MedDRA PTs were coded to the Renal and Urinary Disorders SOC. Of the 178 events, 79 were non-serious and 99 were serious, including 19 events with a fatal outcome. Of the 19 fatal events, the reported PTs were renal failure (n = 11), renal failure acute (n = 6), renal failure chronic (n = 2). The most frequently reported serious AEs were renal failure (n = 48) and acute renal failure (n = 34).

2.6.1. Discussion on clinical safety

Overall, the safety database for carfilzomib is quite large as regards the total number of patients. However, median exposure to carfilzomib in pivotal study PX-171-009 was 70.3 weeks (18.0 cycles) with the numbers of patients yielding safety data at the proposed dose range of RCd with exposure of 6 cycles being 339, exposure of > 6 to ≤12 cycles being 279, exposure of > 12 to ≤18 cycles being 239 and with exposure of >18 cycles being 0, because carfilzomib was administered for up to a maximum of 18 cycles, after which subjects continued on lenalidomide and dexamethasone until disease progression or unacceptable toxicity. Treatment with Kyprolis combined with lenalidomide and dexamethasone for longer than 18 cycles should be based on an individual benefit risk assessment, as the data on the tolerability and toxicity of carfilzomib beyond 18 cycles are limited (SmPC section 4.2).

The safety profile of CRd is characterised by a broad range of adverse events including grade 3/4 AEs and deaths in the setting of AEs. The main reported AEs were thrombocytopenia with associated haemorrhage, neutropenia, severe infections, diarrhoea, vomiting, increased blood creatinine, uric acid, aminotransferases (AST, ALT), vascular disorders. The safety profile also included fatigue, asthenia, infusion reaction, pyrexia, and peripheral oedema, constipation, dyspnoea, cough, cataract, the noted events in the skin SOC, deep venous thrombosis (DVT)/pulmonary embolism (PE) and myocardial infarction; as well as a variety of low electrolyte levels, including hypokalemia, hypomagnesaemia, hypophosphatemia and hypocalcaemia.

Lenalidomide is known to have considerable toxicity, also overlapping with that of carfilzomib and dexamethasone, but the frequency of some important adverse events is several times higher for the CRd arm as compared to Rd arm. However, in this regard, it is of note that in study PX-171-009 there was a relative increase of frequency and severity observed regarding neutropenia and thrombocytopenia for the CRd arm as compared to the Rd arm. The frequencies of all-grade neutropenia were 37.8% vs 33.7%, for the CRd arm as compared to the Rd arm, and of Grade 3 / 4 were (29.6% vs 26.5%), respectively. The frequencies of all-grade thrombocytopenia were 29.3% vs 22.9%, for the CRd arm as compared to the Rd arm, and of Grade 3 / 4 were (16.8% vs 12.3%), respectively.

Carfilzomib like bortezomib are a proteasome inhibitor but carfilzomib is highly selective and inhibits the proteasome irreversibly with minimal off-target activity and is active in bortezomib-refractory cells in vitro and in mouse models. It is of note that in study PX-171-009 there was no increase of frequency and severity observed regarding peripheral neuropathy for the CRd arm. The frequencies of all-grade peripheral neuropathy were 8.7%, and of Grade 3 / 4 were 1.0%.

In study PX-171-009, the subject incidence of the rate of AEs leading to discontinuation of any study drug was 26.0% in the CRd arm and 25.2% in the Rd arm. The most common AEs leading to discontinuation of any study drug in either study arm included thrombocytopenia, insomnia, neutropenia, anemia, pneumonia, and URTI. Adverse events of any grade leading to discontinuation of lenalidomide were also balanced between study arms (18.6% CRd, 18.5% Rd); thus, the addition of carfilzomib did not appear to adversely affect lenalidomide dosing. The AEs most frequently leading to reduction of lenalidomide within this study included neutropenia (12.5% CRd, 8.7% Rd) and thrombocytopenia (7.7% CRd, 3.6% Rd). For the pooled CRd cohort, 55.2% of subjects had an AE leading to dose reduction.

AEs led to delay or non-administration of ≥ 1 dose of any study treatment (ie, carfilzomib, lenalidomide, or dexamethasone) in 78.6% of subjects in the CRd arm and 63.0% of subjects in the Rd arm. Adverse events that led to delay or non-administration of ≥ 1 study treatment with subject incidence ≥ 2% higher in the CRd arm than in the Rd arm included URTI, respiratory tract infection, pyrexia, neutropenia, bronchitis, thrombocytopenia, pneumonia, increased ALT, asthenia, and rash. Amongst the pooled CRd 20/27 mg/m2

cohort, diarrhea led to a delay or nonadministration of ≥ 1 study treatment in 8.1% of subjects, which is ≥ 2% higher than in the Rd arm.

The rare events of PRES and TTP/HUS were not noted in the clinical database and were identified from post marketing reports and/or SAE reports from ongoing Onyx or Investigator Sponsored Trials (ISTs).

In general, deaths on study were balanced between the two study arms of PX-171-009. A total of 6.9% of subjects in each study arm died due to an AE, and deaths due to PD were 0.5% in CRd arm versus 1.3% in Rd arm. Deaths due to cardiac (2.6% vs. 1.8% respectively), renal (0.0% vs. 0.3%), infections (2.3% vs. 2.6%), and other AEs (2.3% vs. 2,6%), were relatively balanced between treatment arms. It is noteworthy that in study PX-171-009 the rate of deaths on-treatment, but not due to the study indication of MM, was higher in the Rd arm (8.5%) compared to the CRd arm (7.7%).

Two subjects in the CRd arm died due to a bleeding event. One subject died due to a subdural hematoma resulting from an accident (subject was hit by a bicycle) and the other as a result of a massive subarachnoid haemorrhage preceded by Grade 4 thrombocytopenia. Both of these deaths occurred within 7 days of the last dose of carfilzomib.

Cardiac-related events

In clinical studies with Kyprolis, cardiac failure (reported in approximately 7% of subjects), myocardial infarction (reported in approximately 2% of subjects) and myocardial ischaemia (reported in approximately 1% of subjects) typically occurred early in the course of Kyprolis therapy (< 5 cycles). Approximately 65% of cardiac failure events, 75% of myocardial infarction events, and 83% of myocardial ischaemia events were grade ⩾ 3 events (SmPC section 4.8).

New or worsening cardiac failure (e.g. congestive cardiac failure, pulmonary oedema, decreased ejection fraction), myocardial ischaemia and infarction have occurred following administration of Kyprolis. Death due to cardiac arrest has occurred within a day of Kyprolis administration and fatal outcomes have been reported with cardiac failure and myocardial infarction (SmPC section 4.4).

While adequate hydration is required prior to dosing in cycle 1, all patients should be monitored for evidence of volume overload, especially patients at risk for cardiac failure. The total volume of fluids may be adjusted as clinically indicated in patients with baseline cardiac failure or who are at risk for cardiac failure (see section 4.2).

Patients should stop Kyprolis for grade 3 or 4 cardiac events until recovery and they should consider whether to restart Kyprolis at 1 dose level reduction based on a benefit/risk assessment (see section 4.2).

Cardiac adverse events were reported in Study PX-171-009 as occurring at a higher frequency in the carfilzomib-treated arm compared to the control arm. The mechanism for the cardiac effects is unclear, however due to the on-target specificity of the carfilzomib molecule and the similarity of the cardiac effects observed pre-clinically and clinically with other proteasome inhibitors such as bortezomib, the effects are likely pharmacological. This cardiac toxicity associated to carfilzomib regimen, was reported in a population with a probably lower cardiovascular risk than in the actual intended population (elderly MM patients). Treatment of these patients should be based on a comprehensive medical assessment and subsequent determination of an acceptable benefit:risk ratio on a patient-by-patient basis. This rationale is based on the large unmet need in subjects with relapsed multiple myeloma who may benefit from carfilzomib together with the precedent that an optimized regimen of cardiac care prior to and during treatment may mitigate the occurrence of heart failure-related adverse events.

Cardiovascular AEs were reported as the primary cause of death in 10 subjects in the CRd arm and 7 subjects in the Rd arm. These included 5 deaths due to ischemic heart disease (ie, myocardial infarction or acute coronary syndrome [3 subjects in CRd arm, 2 subjects in Rd arm]), 7 deaths due to cardiac failure (3 subjects in CRd arm, 4 subjects Rd arm), 2 deaths due to cardiac arrest (both on CRd arm) and 1 death each due to circulatory collapse, left ventricular dysfunction (both on CRd arm), and arrhythmia (Rd arm). Of the 10 deaths due to cardiovascular AEs in the CRd arm, subjects had been receiving study treatment for varying lengths of time ranging from 4 days to 453 days.

Cardiac toxicity (cardiac failure, myocardial ischemia, myocardial infarction & cardiac arrest) has been classified as an identified risk in the Risk Management Plan.

Pulmonary toxicity

Acute respiratory distress syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred in patients receiving Kyprolis. Some of these events have been fatal. Evaluate and stop Kyprolis until resolved and consider whether to restart Kyprolis based on a benefit/risk assessment (SmPC, section 4.4). Pulmonary toxicites have been classified as an identified risk in the Risk Management Plan.

Pulmonary hypertension

Pulmonary hypertension has been reported in patients treated with Kyprolis. Some of these events have been fatal. Evaluate as appropriate. Stop Kyprolis for pulmonary hypertension until resolved or returned to baseline and consider whether to restart Kyprolis based on a benefit/risk assessment (see section 4.2). Pulmonary hypertension has been classified as an identified risk in the Risk Management Plan.

Dyspnoea

Dyspnoea was reported in approximately 30% of subjects in clinical studies with Kyprolis. The majority of dyspnoea adverse reactions were non serious (> 15% of dyspnoea events were grade $\geqslant$ 3 events), resolved, rarely resulted in treatment discontinuation, and had an onset early in the course of study (< 3 cycles) (SmPC, section 4.8).

Dyspnea should be evaluated to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Patients should stop Kyprolis for grade 3 and 4 dyspnoea until resolved or returned to baseline and consider whether to restart Kyprolis based on a benefit/risk assessment (SmPC, section 4.4). Dyspnea has been classified as an identified risk in the Risk Management Plan.

Hypertension including hypertensive crises

Hypertensive crises (hypertensive urgency or hypertensive emergency) have occurred following administration of Kyprolis. Some of these events have been fatal. In clinical studies, hypertension adverse events occurred in approximately 20% of subjects and approximately 30% of these events were grade $\geqslant$ 3, but hypertensive crises occurred in < 0.5% of subjects. The incidence of hypertension adverse events was similar between those with or without a prior medical history of hypertension(SmPC, section 4.8).

All patients should be routinely evaluated for hypertension and treated as needed. If the hypertension cannot be controlled, the Kyprolis dose should be reduced. In case of hypertensive crises, patients should stop Kyprolis until resolved or returned to baseline and they should consider whether to restart Kyprolis based on a benefit/risk assessment (SmC sections 4.2 and 4.4). Hypertension including hypertensive crises has been classified as an identified risk in the Risk Management Plan.

Acute renal failure

Cases of acute renal failure have been reported in patients who received Kyprolis. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received Kyprolis monotherapy. The risk was increased in patients with a decrease in estimated creatinine clearance, calculated using Cockcroft and Gault equation, prior to receiving Kyprolis. Renal function should be monitored monthly with measurement of the serum creatinine and/or estimated creatinine clearance. Dose should be reduced or treatment should be stopped as appropriate (SmPC, sections 4.2 and 4.8). Acute renal failure has been classified as an identified risk in the Risk Management Plan.

Tumour lysis syndrome

Cases of tumour lysis syndrome (TLS), including with fatal outcome, have been reported in patients who received Kyprolis (SmPC, section 4.8). Patients with a high tumour burden should be considered to be at greater risk for TLS. Patients should be well hydrated before administration of Kyprolis in cycle 1, and in subsequent cycles as needed (SmPC, section 4.2). Uric acid lowering medicinal products should be considered in patients at high risk for TLS. Evidence of TLS during treatment should be monitored for, including regular measurement of serum electrolytes, and manage promptly. Kyprolis should be stopped until TLS is resolved (SmPC, section 4.2). Adequate hydration is required before dose administration in cycle 1, especially in patients at high risk of tumour lysis syndrome or renal toxicity (SmPC, section 4.4). Tumour lysis syndrome has been classified as an identified risk in the Risk Management Plan.

Infusion reactions

Infusion reactions, including life-threatening reactions, have been reported in patients who received Kyprolis. Symptoms may include fever, chills, arthralgia, myalgia, facial flushing, facial oedema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of Kyprolis. Dexamethasone should be administered prior to Kyprolis to reduce the incidence and severity of reactions (see section 4.2). Infusion reactions have been classified as an identified risk in the Risk Management Plan.

Thrombocytopenia

Thrombocytopenia was reported in approximately 40% of subjects in clinical studies with Kyprolis and approximately 60% of these events were grade $\geqslant$ 3. Kyprolis causes thrombocytopenia through inhibition of platelet budding from megakaryocytes resulting in a classic cyclical thrombocytopenia with platelet nadirs occurring around day 8 or 15 of each 28-day cycle and usually associated with recovery to baseline by the start of the next cycle (SmPC, section 4.8). Platelet counts should be monitored frequently during treatment with Kyprolis. Dose should be reduced or stopped as appropriate (SmPC, sections 4.2 and 4.4). Thrombocytopenia has been classified as an identified risk in the Risk Management Plan.

Hepatic toxicity

Cases of hepatic failure, including fatal cases, have been reported in < 1% of subjects in clinical studies with Kyprolis. Kyprolis can cause elevations of serum transaminases (see section 4.8). Dose should be reduced or stopped as appropriate (see section 4.2). Liver enzymes should be monitored at treatment initiation and monthly during treatment with carfilzomib, regardless of baseline values (SmPC, sections 4.2, 4.4 and 4.8). Hepatic toxicity has been classified as an identified risk in the Risk Management Plan.

Thrombotic Microangiopathy

Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome (TTP/HUS) have been reported in patients who received Kyprolis. Some of these events have been fatal. Signs and symptoms of TTP/HUS should be monitored for. If the diagnosis is suspected, stop Kyprolis and evaluate patients for possible TTP/HUS. If the diagnosis of TTP/HUS is excluded, Kyprolis can be restarted. The safety of reinitiating Kyprolis therapy in patients previously experiencing TTP/HUS is not known (SmPC, section 4.4). Thrombotic microangiopathy has been classified as an identified risk in the Risk Management Plan.

Posterior reversible encephalopathy syndrome

Cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving Kyprolis. PRES, formerly termed reversible posterior leukoencephalopathy syndrome (RPLS), is a rare, neurological disorder, which can present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension, and the diagnosis is confirmed by neuro radiological imaging. Kyprolis should be discontinued if PRES is suspected. The safety of reinitiating Kyprolis therapy in patients previously experiencing PRES is not known (SmPC, section 4.8). Posterior reversible encephalopathy syndrome (PRES) has been classified as an identified risk in the Risk Management Plan.

Febrile neutropenia

Febrile neutropenia was reported in 1.8% of subjects in the pooled CRd cohort and in 2.0% of subjects in the PX-171-009 CRd arm compared to 1% in the Rd arm. Of the 13 CRd-treated subjects with either a $\geqslant$ Grade 3 AE or SAE of febrile neutropenia, 10 subjects had concomitant (within a 2-week window of the start of febrile neutropenia) AE of infection. Within PX-171-009, the neutropenia was among most frequent $\geqslant$ Grade 3 AEs. Grade 3 and higher AEs reported with a $\geqslant$ 2% subject incidence rate in the CRd arm as compared to the Rd arm included neutropenia. Febrile neutropenia has been classified as an identified risk in the Risk Management Plan. In addition, febrile neutropenia is mentioned in the section 4.2 for dose modification.

Potential risks

Herpes zoster infections: Subject incidence rates of Herpes virus infections were 3.3% (0% ≥ Grade 3) in the CRd arm of PX-171-009, compared to 4.9% (0.3% ≥ Grade 3) in the Rd arm. No subject in the CRd arm of PX-171-009 required dose reduction or treatment discontinuation for this AE.

Antiviral prophylaxis should be considered in patients being treated with Kyprolis to decrease the risk of herpes zoster reactivation. The majority of patients included in studies with Kyprolis received antiviral prophylaxis; due to this fact it is not possible to calculate the true incidence of herpes zoster infection in patients treated with Kyprolis (SmPC, section 4.2). Herpes zoster infections have been classified as a potential risk in the Risk Management Plan.

Reproductive and developmental toxicity: There are no data from the use of carfilzomib in pregnant women. Studies in animals have shown reproductive toxicity. Based on its mechanism of action and findings in animals, Kyprolis can cause foetal harm when administered to a pregnant woman. Kyprolis should not be used during pregnancy unless the clinical condition of the woman requires treatment with Kyprolis. If Kyprolis is used during pregnancy, or if the patient becomes pregnant while taking this medicinal product, the patient should be apprised of the potential hazard to the foetus (SmPC, section 4.6). Reproductive and developmental toxicity has been classified as a potential risk in the Risk Management Plan.

Missing information

Use in patients with hepatic impairment: Patients with hepatic impairment have not been systematically evaluated. This has been adequately reflected in the SmPC (see section 4.2 and 5.2). 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 is ongoing and the final CSR will be submitted by Q2 2016 (see Risk Management Plan).

Cardiac failure: The pronounced increasing risk of AE in the older population, especially the cardiac failure events in subjects >75 y, required additional precautions for use.

The risk of cardiac failure is increased in elderly patients (≥ 75 years). Patients with New York Heart Association (NYHA) Class III and IV heart failure, recent myocardial infarction, and conduction abnormalities uncontrolled by medicinal products were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications. Patients with signs or symptoms of NYHA Class III or IV cardiac failure, recent history of myocardial infarction (in the last 4 months), and in patients with uncontrolled angina or arrhythmias, should have a comprehensive medical assessment, prior to starting treatment with Kyprolis. This assessment should optimise the patient's status, with particular attention to blood pressure and fluid management. Subsequently patients should be treated with caution and remain under close follow-up.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 (SmPC section 4.4).

Data about use in pregnant or breastfeeding is missing. This has been adequately reflected in the SmPC (see sections 4.6 and 5.3) and is reflected in the Risk Management Plan.

Effects on ability to drive and use machines

Kyprolis has minor influence on the ability to drive and use machines. Fatigue, dizziness, fainting, blurred vision, somnolence and/or a drop in blood pressure have been observed in clinical trials. Patients being treated with Kyprolis should be advised not to drive or operate machinery in the event that they experience any of these symptoms (SmPC section 4.7).

Overdose

There is currently insufficient information to draw conclusions about the safety of doses higher than those evaluated in clinical studies. Acute onset of chills, hypotension, renal insufficiency, thrombocytopenia and lymphopenia has been reported following a dose of 200 mg of Kyprolis administered in error.There is no known specific antidote for carfilzomib overdose. In the event of an overdose, the patient should be monitored, specifically for the side effects and/or adverse reactions to Kyprolis listed in section 4.8 of the SmPC (SmPC section 4.9).

Contraception

It cannot be excluded that the efficacy of oral contraceptives may be reduced during carfilzomib treatment (SmPC section 4.5). In addition, due to an increased risk of venous thrombosis associated with carfilzomib, females should avoid the use of hormonal contraceptives that are associated with a risk of thrombosis during treatment with carfilzomib (SmPC section 4.8). If a patient is currently using oral contraceptives or a hormonal method of contraception that is associated with a risk of thrombosis, the patient should switch to an alternative method of effective contraception (SmPC section 4.6).

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been

included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall, there is a pattern of more frequent adverse events and more frequent Grade 3/4 adverse events in patients treated with CRd (83.7%) compared to those treated with Rd (81.2%) with anaemia, fatigue, diarrhoea, thrombocytopenia, nausea, pyrexia, dyspnoea, respiratory tract infection, cough and peripheral oedema being the most common adverse reactions.

The safety profile of CRd was to some extent consistent with the previously known profile of the individual drugs despite the longer duration of therapy, and the use of triplet therapy.

In general the combination of carfilzomib with lenalidomide and low dose dexamethasone in PX-171-009 study seems to increase the toxicity of Rd and the SAEs, however, the adverse event profile is considered acceptable and manageable.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP).

The PRAC considered that the RMP version 2.0 (dated 29 May 2015) could be acceptable if the Applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

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

The CHMP endorsed the RMP version 4.0 (dated 18 September 2015) with the following content:

Summary of the safety concerns

Table 49. Summary of the safety concerns

Important identified risks	• Cardiac toxicity (cardiac failure, myocardial ischemia, myocardial infarction, and cardiac arrest) • Pulmonary toxicities • Pulmonary hypertension • Dyspnoea • Hypertension including hypertensive crises • Acute renal failure • Tumor lysis syndrome • Infusion reactions • Thrombocytopenia • 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), NYHA Class III or IV cardiac failure, uncontrolled angina and uncontrolled arrhythmias • Use in pregnant or breastfeeding women

Pharmacovigilance plan

Table 50. Ongoing and planned studies in the pharmacovigilance development plan

Study/activity Type, title and category	Objectives	Safety concerns addressed	Status	Date for submission 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 [AUC0-last] and area under the curve, from time 0 extrapolated to infinity [AUC0-inf]) of carfilzomib 56 mg/m2 at Cycle 2 Day 1 (C2D1) in subjects with relapsed multiple myeloma.	Carfilzomib exposure (PK) in patients with renal impairment, including those with renal failure, in patients receiving a higher dose (56 mg/m2) of carfilzomib.	Ongoing	Final 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 [AUC0-last] and area under the curve, from time 0 extrapolated to infinity [AUC0-inf]) of carfilzomib at Cycle 1 Day 16 (C1D16) in subjects with relapsed or progressive advanced malignancies.	Use in patients with hepatic impairment	Ongoing	Final CSR Q2 2016 (planned)

Risk minimisation measures

Table 51. Summary Table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
Cardiac toxicity (cardiac failure, myocardial ischemia, myocardial infarction, and 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

Dyspnoea	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
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	None

	Relevant text is provided in the following sections of the package leaflet (PL): • Warnings and precautions • Possible side effects	
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
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
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	None

	sections of the package leaflet (PL): • Warnings and precautions • Possible side effects	
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
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 Relevant text is provided in the following sections of the package leaflet (PL): • Pregnancy and breast-feeding	None

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kyprolis (CARFILZOMIB) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Study PX-171-009 has provided convincing evidence of clinical efficacy of carfilzomib in combination with lenalidomide and dexamethasone in terms of the primary endpoint PFS, compared to lenalidomide and dexamethasone, in adult patients with multiple myeloma who have received at least one prior therapy.

The risk of disease progression or death was reduced by 31% (HR=0.69, 95% CI: 0.57, 0.83; p value <0.0001). The Kaplan-Meier estimated median duration of PFS was 26.3 months vs. 17.6 months in the CRd arm and Rd arm, respectively. In addition, the results were consistent across the pre-specified subgroups for PFS.

The sensitivity analyses (unstratified, bias adjusted, interval censored, censoring by the initiation of non-protocol, anti-cancer therapy versus not initiating such therapy, Onyx's computerized algorithm and investigator assessment) confirmed the reliability of the PFS results, with HRs quite similar among them.

The main secondary endpoint, OS, did not cross the prespecified early stopping boundary for the interim analysis, even though the result points out a clear positive trend in favour of CRd (HR = 0.79 [95% CI: 0.63, 0.99]; log-rank p = 0.0182) with more deaths in the control arm at the time of the cut-off (143 [36.1%] vs 162 [40.9%]).

Regarding the secondary and exploratory variables the use of the combination of CRd seem to provide a positive benefit in terms of ORR (CRd 87.1%; Rd 66.7%; p < 0.0001), duration of response (CRd 28.6 months; Rd 21.2 months), and QoL. More patients in the CRd arm had a Stringent Complete Response (14% vs 3%) CR (18% vs 5%) and VGPR (38% vs 31%).

Uncertainty in the knowledge about the beneficial effects

The uncertainties that were identified during the assessment regarding some subgroup of patients (pure refractory to bortezomib and/or lenalidomide) and the initially proposed indication and the duration of treatment were satisfactorily addressed (see discussion on clinical efficacy).

One remaining uncertainty is the treatment effect in terms of OS associated with CRd. Despite the fact that CRd is pointing out a clear trend in OS benefit, the data are still immature. Additional follow-up will further quantify the OS benefit of CRd over Rd (see discussion on clinical efficacy).

Risks

The most common adverse reactions (occurring in > 20% of subjects) were: anaemia, fatigue, diarrhoea, thrombocytopenia, nausea, pyrexia, dyspnoea, respiratory tract infection, cough and peripheral oedema. The most serious adverse reactions that may occur during the CRd treatment include: cardiac toxicity, dyspnoea, acute renal failure, tumour lysis syndrome, infusion reactions, thrombocytopenia, hepatic toxicity, posterior reversible encephalopathy syndrome and thrombocytopenic thrombotic purpura/haemolytic uraemic syndrome.

A total of 142 subjects (36.2%) in the CRd arm, and 160 subjects (41.1%) in the Rd arm had died at the time of the data cut-off. A total of 30 subjects (7.7%) in the CRd arm and 33 subjects (8.5%) in the Rd arm died on study (ie, within 30 days after their last dose of any study treatment: carfilzomib, lenalidomide, or dexamethasone).Within PX-171-009, the subject incidence of the rate of AEs leading to discontinuation of any study drug was 26.0% in the CRd arm and 25.2% in the Rd arm. AEs led to delay or nonadministration of $\geq$ 1 dose of any study treatment (ie, carfilzomib, lenalidomide, or dexamethasone) in 78.6% of subjects in the CRd arm and 63.0% of subjects in the Rd arm.

Uncertainty in the knowledge about the unfavourable effects

Cardiac adverse events were reported in Study PX-171-009 as occurring at a higher frequency in the carfilzomib-treated arm compared to the control arm. The mechanism for the cardiac effects is unclear, however due to the on-target specificity of the carfilzomib molecule and the similarity of the cardiac effects observed pre-clinically and clinically with other proteasome inhibitors such as bortezomib, the effects are likely pharmacological. This cardiac toxicity associated to carfilzomib regimen, was reported in a population with a probably lower cardiovascular risk than in the actual intended population (elderly MM patients). Treatment of these patients should be based on a comprehensive medical assessment and subsequent determination of an acceptable benefit:risk ratio on a patient-by-patient basis. This rationale is based on the large unmet need in subjects with relapsed multiple myeloma who may benefit from carfilzomib together with the precedent that an optimized regimen of cardiac care prior to and during treatment may mitigate the occurrence of heart failure-related adverse events. These have been adequately reflected in the SmPC (see sections 4.2, 4.4 and 4.8) and cardiac toxicity (cardiac failure, myocardial ischemia, myocardial infarction & cardiac arrest) has been classified as an identified risk in the Risk Management Plan.

Table 52. Effects table for CRd in the treatment of MM patients with at least one prior therapy (data cut-off: 16.06.2014)

Effect	Short Description	Unit	Treatment (CRd)	Control (Rd)	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS	Duration from randomization to the time of PD or death	Median (months) HR	26.3 0.69	17.6	Consistency among subgroups and sensitivity analyses. Duration of treatment limited to 18 cycles	AR (efficacy section of ASPIRE study)
OS	Duration from randomization to death	Median (months) HR	Not reached 0.79	Not reached	Secondary endpoint; It did not cross the prespecified early stopping boundary for the interim analysis	AR (efficacy section of ASPIRE study)
Unfavourable Effects						
AEs [1]	Subjects with at least 1 AE	%	96.9	97.7		
AEs grade 3-4	Subjects with at least 1 AE grade 3-4	%	83.7	81.2		
SAEs [2]	Subjects with at least 1 SAE	%	59.9	54.0		
Cardiac Toxicity (cardiac failure, myocardial ischemia, myocardial infarction & cardiac arrest)	Incidence of	%	6.4 (cardiac failure) 3.3 (Myocardial infarction)	4.1(cardiac failure) 1.3 (Myocardial infarction)		
Pulmonary toxicities	Incidence of	%	2.0 (Acute central respiratory depression) 1.8 (Interstitial lung disease)	2.1 (Acute central respiratory depression) 1.3 (Interstitial lung disease)		
Pulmonary hypertension	Incidence of	%	0.8	0.3		
Dyspnea	Incidence of	%	22.7	18.0		
Hypertension Including Hypertensive Crises	Incidence of	%	15.8	8.2		
Acute renal failure	Incidence of	%	8.4	7.2		
Tumor lysis syndrome	Incidence of	%	0.8	0		
Infusion reactions	Incidence of	%	42.3	N/A		

Effect	Short Description	Unit	Treatment (CRd)	Control (Rd)	Uncertainties/ Strength of evidence	References
Thrombocytopenia	Incidence of	%	32.4	25.2		
Hepatic toxicity	Incidence of	%	12.8 (Liver related investigations, signs and symptoms) 2.0 (Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions)	8.2 (Liver related investigations, signs and symptoms) 0.5 (Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions		
Thrombotic microangiopathy	Incidence of	%	0.0	0.0		
Posterior reversible encephalopathy syndrome (PRES)	Incidence of	%	0.0	0.0		
Febrile neutropenia	Incidence of	%	3.3	1.3		

Abbreviations: AR (assessment report); PFS (progression free survival); OS (overall survival); ORR (overall response rate); Rd (Revlimid (lenalidomide) with low-dose dexamethasone); CRd (Carffilzomib with Revlimid (lenalidomide) with low-dose dexamethasone) ; CR (complete response); IMWG (International Multiple Myeloma Working Group); sCR (stringent complete response); PR (partial response); VGPR (very good partial response); AEs (adverse events) SAEs (serious adverse events).

Notes: (1) The most common adverse reactions (occurring in > 20% of subjects) were: anaemia, fatigue, diarrhoea, thrombocytopenia, nausea, pyrexia, dyspnoea, respiratory tract infection, cough and peripheral oedema. (2) The most serious adverse reactions that may occur during Kyprolis treatment include: cardiac toxicity, pulmonary toxicities, pulmonary hypertension, dyspnoea, hypertension including hypertensive crises, acute renal failure, tumour lysis syndrome, infusion reactions, thrombocytopenia, hepatic toxicity, posterior reversible encephalopathy syndrome and thrombocytopenic thrombotic purpura/haemolytic uraemic syndrome.

Benefit-risk balance

Importance of favourable and unfavourable effects

The gain in PFS of 8.7 months observed with the combination of CRd is considered clinically meaningful. No other treatment for MM has achieved the level of PFS prolongation as the combination of CRd in the proposed line of treatment. In addition, CRd showed a clear trend in OS benefit, although the data is not mature.

Regarding the toxicity associated with CRd there is a pattern of more frequent adverse events and more frequent Grade 3/4 adverse events in patients treated with CRd (83.7%) compared to those treated with Rd (81.2%). However, in the light of the data related to discontinuations, the combination seems tolerable, given the comparable rates of discontinuation between arms in the main study (26% vs 25.2%). The toxicity appears to be manageable within the context of this disease, as reflected in the percentage of patients on treatment at cycle 18 (61% vs 42.2% CRd vs Rd respectively).

Benefit-risk balance

The delay in disease progression observed with CRd is clinically relevant and appears superior to available alternatives in the setting of relapsed MM. Therefore, given the overall accepted safety profile, which is considered manageable in the current context, the benefit risk for CRd is considered positive.

Discussion on the benefit-risk assessment

There is an unmet medical need of better treatments capable of delaying the progression of MM. This is of utmost important given the absence of curative treatment and bearing in mind that eventually patients would become refractory to treatment. During the recent years several new drugs have been incorporated to the therapeutic armamentarium, with proteasome inhibitors and IMIDs standard of care therapies.

Other regimen containing three active treatments, such as bortezomib, thalidomide and high dose dexamethasone (VTD) or bortezomib, lenalidomide and low-dose dexamethasone (VRD), obtained positive results, but far from those achieved by CRd. The combination of VTD obtained a median PFS of 19.5 months (Garderet L et al., 2012), whereas VRD reached 9.5 months of median PFS (Richardson et al., 2014). Even the more recent triplet of panobinostat, bortezomib, and dexamethasone (PVD) showed a lower median of PFS in a comparable population (San-Miguel et al., 2014).

The comparison in terms of ORR also highlights the apparent superiority of CRd vs alternatives (87.1%; 60.7%; 64% in CRd, PVD and VRD respectively).

Only in newly diagnosed multiple myeloma patients, lenalidomide and dexamethasone achieved similar results in PFS to those obtained by CRd in the current application, with medians range between 21 and 26 months (study MM-020). In the study MM-020 dexamethasone was administered as 40 mg once daily on Days 1, 8, 15, and 22 of each 28- day cycle. The latter, low dose of dexamethasone, can be one of the explanations when it comes to analysing the unexpected high PFS results for Rd in the PX-171-009 trial. The reduced toxicity associated to this lower regimen of dexamethasone could partially explain the outcomes.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Kyprolis is not similar to Thalidomide Celgene, Revlimid, Imnovid and Farydak within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the risk-benefit balance of Kyprolis in the treatment of adult patients with multiple myeloma who have received at least one prior therapy in combination with lenalidomide and dexamethasone is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and

any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that carfilzomib is qualified as a new active substance.

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